**National Clinical Guideline Centre**

# Type 1 diabetes in adults

## Type 1 diabetes: diagnosis and management of type 1 diabetes in adults

*Clinical guideline <...>*

*Methods, evidence and recommendations*

*December 2014*

Royal College of Physicians

The Royal College of Surgeons of England

RCGP Royal College of General Practitioners

Royal College of Nursing

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Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

# Contents

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# 4 **Acknowledgements**

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# 1 Introduction

## Aim of this guideline

Type 1 diabetes affects over 370,000 adults in the UK, representing approximately 10% of adults diagnosed with diabetes. Given the complexity of its treatment regimens, successful outcomes depend, perhaps more than with any other long-term condition, on full engagement of the adult with type 1 diabetes in life-long day-by-day self-management. In order to support this, the health service needs to provide informed, expert support, education and training as well as a range of other more conventional biomedical services and interventions.

The number of adults with type 1 diabetes means that, while the condition is certainly not rare, it is not common enough to provide and maintain all the necessary skills in its management for all healthcare professionals who will deal with it. The aim of this guideline is, therefore, to provide evidence-based, practical advice on the steps necessary to support adults with type 1 diabetes to live full, largely unrestricted, lives and avoid the acute and long-term complications of both the disease and of its treatment. NICE last produced such a guideline in 2004. The present guideline is an update of many sections of that guideline, focusing on areas where new knowledge and new treatment opportunities have arisen in the last decade. There have been many such developments, resulting in improving outcomes for adults with type 1 diabetes, but also presenting more challenges in the diversity and complexity of the tools they now have to achieve these outcomes.

## Background

Type 1 diabetes is a long-term hormonal deficiency disorder, in which there is loss of insulin secretion. This results in high plasma glucose concentrations and other metabolic and haematological abnormalities, which have both acute and long-term adverse effects. Type 1 diabetes is usually caused by autoimmune destruction of the insulin-secreting beta cells of the pancreas. These cells make insulin in response to need, with the main driver being circulating glucose concentrations, influenced by a variety of other neurological and endocrine factors signalling the body's state.

Type 1 diabetes can present at any age. Although it commonly presents in children and adolescents, the condition persists into and can start in adult life. Prevalence of type 1 diabetes is highest in the age ranges of 35–60 years.[1] Treatment regimens used to manage diabetes and the demands of living with diabetes are as complex in adults as in younger people.

The treatment of type 1 diabetes is insulin replacement and this insulin is not under endogenous control. In the short term, people with type 1 diabetes face significant challenges to daily living, for example, hyperglycaemia (high plasma glucose) and hypoglycaemia (low plasma glucose), the need for daily administration of insulin and frequent self-monitoring of plasma glucose, and to plan daily activities such as eating and exercising. Over the long term, type1 diabetes carries risk of major complications and reduced life expectancy. At present there is no cure.

Life expectancy for people with type 1 diabetes has increased. In one study from the USA, life expectancy among people diagnosed with type 1 diabetes between 1965 and 1980 improved by 15 years compared with people diagnosed between 1950 and 1964[2], and mortality rates in a UK study are lower than previously reported.[3] Nevertheless, having had type 1 diabetes typically reduces life expectancy in the UK by 11-14 years.[4] Risk of death is 135% higher than for people without diabetes of the same age.[5] Most of the deaths are due to chronic complications, although, death in acute hypoglycaemia or diabetic ketoacidosis may occur. Rates of diabetic ketoacidosis appear to be increasing in the UK.[12] There has also been an increase in the number of people with type 1 diabetes needing treatment for end-stage kidney disease.[12]

Strict plasma glucose control reduces risk of all long-term complications and increases life expectancy among people with type 1 diabetes.[6] Every adult with type 1 diabetes should therefore be encouraged and supported to achieve optimum plasma glucose control, using insulin replacement. Effective replacement of insulin requires detailed knowledge of its actions. The insulin user needs to acquire complex skills in insulin management.

Other risk factors for vascular complications of type 1 diabetes should also be addressed. Higher blood pressure is associated with increased complications[7] and should be aggressively managed.[8,9] Controlling lipids within recommended targets for other forms of diabetes is expected to reduce excess cardiovascular risk associated with type 1 diabetes.[7] Early detection and effective management of type 1 diabetes and its complications are also essential to prevent or limit disability in people with type 1 diabetes.

## Current practice: ideal and achieved

People with type 1 diabetes manage many aspects of their own care, including administering insulin by injection or infusion, monitoring their plasma glucose concentrations, and adjusting insulin doses accordingly on a regular basis. The aim is to maximise the time that achieved glucose concentrations are within the target levels known to minimise risk of complications, while avoiding problems such as hypoglycaemia or ketosis.

People with type 1 diabetes need education and support from healthcare professionals with expertise in insulin physiology and therapeutics to manage their diabetes effectively. Hypoglycaemia remains a problem for people using insulin and can be reduced by structured education programmes[10] yet only about 1% of adults with type 1 were recorded as having attended such programmes in England and Wales in 2011-12.[11] Fewer than 30% of people with type 1 diabetes achieve the 2004 NICE-recommended target for blood glucose control. In the last 4 audit cycles, there has been no significant improvement in the proportion of people who meet this target.[11]

People with type 1 diabetes need regular monitoring for complications of diabetes and for the factors that increase their individual risk of developing these. Where these occur, active management is needed. However, only 41.3% of people with type 1 diabetes in England and Wales have records of receiving all 9 of the care processes recommended by NICE.[11] More than 30% of people with type 1 diabetes miss their annual eye and foot checks for early complications and almost one-half miss screening appointments for kidney complications. Blood pressure within 2004 NICE guidelines is recorded in nearly 75% of adults with type 1 diabetes; but just under 30% have recorded cholesterol of under 4 mmol/litre.[11]

Diabetes management in hospitals and other places for professional healthcare remains suboptimal. Insulin regimens are the most common cause of drug errors in inpatient prescribing

People with type 1 diabetes have traditionally received care primarily from specialist services. However, 15–20% of adults with type 1 diabetes have little or no contact with secondary care services, or are offered only infrequent appointments focussed on annual review.

A small number of people with type 1 diabetes experiencing life-threatening episodes of hypoglycaemia undergo pancreatic transplant or islet cell transplantation. Around 200 pancreas transplants are performed in the UK each year. Around 95 islet transplants have been performed in 65 people in the UK to date.

## Target audience

This guideline is intended to describe the methods for achieving optimal outcomes for adults with type 1 diabetes and inform service design and delivery for them. Its intended audience therefore

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include healthcare professionals involved in delivering services to adults with type 1 diabetes, service managers and commissioners and adults with type 1 diabetes and their families.

## 1.1 Living with type 1 diabetes

Type 1 diabetes is a condition where the power lies primarily with the people. Day-to-day monitoring, control and treatment are undertaken by the patient, not by the healthcare professional (hence RD Lawrence's saying "Every diabetic, their own Doctor"). With power comes responsibility: it is the patient's behaviour and daily decisions which determine the level of success in managing the condition. Adherence to insulin regimes, close monitoring of blood glucose, accurate estimation of carbohydrate intake and administration of appropriate insulin doses profoundly affect both immediate and long-term outcomes.

For patients, effective management of type 1 diabetes involves diligence, self-discipline, attention to detail, an analytical approach and numerous decisions – every day. Developing and then using these behaviours consistently is a considerable challenge in itself. However, type 1 diabetes can add further levels of complexity. Patients trying to emulate as closely as possible the blood glucose control of those without diabetes face the twin risks of hypoglycaemia on one side and hyperglycaemia, with its associated likelihood of long-term complications, on the other. Additionally, an individual's diabetes rarely remains static for long periods due to the influence of hormonal variation, activity, stress and a myriad of other factors. Patients employing carefully evolved strategies and approaches to dietary and insulin dose management can see impeccable blood glucose results one week, followed by apparently illogical variability the next.

For healthcare professionals, the challenge of supporting type 1 patients can be exacerbated precisely because the condition is so individualised. Rather than uniform and universal approaches, most patients seek a personalised package of targets, technologies and techniques that allow them to manage their diabetes in different day-to-day situations with the minimum effort necessary for the best results and the highest quality of life. People with type 1 diabetes prefer to fit the condition into their lives, and not the other way round. However, patients will manage their condition more effectively where they can rely upon informed advice and proven interventions.

This updated Guideline therefore aims, in the light of the most recent evidence, to help healthcare professionals in all settings encourage and support optimum lifestyle choices and self-management strategies among patients. For example, newly diagnosed patients may not be aware that there are different types of diabetes with different treatment opportunities. No longer can a diagnosis be presumed solely on the basis of age or weight. An accurate diagnosis by the healthcare professional is key if the patient is to receive the relevant therapies. Rigorous control of blood glucose from the point of diagnosis onwards will yield benefits for the rest of the patient's life. Structured education programmes are an important mechanism for helping the patient understand and embrace the behavioural changes that will secure these benefits.

A century ago, a diagnosis of diabetes was a death sentence; the chances of survival for any length of time were minimal. Today, people living with diabetes can enjoy long, healthy, active lives with a rich variety of food choices, careers and opportunities: type 1 diabetes need be no restriction. Modern treatment techniques and technologies make near-normal blood glucose profiles increasingly possible; growing numbers of people who have successfully managed the condition for 50, 60 or 70 years bear witness to this. This Guideline invites patients and healthcare professionals to extend the progress already made.

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# 2 Development of the guideline

## 2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a Guideline Development Group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the 'full guideline' contains all the recommendations, plus details of the methods used and the underpinning evidence
- the 'NICE guideline' lists the recommendations
- 'information for the public' is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

## 2.2 Remit

NICE received the remit for the guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

This is a partial update of 'Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults', NICE clinical guideline CG15 (2004). See section 3.4.1 for details of which

sections were updated. We carried out a review of all recommendations to ensure they comply with NICE's duties under equalities legislation.

This update was undertaken as part of the guideline cycle review.

## 2.3 Epidemiology

- Type 1 diabetes is a long-term hormonal deficiency disorder, in which there is loss of insulin secretion. This results in high blood glucose concentrations and other metabolic and haematological abnormalities. It is usually caused by autoimmune destruction of the insulin-secreting beta cells of the pancreas. In the short term, people with type 1 diabetes may face significant challenges to daily living, for example, hyperglycaemia (high blood glucose) and hypoglycaemia (low blood glucose), the need for daily administration of insulin and frequent self-monitoring of blood glucose, and to plan daily activities such as eating and exercising. Over the long term, type1 diabetes is associated with major complications and reduced life expectancy. The condition is treated with insulin replacement therapy and at present there is no cure.

- Approximately 10% of adults diagnosed with diabetes have type 1 diabetes. Currently, it is estimated that 0.34-0.55% of the population of England and Wales are known to have type 1 diabetes. Among people aged between 10 and 80 years, there is little difference in prevalence across age groups.

- Type 1 diabetes can present at any age. Although it commonly presents in children and adolescents, the condition persists into and can start in adult life. Treatment regimens used to manage diabetes and the demands of living with diabetes are as complex in adults as in younger people.

- Effective insulin management requires detailed knowledge of its actions.

- Life expectancy for people with type 1 diabetes has increased. In one study from the USA, life expectancy among people diagnosed with type 1 diabetes between 1965 and 1980 improved by 15 years compared with people diagnosed between 1950 and 1964. Nevertheless, having type 1 diabetes typically reduces life expectancy in the UK by 20 years. People with type 1 diabetes in England are 2.6 times more likely to die than people without diabetes of the same age. Most of the deaths are due to chronic complications, although death in acute hypoglycaemia or diabetic ketoacidosis may occur.

- The Diabetes Control and Complications Trial Research Group[a] confirmed that strict blood glucose control reduces risk of long-term complications and is associated with increased life expectancy among people with type 1 diabetes. Effective insulin management requires detailed knowledge of its actions. The insulin user needs to acquire skill in insulin management.  Control of blood pressure also reduces risk of complications in people with type 1 diabetes. Controlling lipids within recommended targets for other forms of diabetes is expected to reduce excess cardiovascular risk associated with type 1 diabetes.

- Early detection and effective management of type 1 diabetes and its complications are important to prevent or limit disability in people with type1 diabetes.

## 2.4 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as lay members developed this guideline (see the list of Guideline Development Group members and the acknowledgements).

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[a] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986.

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Stephanie Amiel in accordance with guidance from NICE.

The group met every 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

## 2.5 What this guideline covers

This guideline covers adults (aged 18 and over) with type 1 diabetes.

It updates the following clinical areas from CG15:
- Diagnosis of type 1 diabetes: differentiation of type 1 diabetes from other forms of diabetes using c-peptides and antibody testing).
- Education programmes and self-care: structured educational programmes.
- Clinical monitoring of blood glucose control: HbA1c, self-monitoring of blood glucose and continuous glucose monitoring.
- Insulin therapy and adjunctive therapy.
- Needle length and injection site for insulin administration.
- Aspirin for primary prevention of cardiovascular disease.
- Treatment of late-stage complications (acute painful neuropathy of rapid glycaemic control, gastroparesis and erectile dysfunction).
- Inpatient management in relation to insulin replacement.

Other clinical topics from CG15 were not updated; these chapters have been reproduced verbatim from CG15.

The following areas were not covered in CG15 and have been added:
- New insulin formulations, including insulin degludec, insulin degludec-aspart combintaions and insulin detemir.
- Impaired awareness of hypoglycaemia.
- Monitoring for thyroid disease.
- Ketone monitoring: self-monitoring for the prevention of diabetic ketoacidosis and monitoring of diabeteic ketoacidosis.
- Carbohydrate counting and glycaemic index diets.
- Referral criteria for pancreas and islet transplantation.

 For further details please refer to the scope in Appendix A and the review questions in Section 0.

## 2.6  What this guideline does not cover

This guideline does not cover:

- children and young people with type 1 diabetes (this is covered by Diabetes in children and young people, due for publication in August 2015).
- people with type 2 or other types of diabetes (this is covered by Type 2 diabetes in adults, due for publication in August 2015).
- preconception care in women with type 1 diabetes, contraceptive advice in women with type 1 diabetes and diabetes in pregnancy (this is covered by the Diabetes in pregnancy, due for publication in February 2015).
- diabetic foot problems (this is covered by the Diabetic foot problems guideline, due for publication in July 2015).

## 2.7  Relationships between the guideline and other NICE guidance

**NICE technology appraisals to be updated by this guidance**

Guidance on the use of patient education models for diabetes.  NICE technology appraisal guidance 60 (2003).

Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine. NICE technology appraisal guidance 53 (2002).

**NICE technology appraisals to be incorporated in this guidance**

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus.  NICE technology appraisal 151 (2008).

**Related NICE technology appraisals**

Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy.  NICE technology appraisal TA301 (2013).

Ranibizumab for the treatment of diabetic macular oedema.  NICE technology appraisal 274 (2013).

Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion.  NICE technology appraisal 229 (2011).

**Related NICE interventional procedures guidance**

Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus.  NICE interventional procedure guideline 257 (2008).

Gastroelectrical stimulation for gastroparesis.  NICE interventional procedure guide 489 (2014).

**Related NICE clinical guidelines**

Chronic kidney disease (update).  NICE clinical guideline (2014).

Lipid modification.  NICE clinical guideline 181 (2014).

Neuropathic pain – pharmacological management. NICE guideline 173 (2013).

Patient experience in adult NHS services. NICE clinical guideline 138 (2012).

Lower limb peripheral arterial disease.  NICE clinical guideline 147 (2012).

Hyperglycaemia in acute coronary syndromes.  NICE clinical guideline 130 (2011).

Hypertension.  NICE clinical guideline 127 (2011).

Depression with a chronic physical health problem.  NICE clinical guideline 91 (2009).

Depression in adults.  NICE clinical guideline 90 (2009).

Medicines adherence.  NICE clinical guideline 76 (2009).

Coeliac disease. NICE clinical guideline 86 (2009).

Nutrition support in adults.  NICE clinical guideline 32 (2006).

Obesity.  NICE clinical guideline 43 (2006)


**Related NICE public health guidance**

Four commonly used methods to increase physical activity.  NICE public health guidance 2 (2006).

Smoking cessation services.  NICE public health guidance 1 (2006).


**Related NICE guidance currently in development**

Diabetes in pregnancy.  NICE clinical guideline. Publication expected February 2015.

Diabetic foot problems (update). NICE clinical guideline.  Publication expected July 2015.

Type 2 diabetes in adults (update).  NICE clinical guideline.  Publication expected August 2015.

Diabetes in children and young people (update). NICE clinical guideline.  Publication expected August 2015.

Buccal insulin for managing type 1 diabetes.  NICE technology appraisal guidance. Publication date to be confirmed.

# 3   Methods

This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2012.[512]

**Amendments to 2004 text**

All content from the previous guideline CG15 that has not been updated by new evidence reviews has been left unchanged and included verbatim.  Recommendations from 2004 that were not updated were checked to determine whether any changes were essential.  These changes were kept to a minimum in line with the NICE guidance on presenting updates in the NICE guidelines manual 2012.  All recommendations from 2004 were updated to the active style wherever possible. Details of amendments and deleted recommendations are explained in Appendix S.

## 3.1   Developing the review questions and outcomes

Review questions were developed in a patient, intervention, comparison and outcome (PICO) framework for intervention reviews, and an adapted PICO framework was ued for other types of review (such as diagnosis).

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A).

A total of 29 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

**Table 1:    Review questions**

| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| Arterial risk control | Intervention | In adults with type 1 diabetes, is aspirin an effective anti-platelet agent for the primary prevention of cardiovascular events? | • Mortality – all-cause<br>• Mortality – CV<br>• MI – all-cause<br>• MI – fatal<br>• MI – non-fatal<br>• Stroke – all-cause<br>• Stroke – fatal<br>• Stroke – non-fatal<br>• Quality of life – measured by SF-36, DQoL, DSQoL<br>• Adverse events – bleeding or GI complications<br>• HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia |
| Ketone monitoring and management of | Intervention | In adults with type 1 diabetes (including atypical ketosis-prone diabetes), does patient self- | • Hospital admissions – for DKA if specified |

| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| DKA | | monitoring of blood (and urine) ketones reduce the incidence of DKA and hospital admissions? | <ul><li>Duration of admission/length of hospital stay</li><li>DKA</li><li>HbA1c</li><li>Hypoglycaemia</li><li>Severe hypoglycaemia</li><li>Quality of life – measured by PAID, anxiety</li><li>Severity of acidosis at admission - duration of acidosis and degree of acidosis</li></ul> |
| Ketone monitoring and management of DKA | Intervention | In adults with type 1 diabetes does inpatient monitoring of blood ketones by the healthcare professional reduce the length of hospital stay, exposure to IV insulin and the development of in-hospital complications:<br><ul><li>in patients with suspected DKA?</li><li>in patients admitted with DKA and/or those that get it in hospital.</li></ul> | <ul><li>Length of hospital stay</li><li>In-hospital complications of the admission</li><li>Exposure to IV insulin</li><li>How often admission occurs</li><li>HbA1c</li><li>Hypoglycaemia</li><li>Severe hypoglycaemia</li><li>Quality of life</li></ul> |
| Diagnosis | Observational | In adults and young people with diabetes, what is the best marker (C-peptides plus or minus antibodies) to distinguish between type 1 diabetes, type 2 diabetes and other forms of diabetes? | <ul><li>Presence of marker (number or % of patients with marker)</li><li>Concentration of marker (µg/ml)</li><li>Change in marker over time (No. or % of patients with marker)</li><li>Change in concentration of marker over time (µg/ml)</li></ul> |
| Education programmes and self-care | Intervention | In adults with type 1 diabetes, what is the most effective structured education programme? | <ul><li>HbA1c (continuous)</li><li>Hypoglycaemia</li><li>Severe hypoglycaemia</li><li>Hospital admissions</li><li>Hypoglycaemia unawareness</li><li>Quality of life – measured by DQoL, DSQoL, PAID, HADS, fear of hypoglycaemia, anxiety, depression</li><li>Adverse events</li><li>Knowledge</li><li>Adherence</li></ul> |
| Insulin therapy | Intervention | In adults with type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus NPH) for optimal diabetic control? | <ul><li>HbA1c</li><li>Hypoglycaemia</li><li>Severe hypoglycaemia</li><li>Nocturnal hypoglycaemia</li><li>Quality of life – measured by DQoL or any measure used in</li></ul> |

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| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| | | 26 | the studies retrieved<br>• Adverse events – Cancer<br>• Injection site issues<br>• Weight gain/loss<br>• DKA |
| Blood glucose monitoring | Intervention | In adults with type 1 diabetes, is retrospective continuous glucose monitoring more effective than care without continuous glucose monitoring (with SMBG) for improving diabetic control? | • HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia if reported<br>• Quality of life – measured by what is shown in the study or patient satisfaction<br>• Adverse events<br>• Adherence |
| Blood glucose control | Intervention | In adults with type 1 diabetes, is real-time continuous glucose monitoring more effective than SMBG continuous glucose monitoring for optimum diabetic control? | • HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia if reported<br>• Quality of life – measured by what is shown in the study or patient satisfaction<br>• Adverse events<br>• Adherence |
| Blood glucose control | Intervention | In adults with type 1 diabetes, is continuous real-time monitoring more effective than intermittent real-time monitoring for optimum diabetic control? | • HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia if reported<br>• Quality of life – measured by what is shown in the study or patient satisfaction<br>• Adverse events<br>• Adherence |
| Insulin therapy | Intervention | In adults with type 1 diabetes, are metformin (with or without insulin), or GLP1-agonists (with or without insulin) as effective as insulin alone for optimal diabetic control? | • HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Quality of life – measured by what is shown in the papers<br>• Adverse events<br>• Weight loss/change<br>• Dose of insulin |
| Insulin therapy | Intervention | In adults with type 1 diabetes, what are the most effective mixed insulins (degludec-aspart versus glargine versus NPH) for optimal diabetic control? | • HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Quality of life – measured by DQoL or any measure used in the studies retrieved<br>• Adverse events – Cancer |

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| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| | | 27 | • Injection site issues<br>• Weight gain/loss<br>• DKA |
| Blood glucose control | Observational | In adults with type 1 diabetes, what is optimum timing and frequency to self-monitor blood glucose for effective diabetic control? | • Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Time within range (blood glucose)<br>• HbA1c<br>• Quality of life – measured by any measure specified in the study<br>• DKA<br>• Adherence<br>• Unscheduled care use |
| Blood glucose control | Observational | In adults with type 1 diabetes, what is the optimum glucose target or profile for self-monitoring of blood glucose for effective diabetic control? | • HbA1c value<br>• Risk of hypoglycaemia<br>• Risk of severe hypoglycaemia<br>• Risk of nocturnal hypoglycaemia<br>• Risk of complications<br>• Quality of life - any measure reported in the study |
| Blood glucose control | Intervention | In adults with type 1 diabetes, what are the benefits of technologies (bolus calculators and downloads) for self-monitoring of blood glucose? | • Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• HbA1c<br>• Quality of life – measured by whatever is used in the study<br>• Adverse events<br>• Adherence |
| Blood glucose control | Observational | In adults with type 1 diabetes, what is the optimum target HbA1c level that should be achieved to reduce the risk of complications? | • Number of people reaching target HbA1c<br>• Final HbA1c value<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Complications/avoidance:<br>  o CV events (MI, IHD, Stroke, cardiac and peripheral revascularisation, major amputation)<br>  o Hypoglycaemia<br>  o macro- and micro-vascular<br>  o Retinopathy<br>  o Low-level (micro) albuminuria/proteinuria |

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| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| | | 28 | o Renal replacement therapy/ESRF<br>o Neuropathy<br>o Sudden death<br>• Quality of life – measured by whatever is used in the study |
| Blood glucose control | Intervention, observational | In adults with type 1 diabetes, what is the optimum frequency of HbA1c monitoring for effective diabetic control? | • Hypoglycaemia<br>• Severe hypoglycaemia<br>• HbA1c<br>• Quality of life – measured by any measure reported in the study<br>• Adverse events<br>• Adherence<br>• Complications – such as retinopathy |
| Insulin therapy | Intervention | In adults with type 1 diabetes, is once-daily basal insulin more effective than twice-daily basal insulin for optimal diabetic control? | • HbA1c (continuous)<br>• Hypoglycaemia<br>• Severe hypoglycaemia Quality of life – measured by whatever is used in the study<br>• Adverse events |
| Insulin therapy | Intervention | In adults with type 1 diabetes, which are the most effective rapid-acting insulins for meal times: analogues versus human (intermediate NPH), for optimal diabetic control? | • HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Quality of life – measured by DQoL or any measure used in the studies retrieved<br>• Patient satisfaction<br>• Adverse events – Cancer<br>• Injection site issues<br>• Weight gain/loss<br>• DKA |
| Insulin therapy | Intervention | In adults with type 1 diabetes, what is the optimum needle length for insulin delivery? | • Pain<br>• Discomfort )<br>• Patient satisfaction<br>• HbA1c<br>• Quality of life – measured by whatever is used by the study<br>• Adverse events<br>• Adherence |
| Insulin therapy | Intervention | In adults with type 1 diabetes, what is the optimum injection site and rotation for insulin delivery? | • HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Quality of life – measured by |

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| Chapter | Type of review | Review questions | Outcomes |
|---------|---------------|------------------|----------|
| | | | whatever is used in the study |
| | | | • Adverse events |
| | | | • Adherence |
| Management of complications | Intervention | In adults with type 1 diabetes, what is the most effective treatment for insulin-induced neuropathy? | • Pain scores<br>• Retinopathy – incidence<br>• Low-level (micro) albuminuria - incidence<br>• Time to resolution of symptoms<br>• Improved pain scores |
| Management of complications | Intervention | In adults with type 1 diabetes, what is the most effective treatment for gastroparesis? | • Hospital admissions<br>• Severe hypoglycaemia<br>• Vomiting (including frequency)<br>• Weight loss<br>• Quality of Life (SF-36)<br>• HbA1c<br>• Symptom control (as defined by the study) |
| Inpatient management | Intervention | In adults with type 1 diabetes who have been admitted to hospital (elective and emergency), what are the most effective intravenous insulin dose-adjustment devices and regimens for optimal diabetic control? | • Achieving target BG levels (measure used by the study)<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Time spent out of target glucose (hypoglycaemia/hyperglycaemia)<br>• Duration of IV treatment<br>• In-patient stay<br>• In-patient mortality<br>• Infection rate/wound healing<br>• Quality of life – measured by SF-36, DQoL, DSQoL |
| Education and self-care | Intervention | In adults with type 1 diabetes, what is the clinical and cost-effectiveness of carbohydrate counting or restriction for optimal diabetic control? | • HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Quality of life – measured by whatever is used in the study<br>• Adverse events |
| Impaired awareness of hypoglycaemia | Observational | In adults with type 1 diabetes, how is impaired awareness of hypoglycaemia best identified and quantified? | • Ability to predict severe hypoglycaemia (incidence of severe hypoglycaemia)<br>• Ability to predict driving or work related accidents (incidence of accidents) |
| Impaired awareness of | Intervention | In adults with type 1 diabetes and impaired awareness of | • HbA1c<br>• Autonomic |

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| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| hypoglycaemia | | hypoglycaemia, what is the most effective strategy for recovering hypoglycaemia awareness? | symptoms/symptom scores during hypoglycaemia clamp study<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Hospital admissions<br>• Hypoglycaemia unawareness or awareness<br>• Quality of life – measured by DQoL, DSQoL, PAID, HADS, fear of hypoglycaemia, anxiety, depression, cognitive function<br>• Road traffic accidents and work related accidents |
| Management of complications | Observational | How should adults with type 1 diabetes be monitored for thyroid disease, and how frequently? | • Detection of thyroid disease – thyroid tests, for example, TSH, T4<br>• Incidence of thyroid disease<br>• Frequency of treatment |
| Referral for islet or pancreas transplantation | Observational and real-life data | Which adults with type 1 diabetes are most suitable to be considered for a pancreas transplant, or pancreatic islet cell transplantation? | Outcomes<br>• Current UK referral criteria<br>Clinical outcomes from real-life UK data<br>• HbA1c<br>• Severe hypoglycaemia<br>• Longevity of the transplant/organ survival (C-peptide and insulin independence)<br>• Insulin dependence at 1 year and 5 years<br>• Mortality - in-hospital/procedural<br>• Mortality – long-term<br>• Quality of life – any measure used in the paper |
| Education and self-care | Intervention | In adults with type 1 diabetes, what is the clinical and cost-effectiveness of a diet based on the glycaemic index for optimal diabetic control? | • HbA1c<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Quality of life – measured by DQoL or any measure used in the studies retrieved<br>• Patient satisfaction<br>• Adherence |
| Management of | Intervention | What pharmacological treatment | • Erectile function |

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| Chapter | Type of review | Review questions | Outcomes |
|---|---|---|---|
| complications | | should be used to manage erectile dysfunction in men with type 1 diabetes? | • HbA1c<br>• Blood glucose control<br>• Body weight<br>• Lipid parameters<br>• Adverse events |
| Management of complications | Observational study | In adults with type 1 diabetes, what is the most effective treatment for acute painful neuropathy of rapid glycaemic control? | • Pain scores (continuous)<br>• Retinopathy – incidence (dichotomous)<br>• Low-level (micro) albuminuria - incidence (dichotomous)<br>• Resolution of symptoms (continuous)<br>• Improvement in pain scores (dichotomous) |

## 3.2 Searching for evidence

### 3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the guidelines manual 2012[512]. Databases were searched using relevant medical subject headings, free-text terms and study design filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in Medline, Embase and The Cochrane Library. All searches were updated on 28 August 2014. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the dates covered can be found in Appendix F.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on those of organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

• Guidelines International Network database (www.g-i-n.net)

• National Guideline Clearing House (www.guideline.gov)

• National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)

• NICE Evidence Search (evidence.nhs.uk)

### 3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to type 1 diabetes in the NHS Economic Evaluation Database (NHS EED), the

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Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on Medline and Embase using an economic filter, from 2009, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix F. All searches were updated on 28 August 2014. No papers published after this date were considered.

## 3.3 Evidence of effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1:

- Potentially relevant studies were identified for each review question from the search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- Relevant studies were critically appraised using the appropriate checklist as specified in The guidelines manual[512].
- Key information was extracted on the study's methods, PICO factors and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix G).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in GDG meetings:
  o Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
  o Observational studies – comparative studies: data were presented narratively or results were tabulated, and reported in GRADE profiles (for intervention reviews).
  o Observational studies – non-comparative studies: data were presented narratively or results were tabulated.

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**Figure 1:    Step-by-step process of review of evidence in the guideline**
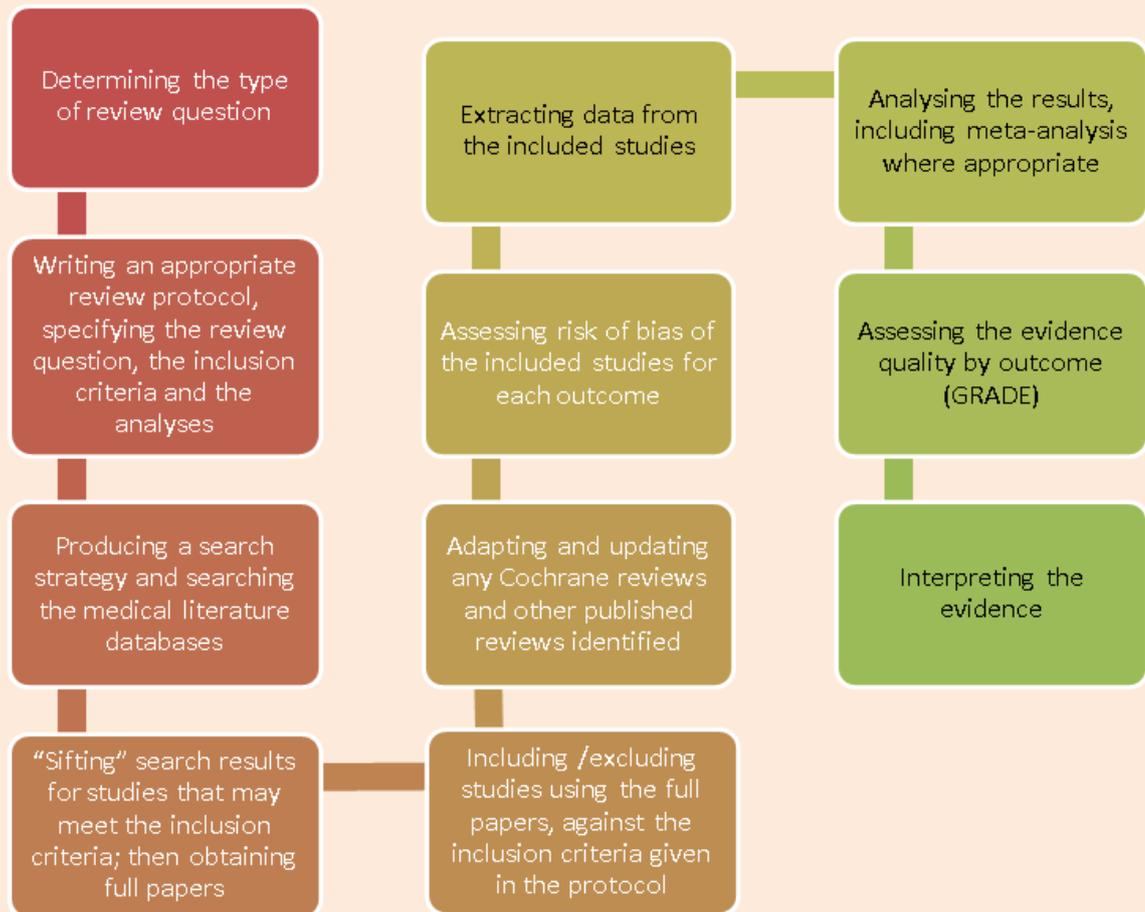


### 3.3.1    Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix K. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

Randomised trials, non-randomised trials, and observational studies were included in the evidence reviews as appropriate.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies, conference abstracts (unless stated in cases where there was limited evidence) and studies not in English were excluded.

The review protocols are presented in Appendix C.

### 3.3.2    Methods of combining clinical studies

#### 3.3.2.1    Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for binary outcomes.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. However, in cases where standard

deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was reported narratively and generally included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type. Where reported, and possible to calculate, time-to-event data was presented as a HR.

Where p values were used as part of calculations for continuous outcomes, if a p value was reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as 'p≤0.001', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then data were reported narratively.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity).

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences (ARDs) were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG. For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

A network meta-analysis (NMA) was conducted for the review on long-acting insulin. This type of analysis simultaneously compares multiple treatments in a single meta-analysis, preserving the randomisation of RCTs included in the reviews of direct comparisons trials. The aim of the NMA was to include all relevant evidence in order both to answer questions on the clinical effectiveness of interventions when no direct comparison was available and to give a ranking of treatments in terms of efficacy. The output was expressed as the mean and 95% credible intervals (CrIs) for the rank of each long-acting insulin regimen and as effect estimates for each of the included outcomes.

A network meta-analysis (NMA) was conducted for the review on long-acting insulin. This type of analysis simultaneously compares multiple treatments in a single meta-analysis, preserving the randomisation of RCTs included in the reviews of direct comparisons trials. The aim of the NMA was to include all relevant evidence in order both to answer questions on the clinical effectiveness of interventions when no direct comparison was available and to give a ranking of treatments in terms of efficacy. The output was expressed as mean and Bayesian 95% credible intervals (CrIs) for the rank of each long-acting insulin regimen and as mean effect estimates and their Bayesian 95% CrIs for each of the included outcomes.

A Bayesian NMA was performed using the software WinBUGS version 1.4.3. That allowed inclusion of multi-arm trials and accounts for the correlation between arms in the trials with any number of trial arms.

The following were the main outputs from the NMA:

- Rate ratios of severe/major hypoglycaemic events (with their 95% CrIs) calculated using direct and indirect evidence
- Changes in HbA1c level (with their 95% CrIs) calculated using direct and indirect evidence
- A ranking of long-acting insulin regimens compared with insulin NPH (twice daily) (with 95% CrIs for the ranks) for each network.

A full technical account can be found in Appendix M.

### 3.3.3    Type of studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C for full details on the study design of studies selected for each review question. It was considered unlikely that the search would find any RCTs.

Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

### 3.3.4    Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and, where appropriate, comparative observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was taken into consideration in the quality assessment and only included in the 'Clinical evidence profile' table if it was apparent from GDG members.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2. Each element was graded using the quality levels listed in Table 3. The main criteria considered in the rating of these elements are discussed below (see Section 3.3.5). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 4).

The GRADE toolbox is currently designed only for randomised trials and comparative observational studies, for non-comparative observational studies, the results, study limitations and overall quality assessment ratings were reported narratively.

**Table 2:    Description of the elements in GRADE used to assess the quality of intervention studies**

| Quality element | Description |
|---|---|
| Risk of bias ('Study limitations') | Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect |
| Inconsistency | Inconsistency refers to an unexplained heterogeneity of results |
| Indirectness | Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed |
| Imprecision | Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision |

| Quality element | Description |
|---|---|
|  | results if the confidence interval includes the clinically important threshold |
| Publication bias | Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies |

**Table 3:    Levels of quality elements in GRADE**

| Level | Description |
|---|---|
| None | There are no serious issues with the evidence |
| Serious | The issues are serious enough to downgrade the outcome evidence by 1 level |
| Very serious | The issues are serious enough to downgrade the outcome evidence by 2 levels |

**Table 4:    Overall quality of outcome evidence in GRADE**

| Level | Description |
|---|---|
| High | Further research is very unlikely to change our confidence in the estimate of effect |
| Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate |
| Low | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate |
| Very low | Any estimate of effect is very uncertain |

### 3.3.5    Grading the quality of clinical evidence: RCTs and comparative observational studies

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High, observational cohort studies as Low.

2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational cohort studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.

3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.

4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality element are discussed further in the following Sections (3.3.8, 3.3.9 and 3.3.10).

### 3.3.6    Grading the quality of clinical evidence: non-comparative observational studies.

A customised quality assessment checklist (adapted from the NICE prognostic studies checklist) has been used for assessing the quality of non-comparative observational studies (for example, cross-sectional studies or case-series), and so for reviews that included these study types, the main criteria considered in assessing study quality were:

- The study design: if it is retrospective or prospective, or cross-sectional. Retrospective studies are more likely to be at higher risk of bias.

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- The study sample is representative of the population of interest with regard to key characteristics, sufficient to limit potential bias to the results
- The outcome of interest is adequately measured in study participants, sufficient to limit bias
- Important potential confounders are appropriately accounted for in the statistical analysis, limiting potential bias with respect to the outcomes of interest, and the presentation of invalid results

All non-comparative observational studies were graded as Low quality due to the inherent high risk of bias associated with these study designs. However, the specific methodological limitations of the studies included in the guideline update, have been summarised in tables within Appendix I, in order to give an overview of the quality of each individual study. As GRADE is currently not designed for these types of study, quality has been assessed by study only, rather than by outcome in the review. Raw data, or odds ratios, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers where appropriate to the review question. Data for the outcomes defined in the review protocols has been summarised in tables within the relevant review chapter. Full data for all the outcomes has been reported in the evidence tables (see Appendix G) for each individual observational study.

### 3.3.7   Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example, multiple replications of the same study would reach the wrong answer on average.

The risk of bias for a given study and outcome is associated with the risk of over- or underestimation of the true effect.

The risks of bias are listed in Table 5.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

**Table 5:    Risk of bias in RCTs**

| Risk of bias | Explanation |
|---|---|
| Allocation concealment | Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example, allocation by day of week, birth date, chart number) |
| Lack of blinding | Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated |
| Incomplete accounting of patients and outcome events | Missing data not accounted for and failure of the trialists to adhere to the intention-to-treat principle when indicated |
| Selective outcome reporting | Reporting of some outcomes and not others on the basis of the results |
| Other risks of bias | For example:<br>• Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules<br>• Use of unvalidated patient-reported outcomes<br>• Recruitment bias in cluster-randomised trials |

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### 3.3.8    Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect.

Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C).

When heterogeneity exists (chi-squared $p<0.1$, I-squared inconsistency statistic of more than 50%, or evidence from examining forest plots), but no plausible explanation can be found (for example, duration of intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I-squared and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

### 3.3.9    Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

### 3.3.10    Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% CI is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate is relevant to decision-making, considering each outcome in isolation. Figure 2 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

<div style="text-align:right">**Update 2015**</div>

**Figure 2: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot**
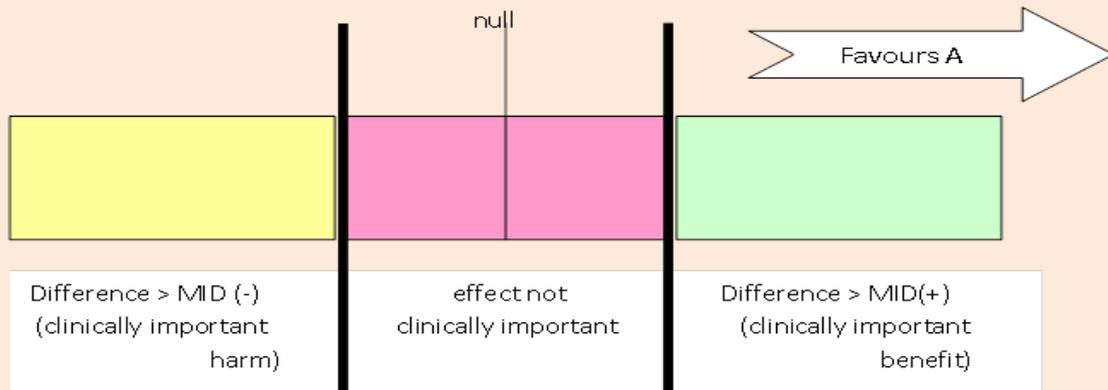


When the confidence interval of the effect estimate is wholly contained in one of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The GDG was asked whether they were aware of any acceptable MIDs in the clinical community but there were none known. Therefore, the GDG agreed that the default values stated in GRADEpro were appropriate for our outcomes. For dichotomous outcomes, the default thresholds suggested by GRADE are a relative risk reduction of 25% (relative risk of 0.75 for negative outcomes) or a relative risk increase of 25% (risk ratio 1.25 for positive outcomes). For continuous outcomes, the default approach of multiplying 0.5 by the standard deviation was employed.

### 3.3.11 Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into ARDs using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies

This assessment was carried out by the GDG for each outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

### 3.3.12 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements encompass the following key features of the evidence:

- the intervention and comparison group under investigation

- the outcome measure being assessed

- an indication of the direction of effect (if one treatment is beneficial or harmful compared with the other, or whether there is no difference between the 2 tested treatments). Determination of benefit, harm, or no difference, is based on the GDG's interpretation of whether the absolute effect could be considered clinically beneficial, clinically harmful, or no clinical effect or difference between the intervention and comparison groups.

- the time-point the outcomes have been assessed at

- a description of the overall quality of evidence (GRADE overall quality).

## 3.4 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[512] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.

- Undertook new cost-effectiveness analysis in priority areas.

### 3.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.

- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).

- Critically appraised relevant studies using the economic evaluations checklist as specified in The guidelines manual.[512]

- Extracted key information about the studies' methods and results into evidence tables (included in Appendix H).

- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

### 3.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix E of the guidelines manual [512] and the health economics review protocol in Appendix C).

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

### 3.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The guidelines manual.[512] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 6 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[536]

**Table 6:    Content of NICE economic evidence profile**

| Item | Description |
|---|---|
| Study | First author name, reference, date of study publication and country perspective. |
| Applicability | An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making[a]: <br>• Directly applicable – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. <br>• Partially applicable – the study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness. <br>• Not applicable – the study fails to meet one or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review. |
| Limitations | An assessment of methodological quality of the study[a]: <br>• Minor limitations – the study meets all quality criteria, or fails to meet one or |

| Item | Description |
|---|---|
| | more quality criteria, but this is unlikely to change the conclusions about cost effectiveness.<br>• Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusions about cost effectiveness.<br>• Very serious limitations – the study fails to meet one or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review. |
| Other comments | Particular issues that should be considered when interpreting the study. |
| Incremental cost | The mean cost associated with one strategy minus the mean cost of a comparator strategy. |
| Incremental effects | The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy. |
| Cost effectiveness | Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects. |
| Uncertainty | A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate. |

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of The guidelines manual (2012)[512]

### 3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[513]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

Full methods for the cost-effectiveness analyses conducted for this guideline are described in Appendix N, O and P.

### 3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[502] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or

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- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[502]

### 3.4.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the GDG and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

## 3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices [G and H].
- Summaries of clinical and economic evidence and quality (as presented in Chapters [6–16]).
- Forest plots and summary ROC curves (Appendix J).
- A description of the methods and results of the cost-effectiveness analysis(ses) undertaken for the guideline (Appendices N-P).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, it was assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared with the economic benefits, current practices, and recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Appendix R).

The wording of recommendations was agreed by the GDG and focused on the following factors:

- The actions health professionals need to take.
- The information readers need to know.

- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the 'recommendations and link to evidence' sections within each chapter.

### 3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

### 3.5.2 Validation process

This guidance is subject to a 12 week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

### 3.5.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

### 3.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

### 3.5.5 Funding

The National Clinical Guideline Centre was commissioned by the NICE to undertake the work on this guideline.

Update 2015

## 3.6 Methods 2004

### 3.6.1 Aims and principles

This chapter describes the resources and techniques used to reach the clinical recommendations in this guideline.

Clinical guidelines have been formally defined as 'systematically developed statements to assist both practitioner and patient decisions in specific circumstances'.6 This guideline aims to offer the best practice advice on the care of adults (defined as those aged 18 years or older) with Type 1 diabetes. It gives guidance on the management, monitoring and support of people with Type 1 diabetes. The context of the intended guidance is the primacy of the needs of the individual with diabetes, reflecting the difficulties of reconciling the problems of insulin replacement therapy with personal lifestyles.

The current guideline is aimed at helping all healthcare professionals provide optimal services for people with Type 1 diabetes by:

- providing healthcare professionals with a set of explicit statements on the best known ways to assist people with diabetes with their most common clinical problems, while maximising the effectiveness of the service in supporting the population with Type 1 diabetes
- giving commissioning organisations and provider services specific guidance on the best way to provide complex services in a way that maximises efficiency and equity (service organisation is, however, outside the scope of this clinical guideline)
- informing people with diabetes of the optimal methods for helping them self-manage their diabetes.

Others, including the general public, may find the guideline of use in understanding the global and clinical approach to Type 1 diabetes. Separate short-form documents for the public and for healthcare professionals are available; they summarise the recommendations without giving full details of the supporting evidence.

The main principles behind the development of this guideline are that it should:

- consider all the most important issues in the management of people with Type 1 diabetes using published evidence wherever this is available
- be useful to and usable by all professionals
- take full account of the perspectives of the person with Type 1 diabetes and their carers
- indicate areas of uncertainty or controversy needing further research.

### 3.6.2 The developers

#### 3.6.2.1 The National Collaborating Centre for Chronic Conditions

The National Collaborating Centre for Chronic Conditions (NCC-CC) is housed by the Royal College of Physicians (RCP) but governed by a multiprofessional partners board, which includes patient groups and NHS management. It was set up in 2000 to undertake commissions from the National Institute for Clinical Excellence (NICE) to develop clinical guidelines for the NHS in England and Wales.

The technical team

The technical team consisted of:

- an information scientist

- a health services research fellow

- a clinical advisor

- a health economist

- the chair of the Guideline Development Group (GDG)

- a project manager

and was supported by administrative personnel. It took part in the GDG meetings, and also met separately each month.

### 3.6.2.2 The Guideline Development Group

The GDG met monthly for 10 months to review the evidence identified by the technical team, to comment on its completeness and to develop and refine clinical recommendations based on that evidence and other considerations.

Editorial responsibility for this guideline rests solely with the GDG.

Nominations for group members were invited from various stakeholder organisations, which were selected to ensure an appropriate mix of clinical professions and patient groups. These made up the Consensus Reference Group (CRG, see below) and from their members the GDG was selected to represent the groups involved in the day-to-day management of Type 1 diabetes. It included two representatives of people with Type 1 diabetes. Each nominee was expected to serve as an individual expert in their own right and not as a mandated representative, although they were encouraged to keep their parent organisation informed of the process. Group membership details can be found at the front of this document.

All group members made a formal 'declaration of interests' at the start of the guideline development and provided updates throughout. The NCC-CC and the GDG Chair monitored these.

- The Consensus Reference Group

The larger Consensus Reference Group (CRG) met twice during the process, once early in the development to ensure the aims and clinical questions (see Appendix A) were appropriate, and again at the end of the process to review the validity of the recommendations drafted by the GDG. The formal consensus technique used for this purpose was developed by the NCC-CC and is a modification of the RAND Nominal Group Technique.

- Involvement of people with Type 1 diabetes

The NCC-CC believes that the views of people with diabetes and their carers are an integral part of the development process of a guideline on Type 1 diabetes. Patient organisation representation (Diabetes UK) was secured on the Guideline Development Group and included a non-healthcare professional with Type 1 diabetes. People with diabetes were also present as part of the GDG and CRG and were involved at every stage of the guideline development process.

### 3.6.2.3 Searching for the evidence

There were four stages to evidence identification and retrieval:

5. The technical team set out a series of specific clinical questions (see Appendix A) that covered the issues identified in the project scope. The CRG met to discuss, refine and approve these questions as suitable for identifying appropriate evidence from within the published literature.

6. A total of 74 questions were identified. The technical team and project executive agreed that a full literature search and critical appraisal process could not be undertaken for all of these areas due to the time limitations of the guideline development process. The technical team identified questions where it was felt that a full literature search and critical appraisal were essential. Reasons for this included an awareness of new or unclear evidence, or a particular clinical need for evidence-based guidance in the area.

7. The information scientist, with the assistance of the clinical advisor, developed a search strategy for each question to identify the available evidence. Identified titles and abstracts were reviewed for relevance to the agreed clinical questions and full papers obtained as appropriate. These were assessed for inclusion according to predefined criteria as developed by the Scottish Intercollegiate Guidelines Network (SIGN).

8. The full papers were critically appraised by the health services research fellow and the pertinent data entered into evidence tables. These were then reviewed and analysed by the GDG as the basis upon which recommendations were formulated.

Due to the large amount of literature potentially relevant to Type 1 diabetes, the inclusion criteria aimed to limit the included studies to those of a higher level (see 2.6) conducted primarily in people with Type 1 diabetes. Where these were not available, lower-level studies, well-conducted studies outside Type 1 diabetes (in Type 2 diabetes or in the non-diabetic population), or more methodologically-limited studies in people with Type 1 diabetes, were included.

Limited details of the databases and constraints used in the searches can be found in Appendix A. No formal contact was made with the authors of identified studies. Additional contemporary articles identified by the GDG on an ad hoc basis, and further published evidence identified by national stakeholder organisations, were incorporated where appropriate after having been assessed for inclusion by the same criteria as evidence provided by the electronic searches.

Searches were rerun at the end of the guideline development process, thus including evidence published and included in the literature databases up to 27 May 2003. Studies recommended by stakeholders or GDG members that were published after this date were not considered for inclusion. The date should be the starting point for searching for new evidence for future updates to this guideline.

### 3.6.2.4 Synthesising the evidence

Abstracts of articles identified by the searches were screened for relevance, and hard copies were ordered of papers that appeared to provide useful evidence relevant to each clinical question. Using a validated appraisal tool, each paper was assessed for its methodological quality against pre-defined criteria. Papers that met the inclusion criteria were then assigned a level according to the evidence hierarchy given under 2.6. Owing to practical limitations, selection, critical appraisal and data extraction were undertaken by one reviewer only. Evidence was, however, considered carefully by the GDG for accuracy and completeness.

Each clinical question dictated the study design that was prioritised in the search strategy. In addition, certain topics within any one clinical question at times required different evidence types to be considered. Randomised control trials (RCTs) were the most appropriate study design for some clinical questions as they lend themselves particularly well to research into medicines. They were not, however, appropriate for all clinical questions, for example the evaluation of diagnostic tests.

RCTs are difficult to perform in areas such as rehabilitation and lifestyle, where interventions are often tailored to the needs of the individual. As a consequence, pharmaceutical inter- ventions tend to be placed higher in the evidence hierarchy than other, equally important, interventions. This should not be interpreted as a preference for a particular type of intervention or as a reflection of

the quality of the evidence, particularly for those clinical areas where non-RCT evidence is valid and most appropriate.

Where available, evidence from well-conducted systematic reviews was appraised and presented. Trials included within these reviews are listed in the evidence table but were not critically appraised. Studies identified in addition to those included in the systematic review were included in the appraisal process.

At times, evidence was not available from studies that included a Type 1 diabetes population. Where a Type 2 or mixed diabetes population, or non-diabetes population, is considered, it is indicated in the relevant evidence statement.

On occasion the group identified a clinical question that could not be appropriately answered through undertaking a rigorous literature review (because the evidence was scarce, or conflicting). These questions were addressed by group consensus, and the group considered a summary of the area in an expert-drafted discussion paper. In these instances there was no formal assessment of the studies cited.

Finally, national and international evidence-based guidelines were referred to during the development process. These were not formally appraised because of the consistency of process and of evidence base can be difficult to ascertain across such documents.

The evidence statements should be read with the following caveats in mind:

- all comparisons discussed are statistically significant unless otherwise stated
- where evidence is available from a good quality systematic review or meta-analysis, then individual studies are not reviewed and referenced. Any additional RCT evidence presented relates to studies published since the completion of systematic review(s) included or those considered relevant to this guideline, but which may not have been suitable for inclusion in the systematic review(s)
- unless explicitly stated, all studies relate to diabetes populations. The inclusion of studies of Type 1, Type 2 or mixed Type 1 and Type 2 diabetes populations varies between questions (see Appendix A)
- descriptions of studies of poor methodological quality in evidence statements include details on all relevant interventions in a specified question. However, no positive recommendations have been based solely on such studies
- evidence statements in this guideline derived from one systematic review may be graded with different hierarchy of evidence in different places, due to some topics within the review being based on a synthesis of the outcomes of well-conducted randomised controlled trials and others being based on a synthesis of non-randomised studies, prevalance studies and diagnotic studies, or on consensus
- when other guidelines are reviewed, some of their recommendations are presented here as evidence statements. These may not necessarily reflect the recommendations made in this guideline and are clearly labelled
- where individual trials are referred to in the evidence statements as small, medium, or large, this equates to the following number of participants (at baseline): small, less than 50; medium, from 50 to 200; large, greater than 200. Exact numbers for each trial can be found in the online evidence tables.

### 3.6.2.5 Health economic evidence

While evidence on cost-effectiveness was extracted from the clinical literature searches wherever it existed, this was rare. As such, a separate search was conducted to isolate the health economic evidence that attempted to identify the cost of, and the benefits accruing from, each strategy or intervention. An a priori study design criterion was not imposed, so information may come from sources other than RCTs and formal economic evaluations.

As the management of diabetes is complex, many of the areas covered by this guideline have little economic evidence; within clinical trials it is not always clear which of a range of inter- ventions and strategies actually improves health. The GDG therefore expected the useful cost- effectiveness evidence to fall within a limited range of areas. Where searching produced either no evidence or insufficient evidence for a substantive health economic evidence statement, this fact is indicated.

The health economist presented the economic evidence to the GDG alongside the clinical evidence. There is no standard measure to assess the quality of the economic evidence, and reported costs and benefits experienced in other healthcare systems may not apply in the UK. The GDG had to assess not only the results but also their applicability.

Health economic analysis can provide a framework for combining information from a variety of sources to form a standard comparison of cost and benefits. However, the task of producing these estimates is complex and labour intensive, and requires a level of clinical evidence that is not always readily available. Evidence on the costs and benefits of a broad range of interventions was presented to the GDG, but the issue of cultured human dermis for foot ulceration was identified as a particularly important area for further economic analysis. The choice was made on the grounds that:

- this treatment does not have good quality economic evidence attached
- it has a potentially large health benefit
- if made available, the treatment could have a large effect on NHS resources given the prevalence of diabetic foot ulcers
- there are uncertainties surrounding both the benefits and resources, and an absence of cost- utility studies.

### 3.6.2.6 Drafting recommendations

- Evidence for each topic was extracted into tables and summarised in evidence statements. The GDG reviewed the evidence tables and statements at each meeting and reached a group opinion. Recommendations were explicitly linked to the evidence supporting them and graded according to the level of the evidence upon which they were based, using the grading system in the table below.
- It should be noted that it is the level of evidence that determines the grade assigned to each recommendation. The grade does not necessarily reflect the clinical importance attached to the recommendation.

| Hierarchy of evidence | |
|---|---|
| Ia | Evidence from meta-analysis of randomised controlled trials. |
| Ib | Evidence from at least one randomised controlled trial. |
| IIa | Evidence from at least one controlled study without randomisation. |
| IIb | Evidence from at least one other type of quasi-experimental study. |
| III | Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies. |
| IV | Evidence from expert committee reports or opinions and/or clinical experience of respected authorities. |
| DS | Evidence from diagnostic studies. |
| NICE | Evidence from NICE guidelines or health technology appraisal programme. |

| Typical grading of recommendations | |
|---|---|
| A | Based on category I evidence. |
| B | Based on category II evidence or extrapolated from category I. |
| C | Based on category III evidence or extrapolated from category I or II. |
| D | Directly based on category IV evidence or extrapolated from category I, II or III. |
| DS | Evidence from diagnostic studies. |
| NICE | Evidence from NICE guidelines or health technology appraisal programme. |

#### 3.6.2.7 Agreeing recommendations

Once the evidence review had been completed and an early draft of the guideline produced, a one-day meeting of the CRG was held to finalise the recommendations. This included a pre- meeting vote on the recommendations and a further vote at the CRG meeting, where the group was asked to consider the draft guideline in two stages:

1. Are the evidence-based statements acceptable and is the evidence cited sufficient to justify the grading attached?

2. Are the recommendations derived from the evidence justified and are they sufficiently practical so that those at the clinical front line can implement them? Three types of recommendation were considered:

   a. A recommendation from the GDG based on strong evidence, usually non- controversial unless there was important evidence that had been missed or misinterpreted

   b. A recommendation that was based on good evidence but where it was necessary to extrapolate the findings to make it useful in the NHS. The extrapolation was approved by consensus

   c. Recommendations for which no evidence existed but which address important aspects of care, and for which a consensus on best practice could be reached.

This formal consensus method has been established within the NCC-CC, drawing on the knowledge set out in a health technology appraisal,7 the work of the Royal College of Nursing Institute1 and practical experience. It approximates to a modification of the RAND Nominal Group Technique and will be fully described in future publications.

#### 3.6.2.8 Writing the guideline

The draft version of the guideline was drawn up by the technical team in accordance with the decisions of the guideline groups. Prior to publication, it was circulated to stakeholders according to the formal NICE stakeholder consultation and validation phase.

Modifications were made to this document in response to comments received. Changes were approved by the Guideline Development Group, who retain the final editorial authority for the content.

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### 3.6.2.9 Structure of the guideline

The part of this document which contains recommendations (chapter 4 onwards) is divided into sections, each of which covers a set of related topics. For each topic the layout is the same:

- the rationale for including the topic is provided in one or two paragraphs that simply set the recommendations in the context of their clinical importance

- the evidence statements, both clinical and health economic, are then given, summarising the evidence (more detail can be found in the evidence tables, available on the web at www.rcplondon.ac.uk/pubs/books/dia/index.asp) Specific health economic evidence statements also follow the clinical evidence when available. The evidence statements and tables aim to contextualise and explain each recommendation

- the evidence statements are followed by a consideration that reflects the thinking of the GDG in making the recommendations. This is intended to explain how the evidence was used to formulate the recommendations

the recommendations follow. These are graded to indicate the level of the evidence behind the recommendation, rather than how valid the GDG believes them to be. In some sections of the guideline, additional text providing more detailed guidance is contained within the recommendations.

# 4 Guideline summary

## 4.1 Algorithms

### 4.1.1 Blood glucose monitoring : frequency, timing and targets

**HbA1c**

Measure HbA1c levels every 3 to 6 months in adults with type 1 diabetes.

Calibrate HbA1c results according to International Federation of Clinical Chemistry standardisation.

→ Consider measuring HbA1c levels more often if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA1c level has risen unexpectedly above a previously sustained target.

→ Use total glycated haemoglobin estimation, or assessment of glucose profiles, if haemoglobinopathy or haemoglobin turnover invalidate HbA1c measurement.

→ Agree an individualised HbA1c target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, co-morbidities, occupation and history of hypoglycaemia.

→ Support adults with type 1 diabetes to achieve an HbA1c target level of 48 mmol/mol (6.5%) or lower to minimise the risk of long-term vascular complications.

**SMBG and CGM**

Support people with type 1 diabetes to test at least four times per day, increasing up to ten times per day

- if target for glycaemic control measured by HbA1c is not achieved or
- if there is increased frequency of hypoglycaemic episodes or
- when there is a legal requirement to do so (for example, before driving in accordance with DVLA requirements) or
- during a period of illness or
- before and after sport or
- in planning and during pregnancy or while breastfeeding or
- where there is a need to know blood glucose levels more than four times a day for other reasons (e.g. impaired awareness of hypoglycaemia, high-risk activities)

→ Enable additional blood glucose testing where dictated by lifestyle issues (for example, driving for a long period of time, undertaking high risk activity/occupation, travel, impaired awareness of hypoglycaemia).

→ Adults with type 1 diabetes should aim for a fasting blood glucose level of 5 to 7 mmol/litre on waking, and pre-meal concentrations of 4 to 7 mmol/litre at other times of the day.

→ If testing post prandially, adults with type 1 diabetes should aim for a post-prandial blood glucose level of 5 to 9 mmol/litre.

→ Consider real-time CGM in adults with type 1 diabetes using principles of flexible insulin therapy with either multiple daily insulin injections or pump, if:

- problematic hypoglycaemia (>1 severe hypoglycaemia with no obviously preventable precipitating cause per year); complete loss of awareness of hypoglycaemia; frequent (>2 per week) asymptomatic hypoglycaemia causing problems with daily activities; extreme fear of hypoglycaemia in a patient, all persisting despite optimised use of insulin therapy and conventional blood glucose monitoring *and*
- the patient is willing to commit to usual use of real-time CGM (at least 70% of the time) and its calibration requirement.

## 4.1.2  Treatment

**Update 2015**

### Long-acting insulin

Offer multiple-daily-injection-basal-bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for adults with type 1 diabetes.

Offer twice-daily insulin detemir for basal insulin replacement to adults with type 1 diabetes.

Support patient in self-adjustment of doses using structured education and skills transfer

**If not tolerated** → Consider, as alternative basal insulin replacement:
- One-daily insulin glargine

**If patient does not want twice daily** → Consider, as alternative basal insulin replacement:
- One-daily insulin glargine

**If patient cannot engage with basal-bolus regimen** → Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes only if a multiple daily injection basal-bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is selected.

**If hypoglycaemia** → Consider a trial of a twice-daily analogue mixed insulin regimen if a person using a twice-daily human mixed insulin regimen has hypoglycaemia that affects their quality of life.

For adults with erratic and unpredictable blood glucose control (hyperglycaemia and hypoglycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered:
- resuspension of insulin and injection technique
- injection sites
- self-monitoring skills
- knowledge and self-management skills
- nature of lifestyle
- psychological and psychosocial difficulties
- possible organic causes such as gastroparesis

Consider insulin pump therapy if HbA1c > 70 mmol/mol (8.5%) or disabling hypoglycaemia

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**If hypoglycaemia** → Consider continuous glucose sensing

Consider referring adults with type 1 diabetes who have recurrent severe hypoglycaemia that has not responded to other treatments to a centre that assesses people for islet and/or pancreas transplantation.

**If renal transplant and immunosuppressive therapy** → Consider an islet or pancreas transplant for adults with type 1 diabetes with suboptimal diabetes control who have had a renal transplant and are currently on immunosuppressive therapy.

### Rapid-acting insulin

Offer rapid acting insulin analogues, injected before meals, for meal-time insulin replacement in adults with type 1 diabetes, rather than rapid-acting soluble human or animal insulins.

### Adjuncts

Consider adding metformin to insulin therapy if an adult with type 1 diabetes has a body mass index above 25 kg/m$^2$ to improve their blood glucose control while minimising their effective insulin dose.

Support patient in self-adjustment of doses using structured education and skills transfer

If an adult with type 1 diabetes has a strong preference for alternative rapid-acting meal-time insulin, respect those wishes and offer the preferred insulin.

**If patient cannot engage with basal-bolus regimen** → Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes only if a multiple daily injection basal-bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is selected.

**If hypoglycaemia** → Consider a trial of a twice-daily analogue mixed insulin regimen if a person using a twice-daily human mixed insulin regimen has hypoglycaemia that affects their quality of life.

For adults with erratic and unpredictable blood glucose control (hyperglycaemia and hypoglycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered:
- resuspension of insulin and injection technique
- injection sites
- self-monitoring skills
- knowledge and self-management skills
- nature of lifestyle
- psychological and psychosocial difficulties
- possible organic causes such as gastroparesis

### 4.1.3  Non-glycaemic management of CV risk factors

**Anti-platelets**

- Primary prevention → Do not offer
- Secondary prevention → Offer in line with NICE guidance for CV disease indication

**Lipid lowering**

- Primary prevention → Offer atorvastatin at a starting dose of 20 mg once a day if:
  - aged over 40 years or,
  - had diabetes for >10 years or,
  - established nephropathy or,
  - other CV risk factors

  Consider for all
- Secondary prevention → Offer in line with NICE guidance for CV disease indication

**BP lowering**

- No evidence nephropathy → Start treatment with a renin-angiotension system blocker if BP >135/85 mmHg; titrate treatment to achieve BP <135/85 mmHg
- Evidence nephropathy: ACR > 3 mg/mmol or CKD 3-5 → Start treatment with a renin-angiotension system blocker titrate treatment to achieve BP <130/80 mmHg

**Update 2015**

## 4.2 Key priorities for implementation

From the full set of recommendations, the GDG selected 8 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The guidelines manual.[512] The reason that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

- Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose adjustment for normal eating) programme. Offer this programme 6 – 12 months after diagnosis, at a time that is clinically appropriate and suitable for the person.

- Support adults with type 1 diabetes to achieve and maintain a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications.

- Agree an individualised HbA1c target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia.

- Support adults with type 1 diabetes to test at least 4 times a day, and up to 10 times a day if any of the following apply:
  o the target for blood glucose control, measured by HbA1c level (see recommendation 39) is not achieved
  o the frequency of hypoglycaemic episodes increases
  o there is a legal requirement to do so (such as before driving, in line with DVLA requirements)[b]
  o during periods of illness
  o before and after sport
  o when planning pregnancy, during pregnancy and while breastfeeding (see the NICE guideline on diabetes in pregnancy[c])
  o if there is a need to know blood glucose levels more than 4 times a day for other reasons (for example, impaired awareness of hypoglycaemia, high-risk activities).

- Advise adults with type 1 diabetes to aim for:
  o a fasting plasma glucose level of 5- 7 mmol/litre on waking and
  o a plasma glucose level of 4-7 mmol/litre before meals at other times of the day.

- Offer multiple daily injection basal-bolus regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes.

- Assess awareness of hypoglycaemia in adults with type 1 diabetes at each annual review.

- Enable adults with type 1 diabetes who are hospital inpatients to self-administer subcutaneous insulin if they are willing and able and it is safe to do so.

**Update 2015**

## 4.3 Full list of recommendations

1.	Diagnose type 1 diabetes on clinical grounds in adults presenting with hyperglycaemia, bearing in mind that people with type 1 diabetes typically (but not always) have one or more of:

- ketosis
- rapid weight loss

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b For DVLA guidance on type 1 diabetes, see the DVLA guidance for people with diabetes.
c This guideline is currently being updated, publication expected February 2015.

- age of onset below 50 years

- BMI below 25 kg/m$^2$

- personal and/or family history of autoimmune disease. [new 2015]

2.  Do not discount a diagnosis of type 1 diabetes if a person presents with a BMI of 25 kg/m$^2$ or above or is aged 50 years or above. [new 2015]

3.  Do not measure C-peptide and/or diabetes-specific autoantibody titres routinely to confirm type 1 diabetes in adults. [new 2015]

4.  Consider further specialist investigation involving measurement of C-peptide and/or diabetes-specific autoantibody titres if:

- type 1 diabetes is suspected but the clinical presentation includes some atypical features (for example, age 50 years or above, BMI of 25 kg/m$^2$ or above, slow evolution of hyperglycaemia or long prodrome) or

- type 1 diabetes has been diagnosed and treatment started but there is a clinical suspicion that the person may have a monogenic form of diabetes, and C-peptide and/or autoantibody testing may guide the use of genetic testing or

- classification is uncertain, and confirming type 1 diabetes would have implications for availability of therapy (for example, continuous subcutaneous insulin infusion [CSII or 'insulin pump'] therapy. [new 2015]

5.  When measuring C-peptide and/or diabetes-specific autoantibody titres, take into account that:

- autoantibody tests have their lowest false negative rate at the time of diagnosis, and that the false negative rate rises thereafter

- C-peptide has better discriminative value the longer the test is done after diagnosis

- with autoantibody testing, carrying out tests for 2 different diabetes-specific autoantibodies reduces the false negative rate. [new 2015]

6.  Advice to adults with type 1 diabetes should be provided by a range of professionals with skills in diabetes care working together in a coordinated approach. A common environment (diabetes centre) is an important resource in allowing a diabetes multidisciplinary team to work and communicate efficiently while providing consistent advice. [2004]

7.  Provide adults with type 1 diabetes with:

- open-access services on a walk-in and telephone-request basis during working hours

- a helpline staffed by people with specific diabetes expertise on a 24-hour basis

- contact information for these services. [2004]

8.  Set up an individual care plan jointly agreed with the adult with type 1 diabetes, review it annually and modify it taking into account changes in the person's wishes, circumstances and medical findings, and record the details. The plan should include aspects of:

- diabetes education, including nutritional advice (see 'Structured education programmes', Section 7.2, and 'Dietary management', Section 7.3)

- insulin therapy, including dose adjustment (see 'Insulin regimens', Section 9.2, and 'Insulin delivery', Section 9.3)

- self-monitoring (see 'Self-monitoring of blood glucose', Section 9).

- avoiding hypoglycaemia and maintaining awareness of hypoglycaemia

- for women of childbearing potential, family planning contraception and pregnancy planning

- arterial risk factor surveillance and management (see 'Arterial risk control', Chapter 14)

- complications surveillance and management (see 'Management of complications', Chapter 16)

- means and frequency of communication with the diabetes professional team

- follow-up consultations, including frequency of review of HbA1c levels and experience of hypoglycaemia, and next annual review. [2004, amended 2015]

9. Use population, practice-based and clinic diabetes registers (as specified by the National service framework for diabetes) to assist programmed recall for annual review and assessment of complications and vascular risk.[2004]

10. The multidisciplinary team approach should be available to inpatients with type 1 diabetes, regardless of the reason for admission (see 'Hospital admission and intercurrent disease', Section 15.1.6). [2004]

11. At the time of diagnosis and periodically thereafter, provide adults with type 1 diabetes with up-to-date information about diabetes support groups (local and national), how to contact them and the benefits of membership. [2004]

12. Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis, at a time that is clinically appropriate and suitable for the person. [new 2015]

13. Explain to adults with type 1 diabetes that structured education is an integral part of diabetes care. [new 2015]

14. Provide an alternative of equal standard for a person unable or unwilling to participate in group education. [new 2015]

15. Ensure that any structured education programme for adults with type 1 diabetes includes the following components[d]:

- It is evidence-based, and suits the needs of the person.

- It has specific aims and learning objectives, and supports the person and their family members and carers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes.

- It has a structured curriculum that is theory-driven, evidence-based and resource-effective, has supporting materials, and is written down.

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d   Components of a structured education programme adapted from the NICE quality standard on diabetes in adults.

- It is delivered by trained educators who have an understanding of educational theory appropriate to the age and needs of the person, and who are trained and competent to deliver the principles and content of the programme.

- It is quality assured, and reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency.

- The outcomes are audited regularly. [new 2015]

16. Provide information about type 1 diabetes and its management to adults with type 1 diabetes at all opportunities from diagnosis onwards. Follow the principles in the NICE guideline on patient experience in adult NHS services. [new 2015]

17. Consider the Blood Glucose Awareness Training (BGAT) programme for adults with type 1 diabetes who are having recurrent episodes of hypoglycaemia (see also Section 11). [new 2015]

18. Carry out more formal review of self-care and needs annually in all adults with type 1 diabetes. Vary the agenda addressed each year according to the priorities agreed between the healthcare professional and the adult with type 1 diabetes. [2004, amended 2014]

19. Offer carbohydrate-counting training to adults with type 1 diabetes as part of structured education programmes for self-management (see Structured Education, section 7.2).[new 2015]

20. Consider carbohydrate-counting courses for adults with type 1 diabetes who are waiting for a more detailed structured education programme or are unable take part in a stand-alone structured education programme.[new 2015]

21. Do not advise adults with type 1 diabetes to follow a low glycaemic index diet for blood glucose control.[new 2015]

22. Provide nutritional information sensitive to personal needs and culture from the time of diagnosis of type 1 diabetes. [2004]

23. Provide nutritional information individually and as part of a diabetes education programme (see Section 8.2). Include advice from professionals with specific and approved training and continuing accredited education in delivering nutritional advice to people with health conditions. Offer opportunities to receive nutritional advice at intervals agreed between adults with type 1 diabetes and their advising professionals. [2004]

24. Discuss the hyperglycaemic effects of different foods an adult with type 1 diabetes wishes to eat in the context of the insulin preparations chosen to match those food choices. [2004]

25. Make programmes available to adults with type 1 diabetes to enable them to make:

- optimal choices about the variety of foods they wish to consume

- insulin dose changes appropriate to reduce glucose excursions when taking different quantities of those foods. [2004, amended 2015]

26. Agree the choice of content, timing and amount of snacks between meals or at bedtime available to the adult with type 1 diabetes, based on informed discussion about the extent and duration of the effects of eating different food types and the insulin preparations available to match them. Modify

those choices based on discussion of the results of self-monitoring tests. [2004]

27.  Make information available on:

- effects of different alcohol-containing drinks on blood glucose excursions and calorie intake

- use of high-calorie and high-sugar 'treats'. [2004, amended 2015]

28.  Make information available about the benefits of healthy eating in reducing arterial risk as part of dietary education in the period after diagnosis, and according to need and interest at intervals thereafter. Include information about fruit and vegetables, types and amounts of fat, and ways of making the appropriate nutritional changes. [2004, amended 2015]

29.  Modify nutritional recommendations to adults with type 1 diabetes to take account of associated features of diabetes, including:

- excess weight and obesity

- underweight

- eating disorders

- hypertension

- renal failure. [2004]

30.  Be aware of appropriate nutritional advice on common topics of concern and interest to adults living with type 1 diabetes, and be prepared to seek advice from colleagues with more specialised knowledge. Suggested common topics include:

- body weight, energy balance and obesity management

- cultural and religious diets, feasts and fasts

- foods sold as 'diabetic'

- sweeteners

- dietary fibre intake

- protein intake

- vitamin and mineral supplements

- alcohol

- matching carbohydrate, insulin and physical activity

- salt intake in hypertension

- comorbidities including nephropathy and renal failure, coeliac disease, cystic fibrosis, or eating disorders

- use of peer support groups. [2004, amended 2015]

31.  Offer dietary advice to adults with type 1 diabetes about issues other than blood glucose control, such as weight control and cardiovascular risk management, as indicated clinically. [new 2015]

32.  Advise adults with type 1 diabetes that physical activity can reduce their enhanced arterial risk in the medium and longer term. [2004]

33.  Give adults with type 1 diabetes who choose to integrate increased physical activity into a more healthy lifestyle information about:

- appropriate intensity and frequency of physical activity

- role of self-monitoring of changed insulin and/or nutritional needs

- effect of activity on blood glucose levels (likely fall) when insulin levels are adequate

- effect of exercise on blood glucose levels when hyperglycaemic and hypoinsulinaemic (risk of worsening of hyperglycaemia and ketonaemia)

- appropriate adjustments of insulin dosage and/or nutritional intake for exercise and post-exercise periods, and the next 24 hours

- interactions of exercise and alcohol

- further contacts and sources of information. [2004]

34. Regard each adult with type 1 diabetes as an individual, rather than as a member of any cultural, economic or health-affected group (see also recommendations 22, 30 and 65 about the cultural preferences of individual adults with type 1 diabetes). [2004, amended 2015]

35. Measure HbA1c levels every 3-6 months in adults with type 1 diabetes. [new 2015]

36. Consider measuring HbA1c levels more often if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA1c level has risen unexpectedly above a previously sustained target. [new 2015]

37. Calibrate HbA1c results according to International Federation of Clinical Chemistry (IFCC) standardisation. [new 2015]

38. Inform adults with type 1 diabetes of their HbA1c results after each measurement and ensure that their most recent result is available at the time of consultation. Follow the principles in the NICE guideline on patient experience in adult NHS services about communication. [new 2015]

39. Support adults with type 1 diabetes to achieve and maintain a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications. [new 2015]

40. Agree an individualised HbA1c target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia. [new 2015]

41. Ensure that achieving, or attempting to achieve, an HbA1c target is not accompanied by problematic hypoglycaemia. [new 2015]

42. Diabetes services should document the proportion of adults with type 1 diabetes in a service who achieve an HbA1c level of 53 mmol/mol (7%) or lower. [new 2015]

43. If HbA1c monitoring is invalid (because of disturbed erythrocyte turnover or abnormal haemoglobin type), estimate trends in blood glucose control using one of the following:

- fructosamine estimation

- quality-controlled plasma glucose profiles

- total glycated haemoglobin estimation (if abnormal haemoglobins). [2004, amended 2015]

44. Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least 4 times a day, including before each meal and before bed. [new 2015]

45. Support adults with type 1 diabetes to test at least 4 times a day, and up to 10 times a day if any of the following apply:

    - the target for blood glucose control, measured by HbA1c level (see recommendation 39), is not achieved

    - the frequency of hypoglycaemic episodes increases

    - there is a legal requirement to do so (such as before driving, in line with DVLA requirements)[e]

    - during periods of illness

    - before and after sport

    - when planning pregnancy, during pregnancy and while breastfeeding (see the NICE guideline on diabetes in pregnancy[f])

    - if there is a need to know blood glucose levels more than 4 times a day for other reasons (for example, impaired awareness of hypoglycaemia, high-risk activities). [new 2015]

46. Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time[e], undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycaemia. [new 2015]

47. Advise adults with type 1 diabetes to aim for:

    - a fasting plasma glucose level of 5-7 mmol/litre on waking and

    - a plasma glucose level of 4-7 mmol/litre before meals at other times of the day. [new 2015]

48. Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5-9 mmol/litre. [new 2015]

49. Support adults with type 1 diabetes to make the best use of data from self-monitoring of blood glucose through structured education (see recommendations 12 and 14). [new 2015]

50. Teach self-monitoring skills at the time of diagnosis and initiation of insulin therapy. [2004, amended 2015]

51. Carry out a structured assessment annually of self-monitoring skills, the quality and use made of the results obtained and the equipment used. Review self-monitoring skills as part of annual review, or more frequently according to need, and reinforce them where appropriate. [2004, amended 2015]

52. Teach self-monitoring of blood glucose levels to adults with type 1 diabetes as part of an integrated package that includes appropriate insulin regimens and education to help choice and achievement of optimal diabetes control. [2004, amended 2015]

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e   For further details about driving, see the DVLA guidance for people with type 1 diabetes.

f   This guideline is currently being updated (publication expected February 2015).

53. Carry out a structured assessment of self-monitoring skills, the quality and use made of the results and the equipment used. Review self-monitoring skills as part of annual review, or more frequently according to need, and reinforce them where appropriate. [2004, amended 2015]

54. Monitoring blood glucose using sites other than the fingertips cannot be recommended as a routine alternative to conventional self-monitoring of blood glucose. [2004, amended 2015]

55. Educate adults with type 1 diabetes about how to measure their blood glucose level, interpret the results and know what action to take. [new 2015]

56. Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. [new 2015]

57. Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following that persist despite optimised use of insulin therapy and conventional blood glucose monitoring:

   • more than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause

   • complete loss of awareness of hypoglycaemia

   • frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities

   • extreme fear of hypoglycaemia. [new 2015]

58. For people who are having continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. [new 2015]

59. Continuous glucose monitoring should be provided by a centre with expertise in its use, as part of strategies to optimise a person's HbA1c levels and reduce the frequency of hypoglycaemic episodes. [new 2015]

60. Offer multiple daily injection basal-bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. [new 2015]

61. Do not offer non-basal-bolus insulin regimens for treating adults newly diagnosed with type 1 diabetes. [new 2015]

62. Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. [new 2015]

63. Consider, as an alternative basal insulin therapy for adults with type 1 diabetes:

   • an existing insulin regimen being used by the person that is achieving their agreed targets

   • once-daily insulin glargine if insulin detemir is not tolerated or if twice-daily basal insulin injection is not acceptable to the person. [new 2015]

64. For guidance on the use of continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes, see Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (NICE technology appraisal guidance 151). [new 2015]

65.     Discuss and respect cultural preferences in agreeing the insulin regimen for an adult with type 1 diabetes. [2004]

66.     Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. [new 2015]

67.     Do not advise routine use of rapid-acting insulin analogues after meals. [new 2015]

68.     If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin.[new 2015]

69.     Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal-bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. [new 2015]

70.     Consider a trial of a twice-daily analogue mixed insulin regimen if a person using a twice-daily human mixed insulin regimen has hypoglycaemia that affects their quality of life. [new 2015]

71.     For adults with erratic and unpredictable blood glucose control (hyperglycaemia and hypoglycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered:

        • injection technique

        • injection sites

        • self-monitoring skills

        • knowledge and self-management skills

        • nature of lifestyle

        • psychological and psychosocial difficulties

        • possible organic causes such as gastroparesis. [2004, amended 2015]

72.     Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. [2004]

74.     Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m$^2$ or above wants to improve their blood glucose control while minimising their effective insulin dose. [new 2015]

75.     Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. [new 2015]

76.     If possible, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. [new 2015]

77.     Advise adults with type 1 diabetes to rotate insulin injection sites and to avoid repeated injections at the same point within sites. [new 2015]

78.     Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. [2004]

79.  Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. [2004]

80.  Provide adults with type 1 diabetes with suitable containers for collecting used needles. Arrangements should be available for the suitable disposal of these containers. [2004]

81.  Check injection site condition at least annually and if new problems with blood glucose control occur. [2004, amended 2015]

82.  Consider referring adults with type 1 diabetes who have recurrent severe hypoglycaemia that has not responded to other treatments (see Section 11) to a centre that assesses people for islet and/or pancreas transplantation. [new 2015]

83.  Consider islet or pancreas transplantation for adults with type 1 diabetes with suboptimal diabetes control who have had a renal transplant and are currently on immunosuppressive therapy. [new 2015]

84.  Assess awareness of hypoglycaemia in adults with type 1 diabetes at each annual review. [new 2015]

85.  Use the Gold score or Clarke score to quantify awareness of hypoglycaemia in adults with type 1 diabetes, checking that the questionnaire items have been answered correctly. [new 2015]

86.  Explain to adults with type 1 diabetes that impaired awareness of the symptoms of plasma glucose levels below 3 mmol/litre is associated with a significantly increased risk of severe hypoglycaemia. [new 2015]

87.  Ensure that adults with type 1 diabetes with impaired awareness of hypoglycaemia have had structured education in flexible insulin therapy using basal-bolus regimens and are following its principles correctly. [new 2015]

88.  Offer additional education focusing on avoiding and treating hypoglycaemia to adults with type 1 diabetes who continue to have impaired awareness of hypoglycaemia after structured education in flexible insulin therapy. [new 2015]

89.  Avoid relaxing individualised blood glucose targets as a treatment for adults with type 1 diabetes with impaired awareness of hypoglycaemia. [new 2015]

90.  Review insulin regimens and doses and prioritise strategies to avoid hypoglycaemia in adults with type 1 diabetes with impaired awareness of hypoglycaemia, including:

   • reinforcing the principles of structured education

   • offering continuous subcutaneous insulin infusion (CSII or insulin pump) therapy

   • offering real-time continuous glucose monitoring. [new 2015]

91.  If impaired awareness of hypoglycaemia is associated with recurrent severe hypoglycaemia despite these interventions, consider referring the person to a specialist centre.[new 2015]

92.  Explain to adults with type 1 diabetes that a fast-acting form of glucose is needed for the management of hypoglycaemic symptoms or signs in people who are able to swallow. [2004, amended 2015]

93.  Adults with type 1 diabetes with a decreased level of consciousness as a result of hypoglycaemia and so are unable to take oral treatment safely should be:

- given intramuscular glucagon by a family member or friend who has been shown how to use it (intravenous glucose may be used by healthcare professionals skilled in obtaining intravenous access)

- monitored for response at 10 minutes, and then given intravenous glucose if their level of consciousness is not improving significantly

- then given oral carbohydrate when it is safe to administer it, and placed under continued observation by a third party who has been warned of the risk of relapse. [2004, amended 2015]

94.  Explain to adults with type 1 diabetes that some hypoglycaemic episodes are an inevitable consequence of insulin therapy in most people using any insulin regimen, and that it is advisable that they should use a regimen that avoids or reduces the frequency of hypoglycaemic episodes while maintaining as optimal a level of blood glucose control as is feasible. Make advice available to all adults with type 1 diabetes to assist in obtaining the best such balance from any insulin regimen (see 'Insulin regimens' Section 10.2 and 'Insulin delivery' Section 10.3). [2004]

95.  If hypoglycaemia becomes unusually problematic or of increased frequency, review the following possible contributory causes:

- inappropriate insulin regimens (incorrect dose distributions and insulin types)

- meal and activity patterns, including alcohol

- injection technique and skills, including insulin resuspension

- injection site problems

- possible organic causes including gastroparesis

- changes in insulin sensitivity (including drugs affecting the renin-angiotensin system and renal failure)

- psychological problems

- previous physical activity

- lack of appropriate knowledge and skills for self-management. [2004]

96.  Manage nocturnal hypoglycaemia (symptomatic or detected on monitoring) by:

- reviewing knowledge and self-management skills

- reviewing current insulin regimen, evening eating habits and previous physical activity

- choosing an insulin type and regimen that is less likely to induce low glucose levels at night. [2004, amended 2015]

97.  Explain to adults with type 1 diabetes that late postprandial hypoglycaemia may be managed by eating snacks between meals or by using rapid-acting insulin analogues before meals. [2004]

98.  If early cognitive decline occurs in adults on long-term insulin therapy, supplement normal investigations by the consideration or investigation of

possible brain damage resulting from overt or covert hypoglycaemia, and the need to ameliorate this. [2004]

99. Consider ketone monitoring (blood or urine) as part of 'sick-day rules' for adults with type 1 diabetes, to facilitate self-management of an episode of hyperglycaemia. [new 2015]

100. In adults with type 1 diabetes presenting to emergency services, consider capillary blood ketone testing if :

- DKA is suspected or

- the person has uncontrolled diabetes with a period of illness, and urine ketone testing is positive. [new 2015]

101. Consider capillary blood ketone testing for inpatient management of DKA in adults that is incorporated into a formal protocol. [new 2015]

102. Professionals managing DKA in adults should be adequately trained, including regular updating, and be familiar with all aspects of its management which are associated with mortality and morbidity. These topics should include:

- fluid balance

- acidosis

- cerebral oedema

- electrolyte imbalance

- disturbed interpretation of familiar diagnostic tests (white cell count, body temperature, ECG)

- respiratory distress syndrome

- cardiac abnormalities

- precipitating causes

- infection management, including opportunistic infections

- gastroparesis

- use of high dependency and intensive care units

- recommendations 103 to 110 in this guideline.

Management of DKA in adults should be in line with local clinical governance. [2004]

103. For primary fluid replacement in adults with DKA, use isotonic saline, not given too rapidly except in cases of circulatory collapse. [2004]

104. Do not generally use bicarbonate in the management of DKA in adults. [2004, amended 2015]

105. Give intravenous insulin by infusion to adults with DKA. [2004]

106. In the management of DKA in adults, once the plasma glucose concentration has fallen to 10–15 mmol/litre, give glucose-containing fluids (not more than 2 litres in 24 hours) in order to allow continued infusion of insulin at a sufficient rate to clear ketones (for example, 6 units/hour monitored for effect). [2004, amended 2015]

107. Begin potassium replacement early in DKA in adults, with frequent monitoring for the development of hypokalaemia. [2004]

108. Do not generally use phosphate replacement in the management of DKA in adults. [2004, amended 2015]

109.	In adults with DKA whose conscious level is impaired, consideration should be given to inserting a nasogastric tube, monitoring urine production using a urinary catheter and giving heparin. [2004]

110.	To reduce the risk of catastrophic outcomes in adults with DKA, ensure that monitoring is continuous and that review covers all aspects of clinical management at frequent intervals. [2004, amended 2015]

111.	In adults with type 1 diabetes who have a low BMI or unexplained weight loss, assess markers of coeliac disease. [2004]

112.	Be alert to the possibility of the development of other autoimmune disease in adults with type 1 diabetes (including Addison's disease and pernicious anaemia). For advice on monitoring for thyroid disease, see recommendation 150. [2004, amended 2015]

113.	Do not offer aspirin for the primary prevention of cardiovascular disease to adults with type 1 diabetes.[new 2015]

114.	Assess arterial risk factors annually, including:

- albuminuria

- smoking

- blood glucose control

- blood pressure

- full lipid profile (including HDL and LDL cholesterol and triglycerides)

- age

- family history of arterial disease

- abdominal adiposity. [2004, amended 2015]

115.	For guidance on tools for assessing risk of cardiovascular disease in adults with type 1 diabetes, see recommendation 1.1.9 in the NICE guideline on lipid modification. [new 2015]

116.	For guidance on the primary prevention of cardiovascular disease in adults with type 1 diabetes, see recommendations 1.3.23 to 1.3.25 in the NICE guideline on lipid modification. [new 2015]

117.	Give adults with type 1 diabetes who smoke advice on smoking cessation and use of smoking cessation services, including NICE guidance-recommended therapies. Reinforce these messages annually for people who currently do not plan to stop smoking, and at all clinical contacts if there is a prospect of the person stopping. [2004]

118.	Advise young adult non-smokers never to start smoking. [2004]

119.	Provide intensive management for adults who have had myocardial infarction or stroke, according to relevant non-diabetes guidelines. In the presence of angina or other ischaemic heart disease, beta-adrenergic blockers should be considered. (For use of insulin in these circumstances, see Section 15). For guidance on secondary prevention of myocardial infarction, see the NICE guideline on MI – secondary prevention. [2004, amended 2015]

120.	Intervention levels for recommending blood pressure management should be 135/85 mmHg unless the adult with type 1 diabetes has albuminuria or 2 or more features of the metabolic syndrome, in which case it should be 130/80 mmHg. See also recommendations 164-166 in Chapter 16.6. [2004]

121. To allow informed choice by the person with hypertension, discuss the following with them:

- reasons for choice of intervention level

- substantial potential gains from small improvements in blood pressure control

- possible negative consequences of therapy.

    See also recommendations 164-165 in Section 16.5.36 [2004, amended 2015]

122. Start a trial of a renin-angiotensin system blocking drug as first-line therapy for hypertension in adults with type 1 diabetes. [2004, amended 2015]

123. Provide information to adults with type 1 diabetes on the potential for lifestyle changes to improve blood pressure control and associated outcomes, and offer assistance in achieving their aims in this area. [2004]

124. Do not allow concerns over potential side effects to inhibit advising and offering the necessary use of any class of drugs, unless the side effects become symptomatic or otherwise clinically significant. In particular:

- do not avoid selective beta-adrenergic blockers where indicated in adults on insulin

- low-dose thiazides may be combined with beta-blockers

- when calcium channel antagonists are prescribed, use only long-acting preparations

- use direct questioning to detect the potential side effects of erectile dysfunction, lethargy and orthostatic hypotension with different drug classes. [2004, amended 2015]

125. For guidance on blood pressure management in adults with type 1 diabetes and evidence of renal involvement, see recommendations 1.6.2-1.6.4 in the NICE guideline on Chronic kidney disease [new 2015]

126. Aim for a target plasma glucose level of 5-8 mmol/litre for adults with type 1 diabetes during surgery or acute illness. [new 2015]

127. Establish a local protocol for controlling blood glucose levels in adults with type 1 diabetes during surgery or acute illness to achieve the target level. [new 2015]

128. Use intravenous in preference to subcutaneous insulin regimens for adults with type 1 diabetes:

- if the person is unable to eat or is predicted to miss more than 1 meal or

- if an acute situation is expected to result in unpredictable blood glucose levels - for example, major surgery, high-dose steroid treatment, inotrope treatment or sepsis or

- if insulin absorption is expected to be unpredictable, for example because of circulatory compromise. [new 2015]

129. Consider continuing the person's existing basal insulin regimen (including basal rate if they are using continuous subcutaneous insulin infusion [CSII or insulin pump] therapy) together with protocol-driven insulin delivery for controlling blood glucose levels in adults with type 1 diabetes during surgery or acute illness. [new 2015]

130. Use subcutaneous insulin regimens (including rapid-acting insulin before meals) if an adult with type 1 diabetes and acute illness is eating. [new 2015]

131. Enable adults with type 1 diabetes who are hospital inpatients to self-administer subcutaneous insulin if they are willing and able and it is safe to do so. [new 2015]

132. From the time of admission, the adult with type 1 diabetes and the team caring for him or her should receive, on a continuing basis, advice from a trained multidisciplinary team with expertise in diabetes. [2004]

133. Throughout the course of an inpatient admission, respect the personal expertise of adults with type 1 diabetes (in managing their own diabetes) and routinely integrate this into ward-based blood glucose monitoring and insulin delivery. [2004, amended 2015]

134. Throughout the course of an inpatient admission, the personal knowledge and needs of adults with type 1 diabetes regarding their dietary requirements should be a major determinant of the food choices offered to them, except when illness or medical or surgical intervention significantly disturbs those requirements. [2004]

135. Members of care teams caring for adults with type 1 diabetes in institutions, such as nursing homes, residential homes and prisons, should follow the recommendations in this section. [2004]

136. Provide optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose, to all adults with type 1 diabetes with threatened or actual stroke. Critical care and emergency departments should have a protocol for such management. [2004, amended 2015]

137. Consider domperidone[g] (in preference to metoclopramide) for treating gastroparesis[h] in adults with type 1 diabetes. [new 2015]

138. Consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes who have gastroparesis. [new 2015]

139. Advise a small-particle-size diet (mashed or pureed food) for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis. [new 2015]

140. Refer adults with type 1 diabetes who have gastroparesis for specialist advice if the interventions in recommendations 138 and 139 are not beneficial or not appropriate. [new 2015]

141. Offer men with type 1 diabetes the opportunity to discuss erectile dysfunction as part of regular review. [2015]

142. Offer a phosphodiesterase-5 inhibitor to men with type 1 diabetes with isolated erectile dysfunction unless contraindicated. Choose the phosphodiesterase-5 inhibitor with the lowest acquisition cost. [new 2015]

143. Consider referring men to a service offering further assessment and other medical, surgical or psychological management of erectile dysfunction if

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g   Although this use is common in UK clinical practice, at the time of consultation (December 2014), domperidone did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

h   Diagnosis of gastroparesis needing specific therapy can only be made in the absence of hyperglycaemia at the time of testing, because hyperglycaemia induces a physiological delay in gastric emptying.

phosphodiesterase-5 inhibitor treatment is unsuccessful or contraindicated. [2015]

144. Reassure adults with type 1 diabetes that acute painful neuropathy resulting from rapid improvement of blood glucose control is a self-limiting condition that improves symptomatically over time. [new 2015]

145. Do not relax diabetes control to address acute painful neuropathy resulting from rapid improvement of blood glucose control in adults with type 1 diabetes. [new 2015]

146. If simple analgesia does not provide sufficient pain relief for adults with type 1 diabetes who have acute painful neuropathy resulting from rapid improvement of blood glucose control, offer treatment as described in the NICE guideline on neuropathic pain – pharmacological management. Simple analgesia may be continued until the effects of additional treatments have been established. [new 2015]

147. When offering medicines for managing acute painful neuropathy resulting from rapid improvement of blood glucose control to adults with type 1 diabetes, be aware of the risk of dependency associated with opioids. [new 2015]

148. Explain to the person that the specific treatments for acute painful neuropathy resulting from rapid improvement of blood glucose control:

- have the aim of making the symptoms tolerable until the condition resolves

- may not relieve pain immediately and may need to be taken regularly for several weeks to be effective. [new 2015]

149. Use of simple analgesics (paracetamol, aspirin) and local measures (bed cradles) are recommended as a first step, but if trials of these measures are ineffective, discontinue them and try other measures. [2004]

150. Measure blood thyroid-stimulating hormone (TSH) levels in adults with type 1 diabetes at annual review. [new 2015]

151. Start eye screening for adults newly diagnosed with type 1 diabetes from diagnosis. [2004]

152. Depending on the findings, follow structured eye screening by:

- routine review in 1 year or

- earlier review or

- referral to an ophthalmologist [2004]

153. Explain the reasons and success of eye screening systems to adults with type 1 diabetes, so that attendance is not reduced by lack of knowledge or fear of outcome. [2004]

154. Implement digital retinal photography for eye screening programmes for adults with type 1 diabetes. [2004]

155. Use mydriasis with tropicamide when photographing the retina, after prior agreement with the adult with type 1 diabetes after discussion of the advantages and disadvantages, including appropriate precautions for driving. [2004]

156. Make visual acuity testing a routine part of eye screening programmes. [2004, amended 2015]

157.    Ensure that emergency review by an ophthalmologist occurs for:

- sudden loss of vision

- rubeosis iridis

- pre-retinal or vitreous haemorrhage

- retinal detachment [2004, amended 2015]

158.    Ensure that rapid review by an ophthalmologist occurs for new vessel formation. [2004, amended 2015]

159.    Refer to an ophthalmologist for:

- referable maculopathy:

i.    exudate or retinal thickening within 1 disc diameter of the centre of the fovea

ii.    circinate or group of exudates within the macula (the macula is defined here as a circle centred on the fovea, of a diameter the distance between the temporal border of the optic disc and the fovea)

iii.    any microaneurysm or haemorrhage within 1 disc diameter of the centre of the fovea, only if associated with a best visual acuity of 6/12 or worse

- referable pre-proliferative retinopathy:

i.    any venous beading

ii.    any venous reduplication

iii.    any intraretinal microvascular abnormalities (IRMA)

iv.    multiple deep, round or blot haemorrhages

(if cotton wool spots are present, look carefully for the above features, but cotton wool spots themselves do not define pre-proliferative retinopathy)

- any large sudden unexplained drop in visual acuity. [2004, amended 2015]

160.    For guidance on managing kidney disease in adults with type 1 diabetes, see the NICE guideline on chronic kidney disease. [new 2015]

161.    Ask all adults with type 1 diabetes with or without detected nephropathy to bring in the first urine sample of the day ('early morning urine') once a year. Send this for estimation of albumin:creatinine ratio. Estimation of urine albumin concentration alone is a poor alternative. Serum creatinine should be measured at the same time. [2004]

162.    Suspect other renal disease:

- in the absence of progressive retinopathy

- if blood pressure is particularly high

- if proteinuria develops suddenly

- if significant haematuria is present

- in the presence of systemic ill health. [2004]

163.    Discuss the significance of a finding of albuminuria with the person concerned. [2004, amended 2015]

164. Start angiotensin-converting enzyme (ACE) inhibitors and, with the usual precautions, titrate to full dose in all adults with confirmed nephropathy (including those with low-level albuminuria [microalbuminuria] alone) and type 1 diabetes. [2004]

165. If ACE inhibitors are not tolerated, substitute angiotensin 2 receptor antagonists. Combination therapy is not recommended. [2004, amended 2015]

166. Maintain blood pressure below 130/80 mmHg by addition of other anti-hypertensive drugs if necessary. [2004]

167. Advise adults with type 1 diabetes and nephropathy about the advantages of not following a high-protein diet. [2004]

168. Referral criteria for tertiary care should be agreed between local diabetes specialists and nephrologists. [2004]

169. For guidance on managing foot problems in adults with type 1 diabetes, see the NICE guideline on diabetic foot problems. [new 2015]

170. In adults with type 1 diabetes who have unexplained diarrhoea, particularly at night, the possibility of autonomic neuropathy affecting the gut should be considered. [2004]

171. Take care when prescribing antihypertensive medicines not to expose people to the risks of orthostatic hypotension as a result of the combined effects of sympathetic autonomic neuropathy and blood pressure lowering medicines. [2004]

172. In adults with type 1 diabetes who have bladder emptying problems, investigate the possibility of autonomic neuropathy affecting the bladder, unless other explanations are adequate. [2004]

173. When managing the symptoms of autonomic neuropathy, include standard interventions for the manifestations encountered (for example, for abnormal sweating and postural hypotension). [2004, amended 2015]

174. Anaesthetists should be aware of the possibility of parasympathetic autonomic neuropathy affecting the heart in adults with type 1 diabetes who are listed for procedures under general anaesthetic and who have evidence of somatic neuropathy or other manifestations of autonomic neuropathy. [2004]

175. For guidance on treating chronic diabetic neuropathy, see the NICE guideline on neuropathic pain – pharmacological management.[new 2015]

176. At the time of diagnosis (or if necessary after the management of critically decompensated metabolism), the diabetes professional team should develop with and explain to the adult with type 1 diabetes a plan for their early care. To agree such a plan will generally require:

   - medical assessment to:
   i. ensure security of diagnosis of type of diabetes
   ii. ensure appropriate acute care is given when needed
   iii. review and detect potentially confounding disease and medicines
   iv. detect adverse vascular risk factors

   - environmental assessment to understand:

     i.    the social, home, work and recreational circumstances of the individual and carers

     ii.    their preferences in nutrition and physical activity

     iii.    other relevant factors, such as substance use

- cultural and educational assessment to identify prior knowledge and to enable optimal advice and planning about:

     i.    treatment modalities

     ii.    diabetes education programmes

- assessment of emotional state to determine the appropriate pace of education.

The results of the assessment should be used to agree a future care plan. Some items of the initial diabetes assessment:

- acute medical history

- social, cultural and educational history/lifestyle review

- complications history/symptoms

- long-term/recent diabetes history

- other medical history/systems

- family history of diabetes/arterial disease

- medication history/current medicines

- vascular risk factors

- smoking

- general examination

- weight/BMI

- foot/eye/vision examination

- urine albumin excretion/urine protein/serum creatinine

- psychological wellbeing

- attitudes to medicine and self-care

- immediate family and social relationships and availability of informal support. [2004]

177.    Elements of an individualised and culturally appropriate plan will include:

- sites and timescales of diabetes education, including nutritional advice (see 'Structured education programmes', Section 7.2, and 'Dietary management', Section 7.3)

- initial treatment modalities, ==including guidance on insulin injection== (see 'Insulin regimens', Section 9.2, and 'Insulin delivery', Section 9.3)

- means of self-monitoring ==and targets== (see 'Self-monitoring of glucose level', Section 14)

- ==symptoms, risk and treatment of hypoglycaemia==

- ==management of special situations, such as driving==

- means and frequency of communication with the diabetes professional team

- management of arterial risk factors (see Arterial risk control', Section 14)

- for women of childbearing potential, implications for pregnancy and family planning advice

- follow-up consultations, including frequency of review of HbA1c levels and experience of hypoglycaemia, and surveillance at annual review (see Section 16) [2004, amended 2015]

178. After the initial plan is agreed, put arrangements in place to implement it without inappropriate delay, and to provide for feedback and modification of the plan over the ensuing weeks. [2004]

179. Members of diabetes professional teams providing care or advice to adults with type 1 diabetes should be alert to the development or presence of clinical or subclinical depression and/or anxiety, in particular if someone reports or appears to be having difficulties with self-management. [2004]

180. Diabetes professionals should:

- ensure that they have appropriate skills in the detection and basic management of non-severe psychological disorders in people from different cultural backgrounds

- be familiar with appropriate counselling techniques and drug therapy, while arranging prompt referral to specialists of those people in whom psychological difficulties continue to interfere significantly with wellbeing or diabetes self-management.

See also the NICE guidelines on common mental health disorders, generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults and depression in adults with a chronic health problem. [2004, amended 2015]

181. Members of diabetes professional teams should be alert to the possibility of bulimia nervosa, anorexia nervosa and insulin dose manipulation in adults with type 1 diabetes with:

- over-concern with body shape and weight

- low BMI

- hypoglycaemia

- poor overall blood glucose control.

See also the NICE guideline on eating disorders. [2004, amended 2015]

182. The risk of morbidity from the complications of poor metabolic control suggests that consideration should be given to early, and occasionally urgent, referral of adults with type 1 diabetes to local eating disorder services. [2004]

183. Make provision for high-quality professional team support at regular intervals with regard to counselling about lifestyle issues and particularly dietary behaviour for all adults with type 1 diabetes from the time of diagnosis (see 'Structured education programmes, Section 7.2 and Dietary management, Section 7.3). [2004]

## 4.4    Full list of research recommendations

1. In adults with diabetes, are diagnostic tests (autoimmune markers and biochemical tests such as urine C-peptide and urine C-peptide/creatinine ratio) useful for defining type 1 diabetes, and if so, what is the optimal time in which they should be measured in order to make the diagnosis?

2. In adults with type 1 diabetes, are diagnostic tests (autoimmune markers and biochemical tests such as urine C-peptide and urine C-peptide/creatinine ratio) good prognostic makers of the complications associated with the 1 diabetes and its treatments?
   *Note: We exclude the use of these markers in trials of immune modulation therapy to alter the course of type 1 diabetes, as this is not a current therapeutic option and the literature was not reviewed by the GDG in this revision.*

3. In adults with type 1 diabetes, what methods can be used to increase the uptake of structured education programmes and to improve their clinical outcomes (particularly achieving and sustaining blood glucose control targets)?

4. In adults with newly diagnosed type 1 diabetes, what is the optimal timing and method of delivering structured education in terms of clinical and cost-effectiveness?

5. In adults with type 1 diabetes, what is clinical and cost effectiveness of bolus calculators used in conjunction with self-monitoring blood glucose meters?

6. In adults with type 1 diabetes, what is the clinical and cost effectiveness of different types of diet and dietary constituents, particularly in terms of the effect on insulin requirement and blood glucose control?

7. What methods and interventions are effective in increasing the number of adults with type 1 diabetes who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?

8. Can a risk stratification tool be used to aid the setting of individualised HbA1c targets for adults with type 1 diabetes?

9. In adults with type 1 diabetes, is HbA1c measurement by laboratory analysis more cost-effective compared to site of care HbA1c testing?

10. In adults with type 1 diabetes, what is the clinical and cost effectiveness of post-prandial blood glucose monitoring?

11. In adults with type 1 diabetes who have chronically poor-control of blood glucose levels, what is the clinical and cost effectiveness of continuous glucose monitoring technologies?

12. In adults with type 1 diabetes, what is the clinical and cost effectiveness of basal insulins with longer action profiles compared to existing regimens, particularly in terms of dose adjustment for flexible lifestyles, such as intermittent exercise or alcohol consumption, and their long term safety data?

13. In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of different intensities of glycaemic control (for example, inpatient intravenous insulin management versus outpatient multiple daily dose insulin injection therapies)?

14. In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of using basal-bolus insulin regimens?

15. In adults with type 1 diabetes, what modifications of rapid-acting insulin use (including but not limited to timing of administration, and the nature of the insulin) could be employed to improve glycaemic control around different meal compositions?

16. In adults with type 1 diabetes, what modifications of rapid-acting insulin (including timing of administration and nature of the insulin) could be employed to improve glycaemic control around different modalities of exercise?

17. In adults with type 1 diabetes and a BMI of ≥25 kg/m$^2$, what is the clinical and cost effectiveness of metformin as an adjunct to insulin, particularly in terms of glycaemic control and weight loss (or reduction in weight gain)?

18. In adults with type 1 diabetes, what is the clinical and cost effectiveness of GLP-1 analogues and other potential pharmacological adjuncts to insulin therapy?

19. In adults with type 1 diabetes, what is the optimum needle length and type for administration of exogenous insulin in terms of clinical and cost effectiveness?

20. In adults with type 1 diabetes, what is the optimum injection site and injection site rotation regimen in terms of clinical and cost effectiveness?

21. For adults with type 1 diabetes, what are the optimum technologies (such as insulin pump therapy and/or continuous glucose monitoring, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions) and how are they best used, in terms of clinical and cost effectiveness, for preventing and treating impaired awareness of hypoglycaemia?

22. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the management of DKA?

23. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the prevention of DKA?

24. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of pre-empting admissions) of self-monitoring blood ketones compared to urine ketones?

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25. In adults with type 1 diabetes, what is the clinical and cost effectiveness of aspirin and other anti-platelet agents who are at high risk for vascular disease (for example, smokers, those with renal disease, those with other evidence of vascular disease)?

26. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of optimal blood glucose control, patient-reported outcomes and experience, length of stay, and short-term complications) of closed loop insulin delivery systems and automated insulin dose advisors during in-hospital care, and could the development of new systems and technologies improve on current clinical outcomes?

27. In adults with type 1 diabetes, clinical and cost effective treatments for diabetic gastroparesis are needed, together with further evidence for the clinical and cost effectiveness of existing treatments such as dopamine antagonists, insulin pump therapy, and gastric electrical stimulation.

28. What is the clinical and cost-effectiveness of constructing a national database and centralising supervision of the management of adults with type 1 diabetes who have painful neuropathy of rapid glycaemic control?

## 4.5 Key research recommendations

1. What methods and interventions are effective in increasing the number of adults with type 1 diabetes who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?

2. In adults with type 1 diabetes who have chronically poor control of blood glucose levels, what is the clinical and cost effectiveness of continuous glucose monitoring technologies?

3. In adults with type 1 diabetes, what methods can be used to increase the uptake of structured education programmes and to improve their clinical outcomes (particularly achieving and sustaining blood glucose control targets)?

4. Can a risk stratification tool be used to aid the setting of individualised HbA1c targets for adults with type 1 diabetes?

5. For adults with type 1 diabetes, what are the optimum technologies (such as insulin pump therapy and/or continuous glucose monitoring, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions) and how are they best used, in terms of clinical and cost effectiveness, for preventing and treating impaired awareness of hypoglycaemia?

**Update 2015**

# 5 Diagnosis

The evidence and recommendations in this chapter have been fully updated by the 2015 guideline development group. The content from the 2004 guideline, NICE CG15, which has been replaced by this update can be found in Appendix S.

## 5.1 Introduction

The diagnosis of type 1 diabetes is usually made on clinical grounds. Type 1 diabetes is characterised by severe insulin deficiency and by ketosis, as the circulating insulin concentrations are not even sufficient to suppress lipolysis and ketogenesis. The type 1 patient generally has a shorter prodromal illness than someone presenting with symptomatic type 2 diabetes and very often is losing weight through increased micturition (due to an osmotic diuresis) and also loss of muscle and fat. Type 1 diabetes can present at any age, although, incidence peaks in early childhood (aged 6 months to 5 years) and again during puberty. Although most type 1 diabetes is autoimmune in aetiology (type 1a); a proportion of type 1 diabetes patients lack any evidence of known markers of such a process (type 1b).

Markers for type 1 diabetes include evidence of the autoimmune process against beta cell antigens. These are typically autoantibodies, which, although not necessarily themselves pathogenic, indicate an active immune process against the beta cells. Evidence for insulin secretory deficiency is also a potential marker for type 1 diabetes, by definition insulin deficient, although, care must be taken in interpreting such data as many adults with type 1 diabetes may retain residual insulin secretion for many years.

The need to substantiate a diagnosis occurs when a clinical feature is atypical. Until recently, in adults, this has most commonly been when the clinical picture is of type 2, but the patient lacks any of the typical risk factors for type 2 at presentation, for example, has no family history, is slim, and not of a high risk ethnicity. Here, evidence of the autoimmune process that underlies most type 1 diabetes may be sought, as knowing a patient is undergoing a type 1 process is likely to influence the choice of therapy. Similarly, identifying an active autoimmune process against islet antigens may influence treatment decisions in adults presenting with slowly evolving autoimmune diabetes, often referred to as latent autoimmune diabetes of adults or LADA, and considered to be a form of type 1 diabetes. Increasingly, however, there are other reasons to wish to substantiate or refute a diagnosis of type 1 diabetes more robustly. With the growing prevalence of obesity, type 1 diabetes may arise in an overweight or obese person, and the clinician (as well as the patient) may seek extra evidence for the underlying pathology, especially if the patient is considering surgical options for the obesity, which may lead to remission of type 2, but not type 1, diabetes. A growing knowledge of single gene defects causing diabetes has also changed the clinical picture, and although this is of more relevance in the differential diagnosis of type 2 diabetes, there have been high profile cases of people with 'type 1 diabetes' diagnosed in the first six months of life later being found to have single gene defects of beta cell glucose sensing and getting better control of their condition with non-injectable therapies. Genetic testing is outside the scope of this guideline: instead, we have sought evidence for the efficacy and limitations of seeking positive markers for the type 1 process – evidence of autoimmunity and evidence of marked endogenous insulin secretory deficiency.

Looking to the future, precise knowledge of the autoimmune process involved in type 1 diabetes may guide immunomodulatory therapies to alter the course of type 1 diabetes, but this is currently an area of ongoing research.

The evidence and recommendations in this chapter have been fully updated by the 2015 guideline development group. The content from the 2004 guideline, NICE CG15, which has been replaced by this update can be found in Appendix S.

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## 5.2 Review question: In adults with diabetes, what is the best marker (C-peptides plus or minus antibodies) to distinguish between a diagnosis of type 1 diabetes, type 2 diabetes and other forms of diabetes?

For full details see review protocol in Appendix C.

**Table 7:    PICO characteristics of review question**

| Population | Adults with all types of diabetes<br>• Adult is defined as ≥18 years<br>• Diabetes types are: type 1 diabetes, type 2 diabetes, latent autoimmune diabetes of adulthood (LADA) and maturity onset diabetes of the young (MODY). |
|---|---|
| Diagnostic tests | C-peptide<br>• Plasma C-peptide (stimulated)<br>• Urinary C-peptide<br>• Urinary C-peptide/creatinine ratio<br><br>Antibody tests:<br>• Anti-islet cell antibody (ICA)<br>• Anti-glutamic acid decarboxylase 65 antibody or anti-glutamic acid decarboxylase antibody (GADA)<br>• Insulinoma-associated (IA-2) autoantibody<br>• Other (zinc transporter 8 (ZnT8); islet-specific glucose-6-phosphatase catalytic subunit (IGRP), anti-ZnT8, anti-IA-2/ICA512 |
| Outcomes | • Presence of marker (no. or % of patients with marker)<br>• Concentration (titre) of marker<br>• Change in marker over time (no. or % of patients with marker)<br>• Change in concentration (titre) of marker over time |
| Study design | Observational studies |

## 5.3 Clinical evidence

We searched for studies that showed the presence of diagnostic markers (C-peptide and/or antibodies) in young people and adults with different types of diabetes (type 1 diabetes, type 2 diabetes, LADA and MODY), with the aim of seeing which markers could be used to distinguish between the types of diabetes and thus, aid diagnosis.

Sixty-two studies were included in the review.[22,32,33,43,46,55,64,68,74,80,83,94,106,108,119,155,160,168,204,272,273,283,308,327,331,334,339,375,402,421,438,444,454,455,458,473,489,496,538,547,575,576,600,601,629-632,651,663,673,686,699,702,718,720,724,736,746,756,764,766] The included studies were all observational, and comprised both case-series (prospective or retrospective) and cross-sectional studies. These studies were therefore not able to be combined in a meta-analysis or GRADE profile. All studies were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below (see Table 8 and Table 9). See also the study selection flow chart in Appendix D, study evidence tables in Appendix G and exclusion list in Appendix K.

Results from studies have been categorised into the following age-groups:

• Adults (aged more than or equal to 18 years)

- Mixed population: adults and young people (aged more than or equal to 11 years)

Due to the huge number of studies retrieved, the following exclusion criteria were applied to the review (including sample size cut-off):

- Studies with mixed population of the following and no subgroup analyses of adults:
  o All ages (children, young people and adults)
  o Adults and young people with sample size of less than 50 (as we have many studies in adults separately already)
- Studies in adults with a sample size of less than 50, if there are more than 20 adult studies retrieved.

After assessing all of the evidence, the GDG decided that, because the prevalence of and the levels of markers tend to diminish over time, the data from studies that only included newly diagnosed patients (diagnosis made up to 1 year before the study) would be separated out from the studies using a population with 'established' diabetes. This was done because it would give a better estimate of the levels of each of the markers in the different types of diabetes patients. Additionally, this would also be the most clinically relevant time to look at the levels of the markers (that is, to help confirm the diagnosis).

There were 26 studies that included newly diagnosed diabetic patients (patients recruited within 1 year of initial diagnosis): [46,55,80,83,155,160,168,204,308,331,334,444,473,547,600,629-632,673,699,703,718,720,736,756,766] The data for these studies has been summarised in 5.3.1.

**Table 8:** **Summary of studies included in the review**

| Study | Sample size and population | Follow-up | Outcomes[a] | Reference/ study no.[b] |
|---|---|---|---|---|
| Adult studies | | | | |
| AGGARWAL 2010 | n=34 suspected LADA, n=66 classic type 2 diabetes | 6 months | C-peptide | 60 |
| AMROUCHE 2008 | n=100 type 2 diabetes | n/a | GAD, IA-2, ICA | 100 |
| ANDERSEN 2014 | n=406 type 1 diabetes, n=911 LADA | n/a | C-peptide | 318 |
| ARIKAN 2005 | n=37 type 2 diabetes and n=17 LADA | n/a | C-peptide, GAD | 102 |
| ARSLAN 2014 | n=52 type 1 diabetes | n/a | GAD, ICA | 319 |
| BARKER 2014 | n=1665 type 1 diabetes | 1 and 5 years | C-peptide | 300 |
| BELL 2004 | n=39 type 2 diabetes and n=39 LADA | n/a | C-peptide | 108 |
| BODALSKA 2006 | n=56 type 2 diabetes | n/a | C-peptide, GAD, IA-2 | 52 |
| BOTTAZZO 2005 | n=4169 type 2 diabetes | n/a | GAD, IA-2, ICA, combi | 41 |
| CASTLEDEN 2006 | n=2059 type 2 diabetes | n/a | GAD | 92 |
| CERNA 2003 | n=80 type 1 diabetes, n=70 LADA, n=131 type 2 diabetes | n/a | C-peptide, GAD, IA-2 | 34 |
| CHOWTA 2010 | n=168 type 2 diabetes | n/a | C-peptide | 2 |

| Study | Sample size and population | Follow-up | Outcomes[a] | Reference/study no.[b] |
|---|---|---|---|---|
| DAVIES 2008 | n=373 type 2 diabetes, n=14 LADA | n/a | C-peptide, GAD, IA-2 | 88 |
| DAVIS 2003 | FDS study: n=119 type 1 diabetes and n=427 type 2 diabetes UKPDS study: n=333 type 2 diabetes | n/a | GAD, IA-2, ICA | 91 |
| DESAI 2007 | n=242 LADA | 6 years | GAD | 40 |
| HAMAGUCHI 2004 | n=835 type 2 diabetes | n/a | C-peptide, GAD | 125 |
| HAMPE 2013 | n=100 type 1 diabetes | n/a | GAD65 | 302 |
| HAWA 2013 | n=114 type 1 diabetes and n=377 LADA | n/a | GAD, IA-2A, ZnT8A | 303 |
| HILLMAN 2009 | n=40 type 1 diabetes and n=43 LADA (HUNT2 /3) | 10-13 years | C-peptide, GAD | 4 |
| HOPE 2013 | n=191 type 2 diabetes | n/a | UCPCR | 320 |
| HOSSZU 2003 | n= 54 LADA, n= 57 type 1 diabetes, n=190 type 2 diabetes | n/a | C-peptide, GAD, IA-2, ICA | 12 |
| HUANG 2013 | n=3062 (n=2798 type 2 diabetes and n=264 LADA) | n/a | GAD, IA-2A, ZnT8 | 304 |
| HWANGBO 2012 | n= 20 LADA, n= 442 type 2 diabetes | n/a | C-peptide, GAD | 11 |
| KIM 2007 | n=35 LADA, n=93 type 1 diabetes (acute onset) | n/a | C-peptide | 14 |
| LEE 2011A | n=174 type 2 diabetes | 6 years | C-peptide, GAD | 89 |
| LINDHOLM 2004 | n=803 type 1 diabetes, n= 3730 type 2 diabetes (n=4956) | n/a | GAD | 135 |
| MAHADEB 2014 | n=524 type 2 diabetes | n/a | GAD | 305 |
| MAIOLI 2010 | n= 251 LADA, n= 2510 type 2 diabetes | n/a | GAD, IA-2 | 49 |
| MARASCHIN 2013 | n=92 type 1 diabetes | n/a | GAD, C-peptide | 306 |
| MCDONALD 2011 | n=508 MODY | n/a | GAD, IA-2 | 85 |
| MONGE 2004 | n=70 LADA, n=150 type 2 diabetes | n/a | C-peptide, GAD, ICA | 115 |
| MURAO 2008 | n=57 LADA | 5 years | C-peptide, GAD, IA-2 | 128 |
| PASCHKE 2013 | n=344 LADA | n/a | GAD, IA-2A, ICA, C-peptide | 307 |
| RADTKE 2009 | n= 943 type 2 diabetes, n= 106 LADA | n/a | C-peptide, GAD | 5 |
| ROGOWICZ 2014 | n=56 LADA | n/a | GAD, IA-2A, ZnT8, ICA, C-peptide | 323 |
| ROH 2013 | n=268 type 2 diabetes | n/a | GAD, C-peptide | 308 |
| SHISHIKURA | n=138 type 2 diabetes | n/a | C-peptide | 324 |

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| Study | Sample size and population | Follow-up | Outcomes[a] | Reference/ study no.[b] |
|---|---|---|---|---|
| 2014 | | | | |
| SORGJERD 2012 | n=120 type 1 diabetes and n=120 LADA (HUNT2) n=147 TID and n=85 LADA (HUNT3) | 10-13 years | C-peptide, GAD, IA-2, ZnT8 | 87 |
| SZEPIETOW SKA 2012 | n=19 LADA, n=186 type 2 diabetes | n/a | C-peptide, GAD | 18 |
| THANABALA SINGHAM 2012 | n= 247 type 1 diabetes, n=322 type 2 diabetes, n=14 MODY (from the 2 groups ) | n/a | C-peptide, GAD | 43 |
| TRABUCCI 2012 | n=271 type 2 diabetes | n/a | GAD, IA-2, ZnT8 | 134 |
| VAZIRI 2010 | n=47 LADA | n/a | GAD, ZnT8 | 131 |
| VERMEULE N 2011 | n=655 type 1 diabetes (n=262 adults) | n/a | GADA, IA-2A, IA-2βA, IAA, ZnT8, Combi. | 250 |
| VLAD 2004 | n=268 type 2 diabetes | n/a | C-peptide, GAD | 113 |
| WILMOT 2013 | n=430 type 1 diabetes | n/a | GAD, IA-2A | 309 |
| YANG 2008 | n=209 type 1 diabetes and n=1296 type 2 diabetes | n/a | C-peptide, GAD | 107 |
| ZAMPETTI 2012 | n=236 LADA and n=450 type 2 diabetes | n/a | GAD, IA-2A, ZnT8 | 310 |
| ZHANG 2012A | n= 11 LADA, n= 70 type 1 diabetes, n=21 type 2 diabetes | n/a | C-peptide, GAD, IA-2, ICA, Combi | 98 |
| Mixed population: adult and young people studies | | | | |
| BESSER 2011 | n=72 type 1 diabetes | n/a | C-Peptide Urinary C-peptide/creatinine ratio | 311 |
| BORG 2003 | n=285 type 1 diabetes, n=81 type 2 diabetes | 1 year | GAD, IA-2, ICA, Combi | 42 |
| BRUNOVA 2002 | n=55 type 1 diabetes, n=137 type 2 diabetes | n/a | C-peptide, GAD | 28 |
| FAN 2013 | n=187 type 2 diabetes | n/a | GAD, IAA, ICA | 301 |
| LAADHAR 2007 | n=261 type 1 diabetes | n/a | C-peptide | 30 |
| LU 2014 | n=140 type 2 diabetes | n/a | C-peptide | 321 |
| MCDONALD 2011 | n=98 type 1 diabetes | n/a | GAD, IA-2 | 85 |
| OTA 2005 | n=101 type 1 diabetes | n/a | C-peptide, GAD, IA-2, Combi | 126 |
| RAJALAKSH MI 2014 | n=150 type 1 diabetes, n=150 type 2 diabetes | n/a | C-peptide | 322 |
| SCHOLIN 2004 | n=100 type 1 diabetes | 12 months | C-peptide, GAD, IA-2 | 144 |
| SCHOLIN 2004A | n=362 type 1 diabetes | n/a | C-peptide, GAD, IA-2, ICA | 112 |
| SCHOLIN 2004B | n=254 type 1 diabetes, n=30 type 2 diabetes | 8 years | C-peptide, GAD, IA-2 | 69 |

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| Study | Sample size and population | Follow-up | Outcomes[a] | Reference/ study no.[b] |
|---|---|---|---|---|
| SCHOLIN 2011 | n=78 type 1 diabetes | 3 years | C-peptide | 93 |
| TRIDGELL 2011 | n= 5,020 type 1 diabetes | n/a | GAD, IA-2, Combi | 46 |
| WENZLAU 2010 | n=506 type 1 diabetes | 2.5 to 12 years | C-peptide, GAD, IA-2, ZnT8 | 55 |

(a) C-peptide was measured as fasting C-peptide in nearly all of the studies; combi is an abbreviation for combination
(b) Study number has been referred to throughout the results section, and appears in brackets within the tables of numerical data, in order to easily identify the relevant studies and where the data has come from.

**Outcomes**

Due to the many studies retrieved from the literature search and included in the review, conference abstracts were excluded.

There were no data reported in any of the studies for the following markers:

- IGRP

### 5.3.1 Results for newly diagnosed patients (recruited within 1 year of initial diagnosis)

#### 5.3.1.1 Adults

**Table 9: Percentage of patients with diagnostic markers: studies in newly diagnosed adults (aged more than or equal to 18 years)**

| Diabetes type | Diagnostic marker, % patients who were Ab+ (reference no). | | | | |
|---|---|---|---|---|---|
| | Fasting C-peptide | ICA | GADA/GAD65+ | IA-2/ICA512 | ZnT8 |
| Type 1 diabetes | - | 45.7% (98) | 64.3% (98) | 30% (98) | - |
| | - | - | 41% (91) | 18% (91) | - |
| | - | 14% (12) | 9% (12) | 0% (12) | - |
| | - | - | 5.3% (107) | - | - |
| | - | - | - | 32% - IA-2βA age 20-29 years (250) | 51% age 20-29 (250) |
| | - | - | - | 19% - IA-2βA age 20-29 years (250) | 39% age 30-39 (250) |
| Median % (range) | - | 30% (14-46%) | 25% (5-64%) | 18% (0-32%) | 45% (39–51%) |
| Type 2 diabetes | - | - | 4% (91) | 0.2% (91) | - |
| | - | 26% (91b) | 26% (91b) | 8% (91b) | - |
| | - | 3% (12) | 2% (12) | 0% (12) | - |
| | - | 5.5% (41) | 10% (41) | 2.2% (41) | - |
| | - | 4.8% (98) | 9.5% (98) | - | - |
| | - | - | 7.7% (134) | 1.1% (134) | 19% (134) |
| | - | - | 1% (18) | - | - |
| | - | - | 9% (107) | - | - |
| | - | - | 6.4% (304) | 1.96% (304) | 1.99% (304) |
| Median % (range) | - | 5% (3-26%) | 7.7% (1-26%) | 1.5% (0-8%) | 10.5% (19%) |

| Diabetes type | Diagnostic marker, % patients who were Ab+ (reference no). | | | | |
| --- | --- | --- | --- | --- | --- |
| | Fasting C-peptide | ICA | GADA/GAD65+ | IA-2/ICA512 | ZnT8 |
| LADA | - | 33% (12) | 26% (12) | 0% (12) | - |
| | - | 36.4% (98) | 100% (98) | 27.3% (98) | - |
| | - | - | 63% (18) | - | - |
| | - | - | - | - | 42% (131) |
| | - | 79.1% (307) | 90.7% (307) | 60.5% (307) | - |
| | - | 42.8% (323) | 83.9% (323) | 62.5% (323) | 33.0% (323) |
| Median % (range) | - | 39.6% (33–43%) | 84.0% (63-100%) | 43.8% (27-63%) | 37.5% (33-42%) |
| MODY | - | - | 1% (85) | 0% (85) | - |
| Median % (range) | - | - | 1% (85) | 0% (85) | - |

**Table 10: Titres of diagnostic markers: studies in newly diagnosed adults (aged more than or equal to 18 years)**

| Diabetes type | Diagnostic marker, mean titre (reference no.) | | | | |
| --- | --- | --- | --- | --- | --- |
| | Fasting C-peptide | ICA | GADA/GAD65+ | IA-2/ICA512 | ZnT8 |
| Type 1 diabetes | 0.30 nM (300) | - | - | - | - |
| LADA | 1.1 ng/ml (323) - | 80 JDRF U in ZnT8+ (323) 20 JDRF U in ZnT8- (323) | 522.3 U/ml in ZnT8+ (323) 282.8 U/ml in ZnT8- (323) | 19.1 U/ml in ZnT8+ (323) 17.3 U/ml in ZnT8- (323) | - - |

**Table 11: Percentage of patients with combinations of diagnostic markers: studies in newly diagnosed adults (aged more than or equal to 18 years)**

| Diagnostic marker, % (reference no.) | Type of diabetes | | | |
| --- | --- | --- | --- | --- |
| | Type 1 diabetes | Type 2 diabetes | LADA | MODY |
| Only GAD+ | 14.3% (98) | - | - | - |
| Only IA-2A+ | 4.3% (98) | - | - | - |
| Only ICA+ | 7.1% (98) | - | - | - |
| GAD+ and/or ICA+ | 75.7% (98) 62% (319) | - | - | 1% (85) |
| Median % (range) | 68.9% (62 –76%) | - | - | 1% (1%) |
| GAD+ and/or IA-2+ | 74.3% (98) - | - - | - 7.6% (304) | - - |
| ZnT8+ and/or GAD+ | - | - | 7.7% (304) | - |
| ZnT8+ and/or IA-2A+ | - | - | 3.2% (304) | - |
| GAD+/IA-2+ | 3% (12) 8.6% (98) - | 0% (12) 0.7% (134) 0.32 (304) | 2% (12) - - | - - - |
| Median % (range) | 5.8% (3-8.6%) | 0.32% (0-0.7%) | 2% (2%) | - |
| GAD+/ICA+ | 19% (12) 20% (98) | 0% (12) - | 22% (12) - | - - |
| Median % (range) | 20% (19-20%) | 0% (0%) | 22% (22%) | - |

Update 2015

| Diagnostic marker, % (reference no.) | Type of diabetes | | | |
|---|---|---|---|---|
| | Type 1 diabetes | Type 2 diabetes | LADA | MODY |
| GAD+ /ZnT8+ | - | 1.5% (134) | - | - |
| | - | 0.20 (304) | - | - |
| | - | - | 84.2% (323) | - |
| Median % (range) | - | 0.85% (0.2 – 1.5%) | 84% (84%) | - |
| GAD+ /ZnT8- | - | - | 83.8% (323) | - |
| IA-2+/ICA+ | 2% (12) | 0% (12) | 0% (12) | - |
| | 4.3% (98) | - | - | - |
| Median % (range) | 3.2% (2-4%) | 0% (0%) | 0% (0%) | - |
| IA-2+/ZnT8+ | - | 0.4% (134) | - | - |
| | - | 0.26 (304) | - | - |
| | - | - | 47.3% (323) | - |
| Median % (range) | - | 0.33% (0.26–0.4%) | 47% (47%) | - |
| IA-2A/ZnT8- | - | - | 41.6% (323) | - |
| ICA/ZnT8+ | - | - | 89.4% (323) | - |
| ICA/ZnT8- | - | - | 51.4% (323) | - |
| GAD+/IA-2+/ICA+ | 32% (12) | 0% (12) | 17% (12) | - |
| | 4.3% (98) | - | - | - |
| | - | - | 49% (307) | - |
| Median % (range) | 18% (4.3-32%) | 0 (0) | 33% (17-49%) | - |
| GAD+/IA-2+/ ZnT8+ | - | 1.1% (134) | - | - |
| | - | 0.49% (304) | - | - |
| Median % (range) | - | 0.80% (0.49–1.1%) | - | - |
| Antibody negative | 21% (12) | 95% (12) | 0% (12) | - |
| | - | 78% (134) | - | - |
| | 18.6% (98) | - | - | - |
| Median % (range) | 19% (21-19%) | 87% (78-95%) | 0% (0%) | - |
| ≥1 positive (GADA+, IA-2A+ or IAA+) | 79% (250) | - | - | - |
| ≥1 positive (GADA+, IA-2A+ or ZnT8+) | 79% (250) | - | - | - |
| | - | - | 8.6% (304) | - |
| ≥2 positive (GADA+, IA-2A+ and/or IAA+) | 49% (250) | - | - | - |
| ≥2 positive (GADA+, IA-2A+ and/or ZnT8+) | 53% (250) | - | - | - |
| 1 positive (of GAD, ICA, IA-2A) | - | - | 19% (307) | - |
| 2 positive (of GAD, ICA, IA-2A) | - | - | 33% (307) | - |

Update 2015

Study no. 250, all age groups:

- The prevalence of both IA-2βA and ZnT8 increased with the no. of conventional Abs present.
- The prevalence of both IA-2βA and ZnT8 decreased with age at diagnosis (particularly after age 20 years).

- When testing for IA-2βA in addition to IAA, GADA and IA-2A, the percentage of patients who were positive for more than or equal to 2 Abs increased from 51% to 56% (SS versus testing without the additional Ab).
- When testing for ZnT8 in addition to IAA, GADA and IA-2A, the percentage of patients who were positive for more than or equal to 2 Abs increased from 51% to 63% (SS versus testing without the additional Ab).
- When testing for both IA-2βA and ZnT8 in addition to IAA, GADA and IA-2A, the percentage of patients who were positive for more than or equal to 2 Abs increased from 51% to 65% (SS versus testing without the additional Abs).
- In patients with the same number of conventional Abs (positive for either 1 or 2 Abs) the prevalence of IA-2βA and ZnT8 were highest when IA-2A was also present. Thus, ZnT8 was preferentially (and IA-2βA almost exclusively) associated with IA-2A.
- ZnT8A testing increased the fraction of double antibody-positive individuals more than IA-2βA.
- Random C-peptide did not vary according to ZnT8 or IA-2βA status.
- The prevalence of both IA-2βA and ZnT8 increased with the no. of conventional Abs present.
- Replacing IAA by IA-2βA as a complement of GADA and IA-2A screening, resulted in lower diagnostic sensitivity.

**Table 12: Changes in markers over time - studies in newly diagnosed adults (aged more than or equal to 18 years)**

| Diagnostic marker, % (reference no.) | Type of diabetes | | |
| --- | --- | --- | --- |
| | LADA | Type 2 diabetes | Type 1 diabetes |
| fC-Peptide<br>Baseline<br>3 years | Study no. 4<br>0.58 nmol/litre<br>0.44 nmol/litre (SS change) | Study no. 4<br>-<br>- | Study no. 4<br>0.22 nmol/litre<br>0.12 nmol/litre (NS change) |
| fC-Peptide<br>Baseline<br>1 year<br>5 years | Study no. 300<br>-<br>-<br>- | Study no. 300<br>-<br>-<br>- | Study no. 300<br>0.30 nM<br>0.30 nM<br>0.17 nM |
| C-pep and GADA<br>Study no. 4 | C-peptide levels were SS lower in type 1 diabetes vs. LADA at clinical onset and after 3 years.<br>All the GADA IgG subclass levels decreased in the group of type 1 diabetes over time, but more sustained in LADA patients over time. | | |

**Table 13: Changes in markers with age studies in newly diagnosed adults (aged more than or equal to 18 years)**

| Type of diabetes | Age groups 18-25 years, 26-35 years and 36-45 years (Study no. 98) |
| --- | --- |
| Type 1 diabetes | % ICA+ decreased with increasing age: 61.5%, 29.2% and 16.7%<br>% IA-2+ decreased with increasing age: 38.5%, 20.8% and 16.7%<br>GADA+ overall increased with increasing age: 64.1%, 60%, 66.4% |

### 5.3.1.2  Mixed population: adults and young people

**Table 14: Percentage of patients with diagnostic markers: studies in mixed population of newly diagnosed adults and young people (aged more than or equal to 11 years)**

| Diabetes type | Diagnostic marker, % of patients who were Ab+ (reference no.) |
| --- | --- |

Update 2015

| | Fasting C-peptide | IAA | ICA | GADA/GAD65+ | IA-2/ICA512 | ZnT8 |
|---|---|---|---|---|---|---|
| Type 1 diabetes | - | - | 59.8% (144) | 71.1 (144) | 56.7 (144) | - |
| | - | - | 54% (42) | 77% (42) | 46% (42) | |
| | - | - | - | 66% (112) | 47% (112) | - |
| | - | - | - | 24.5% (85) | 94.5% (85) | - |
| | - | - | 62% (112) | - | - | - |
| Median % (range) | | | 60 (54-62) | 69 (25-77) | 52 (46-95) | - |
| Type 2 diabetes | - | - | 15% (42) | 21% (42) | 15% (42) | - |
| | - | 10.6% (301) | 3.2% (301) | 4.8% (301) | - | - |
| Median % (range) | - | 10.6 (10.6) | 9.1 (3.2 - 15) | 12.9 (4.8 - 21) | 15 (15) | - |

**Table 15: Titres of diagnostic markers: studies in mixed population of newly diagnosed adults and young people**

| Diabetes type | Diagnostic marker, mean titre (reference no.) | | | | |
|---|---|---|---|---|---|
| | Fasting C-peptide | ICA | GADA/GAD65+ | IA-2/ICA512 | ZnT8 |
| Type 2 diabetes | Ketosis group: 475.8 pmol/litre (321) Non-ketosis group: 348.2 pmol/litre (321) | - | - | - | - |
| | | | | | |

**Table 16: Percentage of patients with combinations of diagnostic markers: studies in newly diagnosed mixed population of adults and young people (aged more than or equal to 11 years)**

| Diagnostic marker, % (study no.) | Type of diabetes | | | |
|---|---|---|---|---|
| | Type 1 diabetes | Type 2 diabetes | LADA | MODY |
| GAD+ and/or IA-2+ | 82% (85) | - | - | - |
| GAD+/IA-2+ | - 10% (42) 37.8% (85) | 17% (42) - - | - - - | - - - |
| Median % (range) | 24.0 (10-38) | 17 (17) | - | - |
| GAD+/ICA+ | 21% (42) | 17% (42) | - | - |
| IA-2+/ICA+ | 3% (42) | 11% (42) | - | - |
| GAD-/IA-2-/ICA- | 19.7% (144) | - | - | - |
| ≥1 positive (GADA+, IA-2A+ or IAA+) | 82% (250) | - | - | - |
| ≥1 positive (GADA+, IA-2A+ or ZnT8+) | 51% (250) | - | - | - |
| ≥2 positive (GADA+, IA-2A+ and/or IAA+) | 56% (250) | - | - | - |
| ≥2 positive (GADA+, IA-2A+ and/or | 63% (250) | - | - | - |

Update 2015

| Diagnostic marker, % (study no.) | Type of diabetes | | | |
|---|---|---|---|---|
| | Type 1 diabetes | Type 2 diabetes | LADA | MODY |
| ZnT8+) | | | | |

**Table 17:   Change in markers over time. Studies in mixed population of newly diagnosed adults and young people (aged more than or equal to 11 years)**

| Type 1 diabetes | Time intervals: baseline 3, 6, 9, 12, 15, 18, 24, 30 and 36 months (93)<br>• % fC-Peptide generally decreased over time: 0.24, 0.26, 0.31, 0.27, 0.27, 0.19, 0.17, 0.16, 0.12, 0.19<br>Time intervals: baseline (at diagnosis) and 8 years follow-up (69)<br>• %ICA+ decreased over time: 64% to 24%<br>• %IA-2+ decreased over time: 46% to 34%<br>• %GADA+ decreased over time: 76% to 65%<br>• %C-peptide ≥0.1 nmol/litre increased over time: 60% to 76%<br>• %C-peptide <0.1 nmol/litre increased over time: 90% to 95% |
|---|---|
| New onset type 1 diabetes (<6 weeks) | Time intervals: baseline, 2.5 years and 12 years follow-up (55)<br>• %C-peptide decreased over time: 100%, 85.7% and not given.<br>• %GADA+ decreased over time: 95.2%, 85.7% and 11.5%<br>• %IA-2+ decreased over time: 90.5%, 90.5% and 4.9%<br>• %ZnT8+ decreased over time: 85.7%, 76.2% and not given. |
| Type 1 diabetes (4 years duration) | Time intervals: baseline, 2.5 years and 12 years follow-up (55)<br>• %C-peptide decreased over time: 100%, 85.7% and not given.<br>• %GADA+ decreased over time: 95.2%, 85.7% and 11.5%<br>• %IA-2+ decreased over time: 90.5%, 90.5% and 4.9%<br>• %ZnT8+ decreased over time: 85.7%, 76.2% and not given. |
| Type 2 diabetes | Time intervals: baseline (at diagnosis) and 8 years follow-up (69)<br>• %C-peptide ≥0.1 nmol/litre was similar over time: 21% to 20%<br>• %C-peptide <0.1 nmol/litre was similar over time: 4% to 3% |

*Note: Number in brackets is the study number.*

**5.3.1.3    Adults (newly diagnosed and 'established' diabetes)**

**Table 18: Percentage of patients with diagnostic markers: studies in adults (aged more than or equal to 18 years)**

| Diabetes type | Diagnostic marker, % patients who were Ab+ (reference no.) | | | | |
|---|---|---|---|---|---|
| | Fasting C-peptide | ICA | GADA/GAD65+ | IA-2/ICA512 | ZnT8 |
| Type 1 diabetes | 100% (34) | - | 50% (34) | 15% (34) | - |
| | - | 45.7% (98) | 64.3% (98) | 30% (98) | - |
| | - | - | 41% (91) | 18% (91) | - |
| | - | - | 59.7% (14) | 17.6% (14) | - |
| | - | 14% (12) | 9% (12) | 0% (12) | - |
| | - | - | 58.7%(43) | - | - |
| | - | - | 51% (135) | - | - |

Update 2015

| Diabetes type | Diagnostic marker, % patients who were Ab+ (reference no.) | | | | |
| --- | --- | --- | --- | --- | --- |
| | Fasting C-peptide | ICA | GADA/GAD65+ | IA-2/ICA512 | ZnT8 |
| | - | - | 5.3% (107) | - | - |
| | - | - | 31.5% (102) | - | - |
| | - | - | - | 32% - IA-2βA age 20-29 (250) | 51% age 20-29 (250) |
| | - | - | 45% (302) | - | - |
| | - | - | - | 19% - IA-2βA age 20-29 (250) | 39% age 30-39 (250) |
| | - | - | 48% (306) | - | - |
| Mean % | 100% | 22.9% | 42.1% | 18.8% | 45% |
| Type 2 diabetes | 100% (34) | - | 0% (34) | - | - |
| | - | - | 4% (91) | 0.2% (91) | - |
| | - | 26% (91b) | 26% (91b) | 8% (91b) | - |
| | - | 3% (12) | 2% (12) | 0% (12) | - |
| | - | 49% (100) | 18% (100) | 42% (100) | - |
| | - | 5.5% (41) | 10% (41) | 2.2% (41) | - |
| | - | 19.6% (52) | 5.3% (52) | 5.3% (52) | - |
| | - | 4.8% (98) | 9.5% (98) | - | - |
| | - | - | 7.7% (134) | 1.1% (134) | 19% (134) |
| | - | - | 7% (92) | - | - |
| | - | 6.6% (125) | - | - | - |
| | rC-PEP 100% (43) | - | - | - | - |
| | - | - | 4.9% (49) | - | - |
| | - | - | 5.8% (135) | - | |
| | - | - | 1% (18) | - | - |
| | - | - | 9% (107) | - | - |
| | - | - | 6.4% (304) | 1.96% (304) | 1.99% (304) |
| | - | - | 5.7% (305) | - | - |
| | - | - | - | 2.9% (310) | 1.6% (210) |
| Mean % | 100% | 16.4% | 7.6% | 7.1% | 22.6% |
| LADA | 100% (34) | - | 100% (34) | 11% (34) | - |
| | - | 33% (12) | 26% (12) | 0% (12) | - |
| | - | 36.4% (98) | 100% (98) | 27.3% (98) | - |
| | - | - | 63% (18) | - | - |
| | - | - | - | 21% (49) | - |
| | - | - | - | - | 42% (131) |
| | - | 79.1% (307) | 90.7% (307) | 60.5% (307) | - |
| | - | - | - | 42% (310) | 32% (310) |
| | - | 42.8% (323) | 83.9% (323) | 62.5% (323) | 33.0% (323) |
| Mean % | 100% | 47.8% | 77.2% | 32.0% | 35.7% |
| MODY | rC-PEP 100% (43) | - | 21%(43) | - | - |
| | - | - | 1% (85) | 0% (85) | - |
| Mean % | 100 | - | 11 | 0 | - |

**Table 19: Titres of diagnostic markers: studies in adults (aged more than or equal to 18 years)**

| Diabetes type | Diagnostic marker, mean titre (reference no.) | | | | |
|---|---|---|---|---|---|
| | C-peptide (mainly fasting) | ICA | GADA/GAD65+ | IA-2/ ICA512 | ZnT8 |
| Type 1 diabetes | 63 pmol/litre (107) | - | 193 ng/ml (107) | - | - |
| | rC-PEP 0.08 nmol/litre (43) | - | - | - | - |
| | 0.476 nmol/litre (12) | - | - | - | - |
| | 0.55 micrograms/litre (14 – acute) | - | - | - | - |
| | 0.4 ng/ml (98) | - | - | - | - |
| | 0.30 nM (300) | - | - | - | - |
| | - | - | 400 U/mL (302) | - | - |
| | 0.17 nmol/litre (306) | - | - | - | - |
| | 0.04 nmol/litre (318) | - | - | - | - |
| Type 2 diabetes | 1.05 pmol/ml (52) | 36.2 JDF U (52) | 89.3 AU (52) | 36.2.AU (52) | - |
| | 593.2 pmol/litre (18) | - | - | - | - |
| | 772 pmol/litre (107) | - | 8 ng/ml (107) | - | - |
| | rC-PEP 0.76 nmol/litre (43) | - | - | - | - |
| | 1.23 nmol/litre (12) | - | - | - | - |
| | 3.4 ng/ml (88) | - | - | 2.2 WHO U (88) | - |
| | 0.97 nmol/litre (2) | - | - | - | - |
| | 0.53 nmol/litre (115) | - | - | - | - |
| | 2.0 ng/ml (11) | - | - | - | - |
| | 377 pmol/litre (5) | - | 0.01 U (5) | - | - |
| | 0.7 nmol/litre (89) | - | - | - | - |
| | rC-PEP 5.1 ng/ml (108) | - | - | - | - |
| | 1.4 ng/ml (98) | - | - | - | - |
| | - | Ref 113<br><br>7.5% low titre (<0.58 ng/ml - may be type 1 diabetes)<br><br>57.8% normal titre (0.58-2.7 ng/ml)<br><br>34.7% high titre (>2.7 ng/ml) | | | |
| | - | - | 29.4 IU/litre (305) | - | - |
| | fC-pep: 2.18 ng/ml (308) | - | 0.07 U/ml (308) | - | - |

Update 2015

| Diabetes type | Diagnostic marker, mean titre (reference no.) | | | | |
| | C-peptide (mainly fasting) | ICA | GADA/GAD65+ | IA-2/ ICA512 | ZnT8 |
|---|---|---|---|---|---|
| | stim C-pep: 5.33 ng/ml (308) | | | | |
| LADA | rC-PEP 1.0 ng/ml (108) | - | - | - | - |
| | 0.63 nmol/litre (128 A) | - | - | - | - |
| | 0.82 nmol/litre (128 B) | - | - | - | - |
| | 0.83 nmol/litre (128 C) | - | - | - | - |
| | 126.4 pmol/ml (18) | - | - | - | - |
| | 609 pmol/litre (107) | - | 379 ng/ml (107) | - | - |
| | 0.53 nmol/litre (12) | - | - | | |
| | 3.4 ng/ml (88) | - | - | 164 WHO U (88) | - |
| | 0.53 nmol/litre (115) | - | - | - | - |
| | 0.83 micrograms/litre (14) | - | - | - | - |
| | 1.2 ng/ml (11) | - | - | - | - |
| | 0.4 ng/ml (98) | - | - | - | - |
| | 130 pmol/litre (5) | - | 0.54 U (5) | - | - |
| | 0.73 nmol/litre (318) | - | - | - | - |
| | 1.1 ng/ml (323) - | 80 JDRF U in ZnT8+ (323) 20 JDRF U in ZnT8- (323) | 522.3 U/ml in ZnT8+ (323) 282.8 U/ml in ZnT8- (323) | 19.1 U/ml in ZnT8+ (323) 17.3 U/ml in ZnT8- (323) | - - |
| MODY | rC-PEP 0.49 nmol/litre (43) | - | - | - | - |

**Table 20: Titre of urinary-C-peptide: studies in adults (aged more than or equal to 18 years)**

| Type 2 diabetes | • One study (Hamaguchi 2004)[272] found that urinary C-peptide titre was lower in adults with type 2 diabetes who were GAD+ compared with those who were GAD- (47.8 micrograms/day vs. 58.1 micrograms/day, respectively). <br> • One study (Hope 2014; 320) found that 13% of adults with type 2 diabetes had UCPCR, ≤0.2 nmol/mmol |
|---|---|

**Table 21: Percentage of patients with combinations of diagnostic markers: studies in adults (aged more than or equal to 18 years)**

| Diagnostic marker, % (reference no.) | Type of diabetes | | | |
| | Type 1 diabetes | Type 2 diabetes | LADA | MODY |
|---|---|---|---|---|
| Only GAD+ | 14.3% (98) | - | - | - |

| | | | | |
|---|---|---|---|---|
| Only IA-2A+ | 4.3% (98) | - | - | - |
| | - | - | 0% (128A) | |
| | - | - | 0% (128B) | |
| | - | - | 20% (128C) | |
| Mean | 4.3% | - | 6.7% | - |
| Only ICA+ | 7.1% (98) | - | - | - |
| Only ZnT8+ | - | - | - | - |
| GAD+ and/or ICA+ | 75.7% (98) | - | - | 1% (85) |
| | 62% (319) | - | - | - |
| Mean | 68.9 | - | - | 1 |
| GAD+ and/or IA-2+ | 74.3% (98) | - | - | - |
| | - | - | 7.6% (304) | - |
| | 56% (309) | - | - | - |
| Mean | 65.2 | - | 7.6% | - |
| ZnT8+ and/or GAD+ | - | - | 7.7% (304) | - |
| ZnT8+ and/or IA-2A+ | - | - | 3.2% (304) | - |
| GAD+/IA-2+ | 3% (12) | 0% (12) | 2% (12) | - |
| | 8.6% (98) | 0.7% (134) | - | - |
| | - | 0.32 (304) | - | - |
| | 14% (309) | - | - | - |
| Mean | 8.5% | 0.34% | 2% | - |
| GAD+/ICA+ | 19% (12) | 0% (12) | 22% (12) | - |
| | 20% (98) | 0% (115) | 43% (115) | - |
| Mean | 19.5% | 0% | 32.5% | - |
| GAD+/ICA- | - | - | 33% (115) | - |
| GAD-/ICA+ | - | - | 10% (115) | - |
| GAD+ /ZnT8+ | - | 1.5% (134) | - | - |
| | - | 0.20 (304) | - | - |
| | - | - | 84.2% (323) | - |
| Mean | - | 0.85 | 84.2 | - |
| GAD+ /ZnT8- | - | - | 83.8% (323) | - |
| IA-2+/ICA+ | 2% (12) | 0% (12) | 0% (12) | - |
| | 4.3% (98) | - | - | - |
| Mean | 3.2% | 0% | 0% | - |
| IA-2+/ZnT8+ | - | 0.4% (134) | - | - |
| | | 0.26 (304) | | |
| Mean | - | 0.33 | - | - |
| IA-2A/ZnT8- | - | - | 41.6% (323) | - |
| ICA+/ZnT8+ | - | - | 89.4% (323) | - |
| ICA/ZnT8- | - | - | 51.4% (323) | - |
| ICA-/GAD+ and/or IA-2+ | - | - | - | - |
| ICA+/GAD- and/or IA-2- | - | - | - | - |
| GAD+/IA-2+/ ICA+ | 32% (12) | 0% (12) | 17% (12) | - |
| | 4.3% (98) | - | - | - |
| | - | - | 49% (307) | - |
| Mean | 18.2% | 0% | 33% | - |

Update 2015

| | | | | |
|---|---|---|---|---|
| GAD+/IA-2+/ ZnT8+ | -<br>13.2% (303)<br>- | 1.1% (134)<br>-<br>0.49% (304) | -<br>9.0% (303)<br>- | -<br>-<br>- |
| Mean | 13.2% | 0.79% | 9.0% | - |
| 1 positive (GADA+ or IA-2A+) | 42% (309) | - | - | - |
| ≥1 positive (GADA+, IA-2A+ or IAA+) | 79% (250) | - | - | - |
| ≥1 positive (GADA+, IA-2A+ or ZnT8+) | 79% (250)<br>- | -<br>- | -<br>8.6% (304) | -<br>- |
| ≥2 positive (GADA+, IA-2A+ and/or IAA+) | 49% (250) | - | - | - |
| ≥2 positive (GADA+, IA-2A+ and/or ZnT8+) | 53% (250) | - | - | - |
| 1 positive (of GAD, ICA, IA-2A) | - | - | 19% (307) | - |
| 2 positive (of GAD, ICA, IA-2A) | - | - | 33% (307) | - |
| IA-2+/ GAD65- | - | - | - | - |
| Antibody negative | 21% (12)<br>-<br>18.6% (98)<br>44% (309) | 95% (12)<br>78% (134) | 0% (12)<br>- | -<br>- |
| Mean | 27.8% | 86.5% | 0% | - |
| General | - | GAD65+ was SS higher when ICA was absent (100) | - | - |

Study no. 250, all age groups:

- The prevalence of both IA-2βA and ZnT8 increased with the number of conventional Abs present.
- The prevalence of both IA-2βA and ZnT8 decreased with age at diagnosis (particularly after age 20 years).
- When testing for IA-2βA in addition to IAA, GADA and IA-2A, the percentage of patients who were positive for more than or equal to 2 Abs increased from 51% to 56% (SS versus testing without the additional Ab).
- When testing for ZnT8 in addition to IAA, GADA and IA-2A, the percentage of patients who were positive for more than or equal to 2 Abs increased from 51% to 63% (SS versus testing without the additional Ab).
- When testing for both IA-2βA and ZnT8 in addition to IAA, GADA and IA-2A, the percentage of patients who were positive for more than or equal to 2 Abs increased from 51% to 65% (SS versus testing without the additional Abs).
- In patients with the same number of conventional Abs (positive for either 1 or 2 Abs) the prevalence of IA-2βA and ZnT8 were highest when IA-2A was also present. Thus ZnT8 was preferentially (and IA-2βA almost exclusively) associated with IA-2A.
- ZnT8A testing increased the fraction of double antibody-positive individuals more than IA-2βA.
- Random C-peptide did not vary according to ZnT8 or IA-2βA status.
- The prevalence of both IA-2βA and ZnT8 increased with the no. of conventional Abs present.
- Replacing IAA by IA-2βA as a complement of GADA and IA-2A screening resulted in lower diagnostic sensitivity.

**Update 2015**

**Table 22: Changes in markers over time - studies in adults (aged more than or equal to 18 years)**

| Diagnostic marker, % (reference no.) | Type of diabetes | | | |
|---|---|---|---|---|
| | LADA, % patients | LADA, titre | Type 2 diabetes | Type 1 diabetes |
| GADA+<br>Baseline<br>0.5 years<br>3 years<br>6 years | <br>100% (100)<br>98% (100)<br>95% (100)<br>98% (100) | WHO U/ml<br>-<br>331 (100)<br>199 (100)<br>284 (100) | | |

GADA+

Ref 100

Although the median titre rose at 6 years, patients who had high titres at 0.5 years remained high and those that had low titres remained low at 3 and 6 years.

| Diagnostic marker, % (reference no.) | LADA | LADA | Type 2 diabetes | Type 1 diabetes |
|---|---|---|---|---|
| fC-Peptide<br>Baseline<br>6 months | <br>-<br>- | ng/ml<br>0.39 (60)<br>0.33 (60) | <br>1.54 (60)<br>1.43 (60) | |
| | | | Ref (2)<br>Negative correlation btw fC-peptide and duration of diabetes (but NS)<br>Disease duration higher in patients with less than normal vs. more than normal fC-peptide. | |
| | | | Ref (89)<br>fC-PEPTIDE concentrations in the GADA+ and GADA- groups were similar at baseline.<br>In GADA- group fC-PEPTIDE did not change significantly over time<br>In GADA+ group fC-PEPTIDE declined over time and became significantly lower than in the GADA- group at 1 year and thereafter.<br>F-C-PEPTIDE concentrations were similar at baseline in high and low-titre GADA subgroups (0.6 nmol/litre and 0.7 nmol/litre respectively)<br>After 3 years fC-PEPTIDE became significantly | |

Update 2015

| Diagnostic marker, % (reference no.) | LADA | Type 2 diabetes | Type 1 diabetes |
|---|---|---|---|
| | | lower in the HIGH titre subgroup than the low titre group. | |
| GADA, IA-2 and ZnT8

C-PEPTIDE | HUNT3 (87)
After 10-13 years 59% of LADA (Ab+ cases) were now Ab- for all 3 Abs.
Less preserved C-pep levels in LADA than type 2 diabetes (492 vs. 700.5) | HUNT3 (87)
No data reported
Better preserved C-pep levels in type 2 diabetes than LADA (700.5 vs. 492) | HUNT3 (87)
After 10-13 years, only 6% of type 1 diabetes were now Ab- for all 3 Abs |
| fC-Peptide
Baseline
3 years | Ref 4
0.58 nmol/litre
0.44 nmol/litre (SS change) | Ref 4
-
- | Ref 4
0.22 nmol/litre
0.12 nmol/litre (NS change) |
| fC-Peptide
Baseline
1 year
5 years | Study no. 300
-
-
- | Study no. 300
-
-
- | Study no. 300
0.30 nM
0.30 nM
0.17 nM |
| C-peptide and GADA
(Ref 4) | C-peptide levels were SS lower in type 1 diabetes vs. LADA at clinical onset and after 3 years.
All the GADA IgG subclass levels decreased in the group of type 1 diabetes over time, but more sustained in LADA patients over time. | | |

**Table 23: Changes in markers with age studies in adults (aged more than or equal to 18 years)**

| Type 1 diabetes | Age groups 18-25, 26-35 and 36-45 (98)
• % ICA+ decreased with increasing age: 61.5%, 29.2% and 16.7%
• % IA-2+ decreased with increasing age: 38.5%, 20.8% and 16.7%
• GADA+ overall increased with increasing age: 64.1%, 60%, 66.4%

Age groups 20-39, 40-59 and ≥60 (135)
• % GADA+ increased with increasing age: 62%, 74% and 83% |
|---|---|
| Type 2 diabetes | There was no difference in GAD+ titre level by age of diagnosis (92) |

Update 2015

**5.3.1.4    Adults and young people (newly diagnosed and 'established' diabetes)**

**Table 24: Percentage of patients with diagnostic markers: studies in mixed population of adults and young people (aged more than or equal to 11 years)**

| Diabetes type | Diagnostic marker, % of patients who were Ab+ (reference no.) | | | | | |
|---|---|---|---|---|---|---|
| | Fasting C-peptide | IAA | ICA | GADA/GAD65+ | IA-2/ICA512 | ZnT8 |
| Type 1 diabetes | - | - | 59.8% (144) | 71.1 (144) | 56.7 (144) | - |
| | - | - | 54% (42) | 77% (42) | 46% (42) | |
| | - | - | - | 59% (126) | 37% (126) | - |
| | - | - | - | 66% (112) | 47% (112) | - |
| | - | - | - | 24.5% (85) | 94.5% (85) | - |
| | - | - | - | 31% (28) | - | - |
| | - | - | 34% (30) | - | - | - |
| | - | - | 62% (112) | - | - | - |
| Mean % | | | 52.5 | 54.8 | 56.2 | - |
| Type 2 diabetes | - | - | 15% (42) | 21% (42) | 15% (42) | - |
| | - | - | - | 6.6% (28) | - | - |
| | - | 10.6% (301) | 3.2% (301) | 4.8% (301) | - | - |
| Mean % | | 10.6% | 9.1% | 10.8 | 15 | - |

**Table 25: Titres of diagnostic markers: studies in mixed population of adults and young people (aged more than or equal to 11 years)**

| Diabetes type | Diagnostic marker, mean titre (reference no.) | | | | |
|---|---|---|---|---|---|
| | Fasting C-peptide | ICA | GADA/GAD65+ | IA-2/ICA512 | ZnT8 |
| Type 1 diabetes | 0.27 nmol/litre (112) | - | - | - | - |
| | 0.295 nmol/litre (144) | - | - | - | - |
| | 0.29 pmol/litre (322) | - | - | - | - |
| Type 2 diabetes | 0.79 pmol/litre (322) | - | - | - | - |
| | Ketosis group: 475.8 pmol/litre (321) | - | - | - | - |
| | Non-ketosis group: 348.2 pmol/litre (321) | - | - | - | - |

**Table 26: Percentage of patients with combinations of diagnostic markers: studies in mixed population of adults and young people (aged more than or equal to 11 years)**

| Diagnostic marker, % (reference no.) | Type of diabetes | | | |
|---|---|---|---|---|
| | Type 1 diabetes | Type 2 diabetes | LADA | MODY |
| Only GAD+ | - | - | - | - |
| Only IA-2A+ | - | - | - | - |
| Only ICA+ | - | - | - | - |
| Only ZnT8+ | - | - | - | - |

Update 2015

| Diagnostic marker, % (reference no.) | Type of diabetes | | | |
|---|---|---|---|---|
| | Type 1 diabetes | Type 2 diabetes | LADA | MODY |
| GAD+ and/or ICA+ | - | - | - | - |
| GAD+ and/or IA-2+ | 68% (79) | - | - | - |
| | 82% (85) | - | - | - |
| Mean | 75% | - | - | - |
| GAD+/IA-2+ | 21% (79) | 17% (42) | - | - |
| | 10% (42) | - | - | - |
| | 27% (126) | - | - | - |
| | 37.8% (85) | - | - | - |
| Mean | 24.0% | 17% | - | - |
| GAD+/ICA+ | 21% (42) | 17% (42) | - | - |
| GAD+/ICA- | - | - | - | - |
| GAD-/ICA+ | - | - | - | - |
| GAD+ /ZnT8+ | - | - | - | - |
| IA-2+/ICA+ | 3% (42) | 11% (42) | - | - |
| IA-2+/ZnT8+ | - | - | - | - |
| ICA+/ZnT8+ | - | - | - | - |
| ICA-/GAD+ and/or IA-2+ | 40% (79) | - | - | - |
| ICA+/GAD- and/or IA-2- | 6% (79) | - | - | - |
| GAD+/IA-2+/ ICA+ | 9% (79) | - | - | - |
| GAD-/IA-2-/ICA- | 19.7% (144) | - | - | - |
| GAD+/IA-2+/ ZnT8+ | - | - | - | - |
| IA-2+/ GAD65- | 10% (126) | - | - | - |
| GAD65+/IA-2- | 32% (126) | - | - | - |

**Table 27: Change in markers with disease duration. Studies in mixed population of adults and young people (aged more than or equal to 11 years)**

| Type 1 diabetes | • % ICA+ was higher in type 1 diabetes with <1 year duration than the whole population (47.7% vs. 33.7%); (30) |
|---|---|
| | Disease duration 0-5 years, 6-13 years and ≥14 years (60) |
| | • % GADA+ decreased with increasing disease duration (70.5%, 65.3% and 42.5%) |
| | • % IA-2A+ decreased with increasing disease duration (53.4%, 42.7% and 26.2%) |
| | • % GADA+ and/or IA-2A+ decreased with increasing disease duration (82.2%, 73.8% and 53.4%) |

**Table 28: Change in markers over time. Studies in mixed population of adults and young people (aged more than or equal to 11 years)**

| Type 1 diabetes | Time intervals: baseline 3, 6, 9, 12, 15, 18, 24, 30 and 36 months (93) |
|---|---|
| | • % fC-Peptide generally decreased over time: 0.24, 0.26, 0.31, 0.27, 0.27, 0.19, 0.17, 0.16, 0.12, 0.19 |
| | Time intervals: baseline (at diagnosis) and 8 years follow-up (69) |
| | • %ICA+ decreased over time: 64% to 24% |
| | • %IA-2+ decreased over time: 46% to 34% |
| | • %GADA+ decreased over time: 76% to 65% |
| | • %C-peptide ≥0.1 nmol/litre increased over time: 60% to 76% |
| | • %C-peptide <0.1 nmol/litre increased over time: 90% to 95% |

Update 2015

| | |
|---|---|
| **New onset Type 1 diabetes (<6 weeks )** | Time intervals: baseline, 2.5 years and 12 years follow-up (55)<br>• %C-peptide decreased over time: 100%, 85.7% and not given.<br>• %GADA+ decreased over time: 95.2%, 85.7% and 11.5%<br>• %IA-2+ decreased over time: 90.5%, 90.5% and 4.9%<br>• %ZnT8+ decreased over time: 85.7%, 76.2% and not given. |
| **Type 1 diabetes (4 years duration)** | Time intervals: baseline, 2.5 years and 12 years follow-up (55)<br>• %C-peptide decreased over time: 100%, 85.7% and not given.<br>• %GADA+ decreased over time: 95.2%, 85.7% and 11.5%<br>• %IA-2+ decreased over time: 90.5%, 90.5% and 4.9%<br>• %ZnT8+ decreased over time: 85.7%, 76.2% and not given. |
| **Type 2 diabetes** | Time intervals: baseline (at diagnosis) and 8 years follow-up (69)<br>• %C-peptide ≥0.1 nmol/litre was similar over time: 21% to 20%<br>• %C-peptide <0.1 nmol/litre was similar over time: 4% to 3% |

**Table 29: Change in markers with age of onset. Studies in mixed population of adults and young people (aged more than or equal to 11 years)**

| | |
|---|---|
| **Type 1 diabetes** | **Study no. 46**<br>Age groups 2-7, 8-13 and >14 years (46)<br>• % of patients who were GADA+ increased with age of onset (35.7%, 47.6%, 58.9%)<br>• % of patients who were IA-2+ decreased with age of onset (43.1%, 53.1%, 40.6%) |

**Table 30: Urinary C-peptide/creatinine ratio (UCPCR) and serum C-Peptide (sCP). Studies in mixed population of adults and young people (aged more than or equal to 11 years)**

| | |
|---|---|
| **Type 1 diabetes** | **Study no. 311**<br>• MMTT 120-minute UCPCR was highly correlated to 90-minute sCP (r=0.97; p<0.0001)<br>• UCPCR ≥0.53 nmol/mmol had 94% sensitivity/100% specificity for significant endogenous insulin secretion (90-minute sCP ≥0.2 nmol/litre).<br>• The 120-minute postprandial evening meal UCPCR was highly correlated to 90-minute sCP (r=0.91; p<0.0001)<br>• UCPCR ≥0.37 nmol/mmol had 84% sensitivity/97% specificity for sCP ≥0.2 nmol/litre.<br>CONCLUSION: UCPCR measured during a mixed meal tolerance test (MMTT) or after a home meal is highly correlated with MMTT sCP. UCPCR testing is a sensitive and specific method for detecting insulin secretion. UCPCR may be a practical alternative to serum C-peptide testing, avoiding the need for inpatient investigation. |

Update 2015

## 5.4 Economic evidence

**Published literature**

No relevant economic evaluations comparing diagnostic tests, C-peptides plus or minus antibodies, to distinguish between a diagnosis of type 1 diabetes, type 2 diabetes and other forms of diabetes were identified.

**Unit costs**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

**Table 31:  Cost of diagnostic tests**

| Diagnostic test | Cost | Reference |
|---|---|---|
| Plasma C-peptide (stimulated) (2 hour MMTT) | £177 | Mark Peakman, Kings College London (personal communication) |
| Plasma C-peptide | £35 | GDG expert opinion |
| Urinary C-peptide/Urinary C-peptide Creatinine Ratio | £10.50 | Mark Peakman, Kings College London (personal communication) |
| GADA, IA-2, ICA512, ZnT8 | £20 – £41 | Mark Peakman, Kings College London (personal communication) |
| ICA (1) | £10.50 | University of Birmingham Clinical Immunology Service – April 2010[125] |
| ICA (2) | £17 | University College London Provider to Provider Tariff 12-13[706] |

## 5.5 Evidence statements

**Clinical**

- Low quality evidence from sixty-two observational studies (case-series and cross-sectional), showed both the percentage of patients with positivity, as well as the actual titre of diagnostic markers (antibodies: GAD, IA-2A, ICA, IAA, and ZnT8; C-peptide; UCPCR) in adults, and adults and young people with type 1 diabetes, type 2 diabetes, LADA, and MODY.
- No studies reported results for IGRP.
- Data were considered for newly diagnosed people (diagnosis within 1 year of the study), separately from those with an 'established' diagnosis.

The results of the studies showed that:
- Antibody tests (in people who were newly diagnosed and those who had an established diagnosis).
  - o Anti-glutamic acid decarboxylase 65 antibody (GAD 65)/anti-glutamic acid decarboxylase antibody (GADA)
    - – Studies reviewed reported a mean prevalence of 54.8 % in mixed populations of adults and young people with type 1 diabetes, 10.8 % in adults and young people with type 2 diabetes, 77.2% in adults with LADA, and 11 % in adults with MODY
  - o Insulinoma-associated autoantibody (IA-2)

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- Studies reviewed reported a mean prevalence of 56.2 % in adults and young people with type 1 diabetes, 15 % in adults and young people with type 2 diabetes, and 32.0% in adults with LADA and 0 % in adults with MODY..
  - o Anti-islet cell antibody (ICA)
    - Studies reviewed reported a mean prevalence of 52.5 % in adults and young people with type 1 diabetes, 9.1 % in adults and young people with type 2 diabetes and 47.8% in adults with LADA, and no data for adults with MODY.
  - o Zinc-transporter antibody (ZnT8)
    - Studies reviewed did not report any data for adults and young people with type 1 diabetes or type 2 diabetes. Studies reported a mean prevalence of 45 % in adults with type 1 diabetes, 22.6 % in adults with type 2 diabetes and 37 % in adults with LADA
  - o Islet-specific glucose-6-phosphatase catalytic subunit (IGRP)
    - No studies reported results for IGRP.
- C-peptide – a low value or absence of C-peptide was considered to be supportive, but not diagnostic, of type 1 diabetes
  - o Plasma C-peptide (fasting or stimulated) – a value of less than 0.2 nmol/litre is used to support a diagnosis of type 1 diabetes, with stimulated values having greater diagnostic accuracy than fasting values
  - o Urinary C-peptide
  - o UCPCR

The evidence indicated that the predictive value of the available tests to support a diagnosis of type 1 diabetes changed with increasing time from first presentation with diabetes. Antibody tests have their greatest positive predictive value in the first year after diagnosis, whilst C-peptide testing has a higher predictive value with increasing time from presentation of diabetes (Borg et al. 2003, Scholin et al. 2004, Hillman et al. 2009, Wenzlau et al. 2010, Sorgjerd et al. 2012).

- Antibody tests (newly diagnosed):
  - o GAD 65/GADA
    - Studies reviewed reported a median prevalence of 69 % in mixed populations of adults and young people with type 1 diabetes, 12.9 % in adults and young people with type 2 diabetes, 84% in adults with LADA, and 1 % in adults with MODY
  - o IA-2
    - Studies reviewed reported a median prevalence of 52 % in adults and young people with type 1 diabetes, 15 % in adults and young people with type 2 diabetes, 43.8% in adults with LADA and 0 % in adults with MODY
  - o ICA
    - Studies reviewed reported a median prevalence of 60 % in adults and young people with type 1 diabetes, 9.1 % in adults and young people with type 2 diabetes and 39.6% in adults with LADA
  - o ZnT8
    - Studies reviewed reported a median prevalence of 45 % in adults with type 1 diabetes, 10.5 % in adults with type 2 diabetes and 37.5% in LADA
  - o IGRP
    - No studies reported results for IGRP.
  - o IAA
    - Studies reviewed reported a median prevalence of 45% in adults and young people with type 1 diabetes,

Update 2015

In addition, the evidence showed that use of a combination of two autoimmune antibody tests increased the specificity of testing (Hosszu et al. 2003, McDonald et al. 2011, Vermeulen et al. 2011, Zhang et al. 2012).

**Economic**

No relevant economic evaluations were identified.

## 5.6    Recommendations and link to evidence

| | |
|---|---|
| | 1. **Diagnose type 1 diabetes on clinical grounds in adults presenting with hyperglycaemia, bearing in mind that people with type 1 diabetes typically (but not always) have one or more of:** <br>• **ketosis** <br>• **rapid weight loss** <br>• **age of onset below 50 years** <br>• **BMI below 25 kg/m$^2$** <br>• **personal and/or family history of autoimmune disease. [new 2015]** <br><br>2. **Do not discount a diagnosis of type 1 diabetes if a person presents with a BMI of 25 kg/m$^2$ or above or is aged 50 years or above. [new 2015]** <br><br>3. **Do not measure C-peptide and/or diabetes-specific autoantibody titres routinely to confirm type 1 diabetes in adults. [new 2015]** <br><br>4. **Consider further specialist investigation involving measurement of C-peptide and/or diabetes-specific autoantibody titres if:** <br>• **type 1 diabetes is suspected but the clinical presentation includes some atypical features (for example, age 50 years or above, BMI of 25 kg/m$^2$ or above, slow evolution of hyperglycaemia or long prodrome) or** <br>• **type 1 diabetes has been diagnosed and treatment started but there is a clinical suspicion that the person may have a monogenic form of diabetes, and C-peptide and/or autoantibody testing may guide the use of genetic testing or** <br>• **classification is uncertain, and confirming type 1 diabetes would have implications for availability of therapy (for example, continuous subcutaneous insulin infusion [CSII or 'insulin pump'] therapy. [new 2015]** <br><br>5. **When measuring C-peptide and/or diabetes-specific autoantibody titres, take into account that:** <br>• **autoantibody tests have their lowest false negative rate at the time of diagnosis, and that the false negative rate rises thereafter** <br>• **C-peptide has better discriminative value the longer the test is done after diagnosis** <br>• **with autoantibody testing, carrying out tests for 2 different diabetes-specific autoantibodies reduces the false negative rate. [new 2015]** |
| **Recommendations** | |
| Relative values of | To determine which markers were the most useful for classifying and distinguishing |

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|---|---|
| different outcomes | between individuals with different types of diabetes, the GDG reviewed the available evidence on the prevalence of C-peptides and antibodies in adults or adults and young people with diabetes, and considered the following factors in order of importance:<br><br>• Correct classification of diabetes, particularly if this was likely to result in a change in treatment (for example, insulin therapy for individuals with type 1 diabetes), or if knowledge of the result was likely to have a significant impact on quality of life.<br><br>   o The clinical importance of obtaining the correct classification of diabetes in an individual<br>   o The impact of the test results on treatment choice<br>   o The consequences of an incorrect clinical diagnosis<br>   o The consequences of not undertaking the diagnostic tests<br>   o The required timing of the tests to give the greatest positive predictive value<br><br>• The impact of using the diagnostic tests in all patients with newly diagnosed diabetes versus their selective use as a confirmatory test in individuals where a diagnosis of type 1 diabetes was suspected clinically before the test.<br><br>• The cost-effectiveness of the diagnostic tests. |
| Trade off between clinical benefits and harms | Benefits and harms will be a function of the ability of the tests correctly to classify diabetes. There are no direct harms apart from the requirement for a blood sample, which causes distress to some children and occasionally to adults. However, misinterpretation of a test, for example, negative antibody testing and/or detection of C-peptide, may lead to misclassification of diabetes as not being type 1, and lead to the mistaken withdrawal of insulin therapy. The GDG therefore concentrated on the discriminatory value of the tests.<br><br>The GDG did not consider any of these tests to be of sufficient predictive accuracy to reliably classify the type of diabetes, and that they should be regarded as supporting information in cases in which standard clinical assessment left room for doubt.<br><br>Where the tests are used, it is necessary to consider timing. The predictive value of the available tests to support a diagnosis of type 1 diabetes changed with increasing time from first presentation with diabetes. Antibody tests have their greatest positive predictive value in the first year after diagnosis, whilst C-peptide testing has a higher predictive value with increasing time from presentation of diabetes (Borg et al. 2003, Scholin et al. 2004, Hillman et al. 2009, Wenzlau et al. 2010, Sorgjerd et al. 2012). The GDG therefore recommended that the guidelines highlighted this information to healthcare workers. |
| Economic considerations | No relevant economic evaluations comparing diagnostic tests, autoimmune antibodies or endogenous C-peptide assessment in the differentiation of types of diabetes were identified.<br><br>The cost of diagnostic tests range from £10.50 for a urine C-peptide to £177 for a plasma C-peptide (stimulated as part of a 2 hour mixed meal tolerance test).<br><br>In making a judgement about the cost-effectiveness of diagnostic testing, the GDG needed to consider not only the quality of life and treatment consequences associated with testing, but also the consequences of not testing. This included consideration of adverse events from misclassification and the impact on overall quality of life. It has been previously reported that in the UK, diabetes type was misclassified in 2.1% of cases.[520] Linear extrapolation of this to the full diabetes population in the UK, an estimated 3 million people, would be equivalent to 60,000 people being misclassified. |

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| | Diagnostic tests only needed a minimal improvement in quality-adjusted life years (QALY) in order to be cost-effective. However, the GDG noted that if every patient with a new diagnosis of diabetes was tested, the majority would experience no or little QALY increase as their management of diabetes might not be changed. Only those who were misclassified and had their management changed would experience a QALY change. The GDG recognised that given the costs of the diagnostic tests and their lack of sensitivity and specificity, their use in all patients with newly diagnosed diabetes could not be recommended. However, the GDG also recognised that the tests might have a cost-effective use in specific cases where uncertainty about the classification of diabetes type remained, and an impact on treatment choice might be made (for example, a switch to insulin therapy in patients classified with type 1 diabetes). |
|---|---|
| Quality of evidence | Sixty-two studies were included in the review; all were observational studies (cross-sectional or case-series). Therefore, the evidence could not be combined in a meta-analysis and the quality assessed by GRADE profiling. Most of the studies reviewed reported results in either type 1 or type 2 diabetes, in isolation, and did not allow analysis of how these tests discriminate between these commoner types and the rarer forms of diabetes.

Following assessment of the evidence, the GDG noted that antibody markers diminish in magnitude with time from diagnosis in individuals with type 1 diabetes, reducing their diagnostic sensitivity. The GDG, therefore, gave greater focus to studies that only included patients with a new diagnosis of diabetes (diagnosis up to 1 year before the study) as this was felt to be the most clinically relevant time to investigate for levels of diagnostic markers. However, the GDG recognised that there would be instances where the investigations might be used several years after diagnosis where classification of diabetes type might be reviewed in individual clinical cases (for example, a diagnosis of MODY in a patient with an assumed diagnosis of type 1 diabetes). |
| Other considerations | The GDG concluded that there is no single test which reliably confirms or refutes the diagnosis of type 1 diabetes. The GDG also noted that the diagnosis of type 1 diabetes is usually made reliably on simple clinical grounds (evidence was not specifically reviewed for this update, but data known to the GDG suggests a 2% misdiagnosis rate). Given this, and the lack of consistent high sensitivity or specificity of the various autoimmune antibodies, the GDG believed it would be inappropriate to use the tests in all patients with newly diagnosed diabetes, as incorrect conclusions might be drawn from the tests.

The GDG recognised that the most important reason supporting the need for the classification of diabetes type in individuals presenting with hyperglycaemia was to ensure that individuals with type 1 diabetes received insulin treatment at an appropriate time to prevent the immediate complication of diabetic ketoacidosis. The GDG also recognised that in the majority of people presenting with a new diagnosis of diabetes, clinical features were utilised to make an initial diagnosis of type 1 or type 2 diabetes (ketosis at diagnosis, rapidity of symptom onset, age at presentation, body mass index and a family history of autoimmune disease). However, there are instances where individuals presenting with a new diagnosis of diabetes might not be readily classified into type 1 or type 2 diabetes due to an overlap of clinical characteristics, and differentiation of diabetes types might become increasingly difficult with increases in body mass index in the population in general. There may also be circumstances where a patient might want to have a diagnosis of type 1 diabetes supported/refuted before investigations for other types of diabetes (for example, genetic testing in patients with a suspected diagnosis of MODY).

The GDG therefore recommended that diagnostic tests would be best employed for |

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individuals where there was uncertainty about the classification of diabetes type, particularly if this might lead to a change in treatment. It was considered important to emphasise that the tests must be interpreted in the context of the clinical picture.

The GDG recognised that urine C-peptide and urine C-peptide/creatinine ratios might be used to assess endogenous insulin production and aid classification of the type of diabetes in an individual. However, further research and evidence is required into their use and timing as a diagnostic test in diabetes before any recommendations can be made on their use.

Finally, the GDG recognised that in the future, knowledge of antibody status confirming autoimmune type 1 diabetes (WHO classification type 1a) may be important in applying immunomodulatory therapies to alter the progress of the disease, but this is still a research question, with no evidence for clinical utlity at the present time.

Please see section 16.10.5 for recommendations from 2004 regarding early care for newly diagnosed adults with type 1 diabetes.

## 5.7 Research recommendation

1. **In adults with diabetes, are diagnostic tests (autoimmune markers and biochemical tests such as urine C-peptide and urine C-peptide/creatinine ratio) useful for defining type 1 diabetes, and if so, what is the optimal time in which they should be measured in order to make the diagnosis?**

2. **In adults with type 1 diabetes, are diagnostic tests (autoimmune markers and biochemical tests such as urine C-peptide and urine C-peptide/creatinine ratio) good prognostic makers of the complications associated with the 1 diabetes and its treatments?**

*Note: We exclude the use of these markers in trials of immune modulation therapy to alter the course of type 1 diabetes, as this is not a current therapeutic option and the literature was not reviewed by the GDG in this revision.*

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# 6 Care process and support [2004]

This section was not updated by the 2015 GDG and is the work of the 2004 GDG, included from CG15.

## 6.1 Scope of this chapter [2004]

It is outside the scope of this guideline to consider service delivery issues. Accordingly no recommendations are made regarding site of care; the emphasis is on the process of care necessary for the individual person with Type 1 diabetes to achieve optimal yet cost-effective outcomes. For example, while it is evidence-based that multidisciplinary team care leads to a reduced rate of complications, and it is known that no health professional alone possess all the necessary skills, no recommendation is made about the membership of such teams, or where they are sited. Nevertheless, where an evidence base exists for an activity associated with a health professional this has been appraised (because it influences the skillmix required), even if it is not used directly in the recommendations.

Equally, a term such as 'diabetes centres' should be read as a group of people working together as a resource with access to appropriate healthcare equipment and supporting all those in the local area providing diabetes care. This should not be interpreted as buildings sited in a primary or secondary care environment, or to sole sites of care. Some items of equipment (telephones, structured records, diabetes recall registers) are necessary components of the process of care (for example retinopathy screening) discussed in other parts of this guideline.

## 6.2 Optimal healthcare processes [2004]

### 6.2.1 Rationale

The management of diabetes is multidimensional, and each dimension multifaceted. Notable dimensions include diagnosis and associated management, preventative long-term care, hospital and emergency management, and detection and management of late-developing complications. With each of these dimensions a number of care areas are found (for example in long-term prevention, glucose control, blood pressure control, risk factor surveillance, blood lipid control and smoking), and for each care area a number of deliverables addressed (for example in blood glucose control: knowledge and basis of targets, injection skills, self-monitoring, dose adjustment, dietary matching, hypoglycaemia management, sick day management) by a number of different members of a multidisciplinary team. This multidimensional care delivery requirement has spawned diverse attempts aimed at ensuring optimal care is available to all those with diabetes. This section of the guideline seeks to examine what evidence is available to support some of those approaches.

### 6.2.2 Evidence review

It was recognised that the systems underlying structured organisation of care (for example diabetes centres) do not easily lend themselves to comparison by higher level studies (RCTs and cohort studies). Some technologies within such systems (for example a foot care information initiative) may on occasion be so approachable, but for the most part such technologies are offered and may only be applicable as part of an integrated care package. Accordingly, for the purposes of evidence review, no limits to study type were placed on the papers sought. Of 348 titles identified, 58 were selected as relevant for critical appraisal.

Additionally the major national and international guidelines were reviewed for consistency of recommendations. As the current question was considered at the end of the guideline process, a

review of generic structures of care already inherent or explicit in agreed recommendations within the current guideline was also made.

Only rarely did the ascertained primary literature distinguish type of diabetes. On occasion, insulin-treated people from both major types of diabetes were considered separately from people with Type 2 diabetes managed without insulin injections. Historically, people using insulin have been managed in specialist care; papers addressing issues of delivery of care by family doctors without reference to insulin-treated diabetes were also excluded from consideration, except in regards of complications surveillance.

### 6.2.3    Evidence statements

**Multidisciplinary care**

The Diabetes Control and Complications Trial (DCCT),[165] and smaller RCTs using improved management to judge the effect on patient outcomes, used multidisciplinary team input (in particular from specialist nurses and dietitians) as part of an integrated package to improve metabolic intermediate outcomes. A Cochrane review[443] of diabetes specialist nurse input identified six heterogeneous studies unsuitable for meta-analysis, and found little evidence of longer term impact on intermediate outcomes. An RCT[615] of the impact of structured team care as compared to usual care showed improved satisfaction and blood glucose control at 6 months. An RCT[691] of the use of diabetes specialist nurses to adjust insulin doses over the telephone showed improved blood glucose control (**Ib**).

A nurse specialist approach has been justified by a number of before and after studies and case series with such input (**II**).[90,286,385,412,759]

A number of studies of variable quality address the impact of inclusion of podiatrists compared to normal care within what is then usually called a diabetes foot care team. These studies included one RCT showing more patient knowledge and less callosities at 1 year, and a controlled study[153] (it is unclear whether that study is randomised) showing less foot ulceration (**Ib**).

A number of historically-controlled or descriptive studies support this approach, mainly reporting on patient preference outcomes (**IV**).[40,135,229,412]

The current guideline and all examined guidelines advise the use of members of a multidisciplinary team or more specifically nurses with training in teaching skills and adult education in a number of aspects of patient education, and formally trained dietitians and podiatrists within the specifically relevant areas of diabetes care (**IV**).

**Annual review**

No RCTs address the concept of integrated annual review. Newly- implemented structured annual review has been subject to a descriptive review,[591] suggesting improved satisfaction with care and improved patient motivation. Few full-length descriptions of the review process are available,[85] most references being editorials and letters (**IV**).

The current guideline suggests annual surveillance of a number of potentially developing late complications (as do all other guidelines for the most complications). The International Diabetes Federation's European guideline recommends integration of these activities into one patient visit.[341] Annual review also is the basis of many quality control structures proposed for diabetes care,[262] including (implicitly) that of the UK Audit Commission (**IV**).

**Diabetes registers**

A series of descriptive papers appear to demonstrate the feasibility of establishing population-based and clinic-based diabetes registers, with varying densities of information.[51,98,99,193,280,332,369,376,382,390,717] A system of database-driven recall for complications surveillance is implicit in the recommendations for annual complications surveillance of this and published guidelines. Issues of data security and confidentiality are not reported to have proved to be problematic obstructions to the deployment of diabetes registers (**IV**).

**Diabetes centres and structured care**

Most papers in this area are descriptive, and there is inevitable overlap with deployment of multidisciplinary teams and provision of diabetes information and foot care. Using historical controls a study[161] suggests improved blood glucose control, while another non-randomised study which suggests improved survival (presumably mainly in people with Type 2 diabetes (**IIb**).

**Structured records and care cards**

Although papers were ascertained addressing these areas, the papers were descriptive with no useful analysis of patient-related outcomes (**IV**).[88,158,194-197,214]

**Electronic patient records and computer data analysis**

A number of descriptive papers were identified,[113,260,564,660] suggesting such approaches can be feasible and have utility, but not demonstrating comparative advantage to traditional approaches (**IV**). However when such records were used to send judgmental letters to people with diabetes,[671] randomising sites of care, intermediate outcomes were significantly improved (probably mainly in people with Type 2 diabetes) (**Ib**).

**Telemedicine**

A number of approaches to medical care without direct patient contact are described in the literature. One RCT of a telecare system for insulin[70] provided equivalent control at reduced cost, while another study[691] using nurses resulted in improved blood glucose control (**Ib**).

In more rural and remote situations telemedicine can similarly provide apparent time and cost savings where images of foot problems[475] and eye photographs[145] need to be reviewed by specialists (**Ib**).

**Inpatient care**

Three papers using historical controls or randomised controls address the value of multidisciplinary teams with a specialist interest in diabetes management in the care of inpatients on non-diabetes wards.[391,430,471] Reduced length of inpatient stay is consistently reported. One study suggests

improved glucose control.[391] One study, also using historical controls, addresses length of stay in a developing country in newly-diagnosed people with diabetes, showing much reduced stays with multidisciplinary team input (**Ib/IIa**).

**Guidelines**

No literature on the deployment or impact of diabetes guidelines was identified.

### 6.2.4 Health economic evidence

Two potentially useful papers consider the type of treatment facility used to deliver care to those with Type 1 diabetes.[567,665] One German study[567] found that the treatment facility (polyclinics, specialist clinics or general practitioners) makes no difference to diabetes-specific knowledge when this was controlled for age, sex and education. One UK study[665] found no difference between hospital- and general practice-based care on a range of outcome measures for metabolic control, satisfaction with treatment or beliefs about diabetic control for a mixed diabetic population. Some differences were observed in the surveillance for complications, with more frequent testing in integrated care. Whilst costly, it is worth noting that fewer patients defaulted from general practice-based care than conventional care, although this cannot be established on the basis of this study.

One UK-based study[156] suggested that the provision of a hospital-based diabetes specialist nurse lowered the cost per patient admission without producing a significant difference in readmission, quality of life, or patient satisfaction.

**Consideration**

The group endorsed the approaches suggested by the evidence, but noted that attempts to implement some of the recommendations in the past had been inhibited by funding difficulties. This, however, was not felt to be a barrier to reiterating the health gains to be obtained. It was noted that recent publications (beyond the cut-off date of the searches) supported some of the recommendations further, including those relating to specialist nurses. The UK's national service framework for diabetes was noted to have endorsed diabetes registers. The group recognised the lack of any kind of formal evidence relating to walk-in, telephone-request, and out-of-hours services.

### 6.2.5 Recommendations

6. **Advice to adults with type 1 diabetes should be provided by a range of professionals with skills in diabetes care working together in a coordinated approach. A common environment (diabetes centre) is an important resource in allowing a diabetes multidisciplinary team to work and communicate efficiently while providing consistent advice. [2004]**

7. **Provide adults with type 1 diabetes with:**
   - **open-access services on a walk-in and telephone-request basis during working hours**
   - **a helpline staffed by people with specific diabetes expertise on a 24-hour basis**
   - **contact information for these services. [2004]**

8.  **Set up an individual care plan jointly agreed with the adult with type 1 diabetes, review it annually and modify it taking into account changes in the person's wishes, circumstances and medical findings, and record the details. The plan should include aspects of:**

    - **diabetes education, including nutritional advice (see 'Structured education programmes', Section 7.2, and 'Dietary management', Section 7.3)**
    - **insulin therapy, including dose adjustment (see 'Insulin regimens', Section 9.2, and 'Insulin delivery', Section 9.3)**
    - **self-monitoring (see 'Self-monitoring of blood glucose', Section 9).**
    - **avoiding hypoglycaemia and maintaining awareness of hypoglycaemia**
    - **for women of childbearing potential, family planning contraception and pregnancy planning**
    - **arterial risk factor surveillance and management (see 'Arterial risk control', Chapter 14)**
    - **complications surveillance and management (see 'Management of complications', Chapter 16)**
    - **means and frequency of communication with the diabetes professional team**
    - **follow-up consultations, including frequency of review of HbA1c levels and experience of hypoglycaemia, and next annual review. [2004, amended 2015]**

9.  **Use population, practice-based and clinic diabetes registers (as specified by the [National service framework for diabetes](#)) to assist programmed recall for annual review and assessment of complications and vascular risk.[2004]**

10. **The multidisciplinary team approach should be available to inpatients with type 1 diabetes, regardless of the reason for admission (see 'Hospital admission and intercurrent disease', Section 15.1.6). [2004]**

## 6.3   Support groups [2004]

### 6.3.1   Rationale

As having Type 1 diabetes can have a major impact on lifestyle and self-esteem, it would appear that support groups could have a role in providing for some needs outside the professional environment and even separately from immediate carers. The range of such potential input is large and might stretch from simply fulfilling a need for belonging, through to helping with diabetes-related financial problems (such as insurance), and even providing a further source of diabetes related information.

Coping with diabetes, or any other condition, is influenced not only by psychological characteristics of the individual but also by social relationships (e.g. support and communication by healthcare team, family and friends). Informal interpersonal variables, such as social resources and support, have been found to be associated with better diabetes self-management,[298,364] family environment,[218,278,625] and marital interaction.[52] A medical condition is only one aspect that affects the make-up of an individual's personal identity, and for some may be perceived as a minor factor compared to their environmental and social circumstances.

A 'support group' is defined in this guideline as a group of people with Type 1 diabetes that comes together to provide support to themselves and others in their locality. Members are usually unpaid and many will be supported under the auspices of national (or local) voluntary organisations. Support groups have become commonplace throughout health and social care.

Patients and carers may choose to contact or be involved with support groups to gain information and support to benefit their own needs, or with a wider altruistic aim of helping other people within

the local community. It was not possible to find specific research identifying patient and carer preferences for support groups, or indeed to identify specific groups or types of people who may benefit more than others. Some people attend meetings of groups regularly whilst other individuals are reassured by being aware of a group's existence and the opportunity to contact the group at a later date if problems arise and/or support is required. Preferences are dependent on what stage people are at in their lives and what information is taken (or needs to be taken) on board.

## 6.3.2 Evidence statements

The Diabetes Attitudes, Wishes and Needs (DAWN) questionnaire study[8] highlighted that emotional support, along with family support, was a key factor in how well people with diabetes manage their condition, with support networks being considered at least as important as the medication they take in helping them manage their diabetes. Interim results also indicate that people who do not have access to a community of support, especially the young or elderly living alone, may be less likely to be concordant with their medication regimes, putting them at risk of inadequate control of their diabetes (**III**).

There are still significant numbers of people emerging from the confirmation of a diagnosis who are under informed and unsupported.[174] Qualitative research of various designs examining the views and experiences of people with diabetes and carers has identified that many perceived benefits exist from meeting other people with diabetes. It has helped many to overcome the feelings of isolation and is seen as an opportunity to talk to others going through the same experience (**IV**).[314]

Research evaluating the effectiveness of support groups for patients and carers, across numerous conditions and groups (not necessarily diabetes) has shown specific benefits including:

- psychological and emotional benefits[6] including lower pain perception, and improved ability to cope with stress[174,384,697]
- reduction of carers' burdens and stresses[404,537]
- improvement in quality of life[275,465]
- improved self-care through health promotion strategies which have been helpful in smoking cessation and management of chronic conditions[215,490]
- improved access to health service provision[528]
- reduced isolation, overcoming depression and loss of self-esteem[314]
- better understanding of conditions, symptoms and healthcare systems through education and information[697] (**III**).

The Diabetes UK network of support groups recorded 175,426 members in July 2003, with around 7% under the age of 20 years and around 30% aged 70 years or over. Around 40% had paid for annual adult membership, 50% had a reduced rate membership (including children), and 10% had chosen life membership. The Diabetes UK Careline is, at the time of writing, one of the busiest sources of information for all people with Type 1 diabetes in the UK. In 2002, Careline were contacted 40,747 times (81% telephone, 13% e-mail, 6% post). The five most frequent topics of enquiry recorded were[131,230]:

- diet
- insulin
- medicines other than insulin
- new diagnosis
- travel (**III**).

**Health economic evidence**

Two studies were identified as potentially useful in this area.[36,305] As neither paper included cost information, the cost-effectiveness of support interventions cannot be ascertained.

### 6.3.3   Recommendations

11. At the time of diagnosis and periodically thereafter, provide adults with type 1 diabetes with up-to-date information about diabetes support groups (local and national), how to contact them and the benefits of membership. [2004]

## 6.4   Quality audit and monitoring [2004]

### 6.4.1   Rationale

It is generally accepted now that any system delivering a product, including healthcare systems, can benefit from review of its performance. The diabetes care espoused by this guideline is both complex and systematic, and thus lends itself to the kind of data collection needed for quality development. That very complexity, however, means that monitoring the structures, process and outcomes of all sectors can seem overwhelming, necessitating consideration of how limited monitoring activity can be undertaken without distorting the areas gaining attention for improvement. Monitoring of quality of life would seem *a priori* to be of particular importance in diabetes care, but presents its own difficulties of data acquisition and of analysis of temporally different outcomes.

Audit criteria are suggested in Section 3.3 of this guideline to assist local users in promoting implementation and monitoring ongoing improvements in process and outcome. They have been informed where possible by existing validated measures, principally those of the National Centre for Health Outcome Development. [320]

# 7 Education programmes and self-care

The 2015 GDG updated the evidence and recommendations for structured education programmes (Section 7.2). Evidence reviews and recommendations for carbohydrate counting and glycaemic index (GI) diets evidence reviews have been added to the dietary management section (Section 7.3). Other aspects of education and self-care were not updated (dietary management other than carbohydrate counting and GI diets, physical activity and cultural and individual lifestyle). The content from the 2004 guideline that has been replaced by the new evidence reviews can be found in Appendix S.

## 7.1 Rationale [2004]

Having diabetes involves acquiring a great range of new skills and knowledge, including insulin therapy, dietary changes, self-monitoring, hypoglycaemia, jobs, travel, physical exercise, coping with concurrent illness, foot care, arterial risk control, avoiding complications. The history of education and information giving in diabetes care goes back to the earliest dietary interventions several centuries ago, and the use of education professionals to impart skills associated with insulin therapy dates from the time of discovery and isolation of insulin. Accordingly patient education is a true cornerstone that enables self-management of diabetes, and most diabetes management is self-management. Review of other parts of this NICE guideline will reveal that education and information giving are parts of nearly all of them, from enabling patient choice in determining features of self-management, to acquisition of skills needed to perform tasks and make judgements, to self-care where high risk complications have developed, and to skills in handling healthcare professionals to ensure that issues of importance to the person with Type 1 diabetes are addressed.

## 7.2 Structured education programmes [updated 2015]

### 7.2.1 Introduction

People with type 1 diabetes have an absolute need for insulin replacement therapy. The body's requirement for insulin varies greatly by time of day, food eaten, energy expended, state of health and other factors. Historically, people with type 1 diabetes were prescribed specific insulin regimens and a lifestyle to match it, with times of eating and quantities of food eaten made as reproducible as possible. Modern management aims to support a more flexible lifestyle with minimal restrictions as a route to optimal biomedical outcomes and good quality of life. In order to achieve these aims, the person with diabetes needs knowledge and skills traditionally taught to healthcare professionals.

Therapeutic education aims to help people with long-term conditions better manage their treatment and, in the case of diabetes, adapt the diabetes control to the constant changes in daily life.[49] "Structured education" is a method of therapeutic education defined as "a planned and graded process that facilitates the knowledge, skills and ability for diabetes self-management and empowers individuals to live healthily, to maintain and improve their quality of life, and assume an active role in their diabetes care team".[220] The essential requirements of a structured education programme are that it has a philosophy that guides its delivery; a formal, written curriculum; appropriately trained educators to deliver it; and that it is both quality assured and regularly audited.[220] The Department of Health and the Diabetes UK Patient Education Working Group stated that any programme should be evidence-based, should suit the needs of the individual with specific aims and learning objectives, and be able to support the patient plus his or her family and carers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes.[356] Programmes for people with type 1 diabetes should empower individuals to make day-to-day decisions about their diabetes treatment and lifestyle, with the best outcomes for their health.[505] It is recommended that structured patient education is made

available to all people with diabetes at the time of initial diagnosis and then, as required on an ongoing basis, based on formal, regular assessment.[505]

Multiple packages offer structured education for adults with type 1 diabetes in the UK.[263] The question addressed in this chapter is "In adults with type 1 diabetes, what is the most effective structured education programme?"

### 7.2.2 Review question: In adults with type 1 diabetes, what is the most effective structured education programme?

For full details see review protocol in Appendix C.

**Table 32:  PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
|---|---|
| Intervention(s) | Structured education programme |
| Comparison(s) | • Other education programmes<br>• Usual care/no treatment<br>• SMBG |
| Outcomes | • HbA1c<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported<br>• Hospital admissions<br>• Hypoglycaemia unawareness<br>• Quality of life – measured by DQoL, DSQoL, PAID, HADS, fear of hypoglycaemia, anxiety, depression<br>• Adverse events<br>• Knowledge<br>• Adherence |
| Study design | RCTs |

### 7.2.3 Clinical evidence

We searched for randomised trials comparing the effectiveness of structured education programmes versus other education programmes or usual care/no treatment in adults with type 1 diabetes. Studies cited in the original 2004 type 1 diabetes guideline[506] were also assessed and included where appropriate.

The original 2004 NICE guideline based the main bulk of its review of the evidence for education on the 2002 unpublished report[579] of the HTA published in 2003[443] that looked at structured education in diabetes. Therefore, any RCTs in the HTA that were type 1 diabetes-specific and looked at structured education programmes were included in our review. The 2004 NICE guideline also included three additional RCTs which assessed education programmes [162,392,427] and these were therefore included in our review.

In 2003, NICE published a TA (TA60)[505] on the use of patient education models for people with type 1 and type 2 diabetes. As for the 2004 NICE type 1 diabetes guideline, this was based on the 2002 unpublished report[579] of the HTA published in 2003[443], as well as some additional studies. Of the additional studies found, only 2 RCTs were reported that assessed education in type 1 diabetes. One of these RCTs was not suitable for our review and thus, would have been excluded because it looked at intensive insulin treatment in combination with an educational component (SDIS study)[587] rather than the effects of an intensive/structured education programme. The second RCT[684] met our inclusion criteria and was therefore included in our review

From our updated literature search, we found 10 relevant RCTs that had been published since the original 2004 guideline and these were included in our review.

Overall, fifteen RCTs were included in our review (DAFNE study[31], BGATTIII study[624], BITES study[245], [162]HAATT study[139], HYPOS study[300], [392,427]BGAT study[662], Rossi 2010[604], Terent 1985[684], Trento 2005[700],Trento 2011[701]PRIMAS,[301] Rossi 2013[605]). Evidence from the included studies are summarised in Table 33. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence in Appendix G.

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**Table 33: Summary of studies included in the review**

| Study | Intervention | Content | Delivered by | Comparison | CHO counting component | Population | Inclusion: with IAH or frequent severe hypoglycaemia only | Follow-up |
|---|---|---|---|---|---|---|---|---|
| BGAT (Snoek 2008) [662] | BGAT<br><br>Psychoeducational programme | Prevent and correct in a timely fashion, extreme blood glucose excursions<br>Done by improving symptom discrimination and understanding of the interaction between insulin, food intake and physical activity | Diabetes nurse educators and clinical psychologist | CBT | X | n=86<br>Type 1 diabetes<br>18 years duration | X | 6 week course (1/week)<br>3, 6 and 12 months follow-up |
| BGAT III study 2005 [624] | BGATIII<br><br>Psychoeducational programme | Using signals to accurately recognise when blood glucose is too high or low<br>Signals: physical symptoms, disruptions in cognitive and motor performance, mood changes<br>Predicting when blood glucose likely to rise or fall based on - previous insulin injections, food consumption, physical exercise | Physician-psychologist team | Self-help group | X | n=138<br>Type 1 diabetes on intensified insulin regimen<br>23 years duration | Mostly patients with frequent hypoglycaemic episodes | 8 week course (1 hour/week)<br>6 and 12 months follow-up |
| BITES study 2008 [245] | BITES<br><br>Psychoeducational programme | Problem solving; psychoeducational.<br>Fictitious individual with type 1 diabetes throughout the course who they mentored throughout and discussed helping them with change.<br>Specific content details not given | DSN and SDD | Usual care | X | n=114<br>Type 1 diabetes<br>19.5 years duration | X | 6 week course (2.5 days total)<br>3, 6 and 12 months follow-up |

**Update 2015**

| Study | Intervention | Content | Delivered by | Comparison | CHO counting component | Population | Inclusion: with IAH or frequent severe hypoglycaemia only | Follow-up |
|---|---|---|---|---|---|---|---|---|
| DAFNE study 2002[31] | Immediate DAFNE<br><br>Educational training course | CHO intake and matching insulin<br>Adjusting insulin to suit lifestyle<br>Confidence and autonomy | DSNs and dietitians | Delayed DAFNE (waiting list/usual care) | Yes - in intervention group | n=169<br>Type 1 diabetes<br>16 years duration | X | 5 day course<br>6 months follow-up |
| deWeerdt 1991[162] | Education<br><br>Included motivational aspects | Highly structured<br>Video film, a book, and some practice materials were used as part of the programme.<br>The lessons also had a motivational function<br>Content details not given | Trained nurse, dietitian or patient with diabetes | Usual care | X | n=558<br>Insulin-treated diabetics<br><br>13 years duration | X | 4 week course (3 hours/week)<br>6 months follow-up |
| HAATT study 2004[139] | HAATT + SMBG<br><br>Psychoeducational programme | Anticipation, prevention, recognition and treatment of hypoglycaemia<br>Insulin kinetics and how to anticipate when their insulin action is at its peaks and nadir<br>CHO counting and matching insulin and exercise<br>Demands of physical activity/insulin adjustment | Physician | SMBG | X | n=60<br>Type 1 diabetes and ≥2 severe hypo episodes in past year<br>14 years duration | Yes | 7 week/2 months course (once/week)<br>6, 13 and 18 months follow-up |
| HYPOS study 2007[300] | HyPOS<br><br>Bio-psychosocial training/education programme | Causes and correct treatment of hypoglycaemia Unawareness<br>Avoiding hypoglycaemia.<br>Symptoms of hypoglycaemia.<br>Detection of hypoglycaemia<br>Coping with activities that may | Diabetologist and diabetes educators | Standard education | Yes - in comparison group only | n=164<br>Type 1 diabetes and hypoglycaemia | Yes | 5 week course (90 minutes/week)<br>6 months follow-up |

| Study | Intervention | Content | Delivered by | Comparison | CHO counting component | Population | Inclusion: with IAH or frequent severe hypoglycaemia only | Follow-up |
|---|---|---|---|---|---|---|---|---|
| | | pose risk of hypoglycaemia | | | | 20 years duration | | |
| Korhonen 1983[392] | Intensive education<br><br>Group and individual | Education programme<br>Details not given<br>Instructed to adjust insulin dose during sick days and in other special situations and call the nurse whenever had problems from diabetes. | physician, dietitian, and teaching nurse | Traditional education | X | n=77<br>Type 1 diabetes (insulin-dependent)<br>8 years duration | X | 5 day intense course<br>1 year follow-up |
| Lennon 1990[427] | Education<br><br>Motivational and behavioural features | aspects of diabetes treatment and technical skills<br>diet, insulin, hypoglycaemia, diabetic control, exercise and illness,<br>ketones, hyperglycaemia, new diet,<br>complications of diabetes,<br>new developments in research,<br>practical problems in self-management | Not given – individual and group sessions | Usual care | X | n=74<br>Insulin treated Type 1 diabetes<br>13.7 years duration | X | 1 year course (once a month meeting)<br>No additional follow-up |
| PRIMAS study (Hermanns 2013) [301] | PRIMAS education programme<br><br>Group education | CHO counting.<br>Self-management/empowerment approach.<br>Detection and treatment of acute complications | Diabetes educators | DTTP education programme | Yes – in both groups | n=160<br>Type 1 diabetes<br>19 years duration | X | 6 weeks course<br>6 months follow-up |
| Rossi 2010[604] | CHO counting education | CHO counting programme - further details not given | Not mentioned | Diabetes interactive | Yes – in both groups | n=130<br>Type 1 | X | 3 month course |

| Study | Intervention | Content | Delivered by | Comparison | CHO counting component | Population | Inclusion: with IAH or frequent severe hypoglycaemia only | Follow-up |
|---|---|---|---|---|---|---|---|---|
| | programme<br><br>Standard educational approach | | | diary telemedicine | | diabetes<br>16 years duration | | (days/week not mentioned)<br>6 months follow-up |
| Rossi 2013 [605] | Standard educational approach | Standard education programme - further details not given | Not mentioned | Diabetes interactive diary telemedicine | Yes – in DID unclear in educated (but likely as for Rossi 2010 study) | n=127<br>Type 1 diabetes<br>15.5 years duration | X | Length of course not stated.<br>6 months follow-up |
| Terent 1985[684] | Education<br><br>Formal education | Explain interplay between food consumption, blood glucose levels, insulin and urinary glucose. Excretion<br>hypo- and hyperglycaemia, footcare, injections, and urine testing techniques<br>Social aspects<br>Encouraged to test urine for glucose and ketone bodies | physicians and dietitian | Standard therapy | X | n=19[a]<br>Type 1a diabetes<br>9 years duration | X | 6 month course (days/week not mentioned)<br>6, 12 and 18 months follow-up |
| Trento 2005[700] | Structured education programme (group care)<br><br>Group education | differences between type 1 diabetes and type 2 diabetes<br>principles of nutrition and classification of nutrients; composition of food and food exchanges<br>physical exercise and adjusting | Pyschopaed agogist | Usual care (1:1 consultations every 2-3 months) | X | n=62<br>Type 1 diabetes<br>16 years duration | X | 18-27 months (9 education sessions; one every 2-3 months) |

| Study | Intervention | Content | Delivered by | Comparison | CHO counting component | Population | Inclusion: with IAH or frequent severe hypoglycaemia only | Follow-up |
|---|---|---|---|---|---|---|---|---|
| | | insulin<br>hypoglycaemia and hyperglycaemia – causes, recognition, management and informing relatives and friends<br>areas of insulin injection and their rotation<br>retinopathy, neuropathy, low-level (micro) albuminuria and nephropathy (self-care, when and how to screen);<br>hypertension and CV aspects.<br>HbA1c<br>day-to-day problems | | | | | | 6 additional visits over the remainder of the 3 years)<br>3 years follow-up |
| Trento 2011[701] | CHO counting programme<br><br>Programme included cognitive and psychomotor abilities | CHO counting<br>Hypoglycaemia, recognition and treatment<br>motivational aspects, acceptance of diabetes, psychosocial problems, and coping strategies<br>included cognitive and psychomotor abilities | Doctor, psychopedagogist, dietitian and nurse | Continuing education programme | Yes - in intervention group | n=56<br>Type 1 diabetes<br>22 years duration | X | 8 sessions every 3-4 months<br>30 months follow-up |

Abbreviations: IAH, impaired awareness of hypoglycaemia.

(a) This study had 2 levels of randomisation of n=37 patients. First randomisation: education versus standard therapy; second randomisation: education plus SMBG versus education, versus SMBG versus Standard therapy. Data used in this review are for the n=19 patients who remained in the education versus standard therapy groups throughout the entire study period.

**Outcomes**

Conference abstracts were excluded for this review question because there was sufficient RCT data found for the critical outcomes. However, there was no data reported in any of the studies for the following outcomes:

- HADS score
- Adverse events

Outcomes were grouped into the following categories based on time-points:

- less than or equal to 6 months (or the one nearest to 6 months if multiple time-points are given in the study)
- more than 6 months (or the longest one if multiple time-points are given in the study).

**Heterogeneity**

For the outcomes of HbA1c%, at both 6 and 12 months, when data were pooled into the meta-analysis, there was significant heterogeneity (p<0.1 and $I^2$ more than 50%) between the trials (see GRADE profiles in Appendix I and the forest plots in Appendix J). Three pre-specified subgroup analyses were conducted in order to try to explain the heterogeneity, based on:

1. The type of comparison used in the studies - because the studies varied in the type of comparison group that was used (see forest plots Figure 2 and Figure 29 in Appendix J).
1. Whether the structured education programme included a carbohydrate counting component (see forest plots Figure 3 and Figure 30 in Appendix J).
2. Whether the patients recruited in the trials included those with impaired awareness of hypoglycaemia (IAH) and/or severe hypoglycaemia or not (see forest plots Figure 4 and Figure 31 in Appendix J).

**Less than or equal to 6 months**

At less than or equal to 6 months (see Figure 2 in Appendix J) the heterogeneity could be partly explained by the type of comparison used (test for subgroup differences shows p=0.005). The analysis showed that structured education was favoured in lowering HbA1c when compared with usual care, but there was no difference in HbA1c when structured education was compared with other education groups or types of support.

Additionally, when using the pre-specified subgroup analysis of whether the structured education included a carbohydrate counting component (see Figure 3 in Appendix J), the heterogeneity could be partly explained (test for subgroup differences shows p=0.0002). The analysis showed that structured education programmes that included carbohydrate counting were favoured in lowering HbA1c when compared with usual care, but there was no difference between structured education and the control group in HbA1c when only the control group had carbohydrate counting, when both the groups included carbohydrate counting, and when neither of the groups included carbohydrate counting.

An additional subgroup analysis was also performed to determine whether trials that included only people with problematic hypoglycaemia (impaired awareness and/or a history of severe hypoglycaemia versus trials with unselected type 1 diabetes patients or from which people with problematic hypoglycaemia were excluded could explain the heterogeneity (see Figure 4 in Appendix J). This analysis showed that heterogeneity could not be explained by the inclusion of only hypoglycaemic patients in the study (test for subgroup differences shows p=0.05 and $I^2$ =74.8%).

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**More than or equal to 12 months**

At more than or equal to 12 months (see Figure 29 in Appendix J) the heterogeneity could be explained by the type of comparison used (test for subgroup differences shows p<0.00001). The analysis showed that structured education was favoured in lowering HbA1c when compared with usual care, but was worse when compared with other education groups or types of support (that is, other education groups or types of support were better for lowering HbA1c).

Additionally, when using the pre-specified subgroup analysis of whether the structured education included a carbohydrate counting component (see Figure 30 in Appendix J), the heterogeneity could be explained (test for subgroup differences shows p<0.00001). The analysis showed that structured education programmes that included carbohydrate counting were worse in lowering HbA1c when compared with usual care (but, this was due to a single study, Trento 2011, of only 56 patients), but when there was no carbohydrate counting in either the structured education programmes or the control groups, structured education was favoured in lowering HbA1c.

The subgroup analysis to see whether trials that included only patients with problematic hypoglycaemia explained the heterogeneity was not conducted, as all the trials at 12 months were in unselected type 1 diabetes patients.

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**Table 34: Structured education programme versus control - usual care or other type of education (less than or equal to 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Structured education | Control event rate (per 1000 patients) or final value in control group<br><br>Control |
|---|---|---|---|---|---|
| HbA1c, % | 8 studies (n=1396) | Not serious | VERY LOW | MD 0.15 lower (0.27 to 0.03 lower) | 8.0 final value in control group |
| HbA1c, % - MD only given | 1 study (n=114) | Serious | VERY LOW | MD 0.06 lower (0.32 lower to 0.2 higher) | Not given |
| HbA1c, % - SD not given | 1 study (n=60) | Very serious | VERY LOW | Data provided: HAATT 8.0% and SMBG 8.1% | |
| Severe hypoglycaemia (episodes/study) | 2 studies (n=269) | Very serious | VERY LOW | 14 more per 1000 (from 36 fewer to 121 more) | 81 |
| Severe hypoglycaemia (episodes/6 months) | 1 study (n=111) | Not serious | LOW | MD 0.94 lower (1.7 to 0.18 lower) | 1.07 |
| Severe hypoglycaemia (episodes/month) | 1 study (n=558) | Not serious | LOW | MD 0.05 higher (0.04 lower to 0.14 higher) | -0.1 |
| Severe hypoglycaemia (episodes/patient/year) | 3 studies (n=433) | Not serious | HIGH | MD 0.04 lower (0.37 lower to 0.29 higher) | 1.2 |
| Severe hypoglycaemia (episodes/person) - SD not given | 1 study (n=60) | Very serious | VERY LOW | Data provided: HAATT 0.4 and SMBG 1.7; p=0.03 | |
| ADDQoL - impact | 1 study (n=139) | Not serious | LOW | MD 0.4 higher (0.34 lower to 0.46 higher) | 0 |
| ADDQoL - impact and importance | 1 study (n=146) | Not serious | LOW | MD 0.1 lower (0.36 lower to 0.16 higher) | 1.1 |
| DTSQ - total satisfaction | 1 study (n=139) | Not serious | LOW | MD 8.76 higher (7.09 to 10.43 higher) | 22.8 |
| SF-36 physical | 1 study (n=130) | Not serious | MODERATE | MD 0.4 lower (2.53 lower to 1.73 higher) | 1.0 |
| SF-36 physical health - MD only given | 1 study (n=60) | Very serious | VERY LOW | MD 2.2 higher (0.7 lower to 5 higher); p=0.14 | |
| SF-36 mental | 1 study (n=130) | Not serious | MODERATE | MD 5 higher (1.09 to 8.91 higher) | -0.8 |

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| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000 patients) or final value in control group |
|---|---|---|---|---|---|
| | | | | Structured education | Control |
| Hospital admissions | 1 study (n=130) | Not serious | MODERATE | 0 admissions in both groups | |
| Symptomatic hypoglycaemia (perceived frequency, scale 0-6) | 1 study (n=139) | Serious | VERY LOW | MD 0.24 lower (0.67 lower to 0.19 higher) | 2.4 |
| Hypo unawareness (more recognition of low blood glucose, % of patients) | 1 study (n=111) | Serious | VERY LOW | MD 12.40 higher (2.41 to 22.39 higher) | 45.8 |
| Hypo unawareness (HAQ) | 1 study (n=146) | Serious | VERY LOW | MD 0.3 lower (0.67 lower to 0.07 higher) | 0.6 |
| Hypo unawareness (change in Clarke score, max 7) | 1 study (n=160) | Not serious | HIGH | MD 0.1 lower (0.52 lower to 0.32 higher) | 1.2 |
| Hypo unawareness (VAS) – SD not given | 1 study (n=146) | Very serious | VERY LOW | MD 0.8 higher (0.2 to 1.4 higher); p=0.05 | 5.3 |
| Hypoglycaemia unawareness (%detection of low blood glucose) – no SD given | 1 study (n=60) | Very serious | VERY LOW | Data provided: HAATT 70% and SMBG 55%, p=0.005 | |
| Fear of hypo (Hypo fear survey) - Worry | 1 study (n=111) | Not serious | LOW | MD 0.60 higher (3.42 lower to 5.12 higher) | 14.6 |
| Fear of hypo (Hypo fear survey) - Behaviour | 1 study (n=111) | Serious | VERY LOW | MD 2.10 higher (0.63 lower to 4.83 higher) | 11.6 |
| Fear of hypo (change in DSQoL) | 1 study (n=127) | Not serious | MODERATE | MD 5.34 lower (12.11 lower to 0.23 higher) | -3.91 |
| Fear of hypo (Hypo fear survey) – Worry – MD only given | 1 study (n=111) | Very serious | VERY LOW | MD 2.4 lower (7.2 lower to 2.4 higher); p=0.33 | |
| Fear of hypo (Hypo fear survey) – Behaviour – MD only given | 1 study (n=111) | Very serious | VERY LOW | MD 0.01 lower (2.9 lower to 2.9 higher); p=0.99 | |
| Depression (CES-D) | 2 studies (n=306) | Not serious | MODERATE | MD 0.2 lower (0.85 lower to 1.45 higher) | 6.2 |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Structured education | Control event rate (per 1000 patients) or final value in control group<br><br>Control |
|---|---|---|---|---|---|
| Depression (CES-D) - no SD given | 1 study (n=86) | Very serious | VERY LOW | Data provided: BGAT 15.8 and Control 13.5, p=0.74 | |
| Anxiety (STAI) | 1 study (n=146) | Not serious | LOW | MD 0.50 higher (1.54 lower to 2.54 higher) | 37.1 |
| PAID | 1 study (n=146) | Not serious | LOW | MD 0.70 lower (4.45 lower to 3.05 higher) | 24 |
| PAID - no SD given | 1 study (n=86) | Very serious | VERY LOW | MD 0 higher (0 to 0 higher) | 38.7 |
| Knowledge, % correct answers | 1 study (n=77) | Not serious | LOW | MD 7.50 higher (6.63 to 8.37 higher) | 72 |
| Knowledge (change score out of 11) | 1 study (n=160) | Not serious | HIGH | MD 0.10 higher (0.4 lower to 0.6 higher) | 0.6 |
| Adherence | 1 study (n=160) | Very serious | LOW | 13 fewer per 1000 (from 24 fewer to 108 more) | 250 |

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**Table 35: Structured education programme versus control - usual care or other type of education (more than or equal to 12 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Structured education | Control event rate (per 1000 patients)<br><br>Control |
|---|---|---|---|---|---|
| HbA1c, % pooled | 5 studies (n=300) | No serious | VERY LOW | MD 0.08 higher (0.01 lower to 0.17 higher) | 10.4 |
| HbA1c, % (between 6 and 12 months) | 1 study (n=86) | Very serious | VERY LOW | Study reported that there was NS change in either of the groups | |
| HbA1c, % - MD only given | 1 study (n=114) | Serious | VERY LOW | MD 0.01 higher (0.3 lower to 0.32 higher); p=0.94 | |
| Severe hypoglycaemia (episodes/study) | 1 study (n=56) | Very serious | VERY LOW | 21 fewer per 1000 (from 143 fewer to 331 more) | 207 |
| Severe hypoglycaemia (episodes/6 months) | 1 study (n=111) | Serious | VERY LOW | MD 1.65 lower (2.86 to 0.44 lower) | 1.78 |
| Severe hypoglycaemia (episodes/12 months) - SD not given | 1 study (n=114) | Very serious | VERY LOW | MD 0.05 lower (0.61 lower to 0.5 higher); p=0.94 | |
| Severe hypoglycaemia (episodes/person) - SD not given | 1 study (n=60) | Very serious | VERY LOW | Data provided: HAAT 1.76 and SMBG 3.65; p<0.023 | |
| DQoL | 2 studies (n=114) | Not serious | LOW | MD 2.40 lower (3.13 to 1.67 lower) | 4.27 |
| SF-36 physical health - MD only given | 1 study (n=60) | Very serious | VERY LOW | MD 1.9 higher (0.8 lower to 4.6 higher); p=0.17 | |
| Hypo unawareness (more recognition of low blood glucose, % of patients) | 1 study (n=111) | Serious | VERY LOW | MD 17.2 higher (7.77 to 26.63 higher) | 48.0 |
| Fear of hypoglycaemia (Hypo fear survey) - Worry | 1 study (n=111) | Serious | VERY LOW | MD 1.50 lower (5.78 lower to 2.78 higher) | 14.7 |
| Fear of hypoglycaemia (Hypo fear survey) - Behaviour | 1 study (n=111) | Not serious | LOW | MD 0.60 lower (3.48 lower to 2.28 higher) | 12.2 |
| Fear of hypoglycaemia (Hypo fear survey) – Worry – MD only given | 1 study (n=102) | Very serious | VERY LOW | MD 1.4 lower (6.2 lower to 3.4 higher); p=0.57 | |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Structured education | Control event rate (per 1000 patients)<br><br>Control |
|---|---|---|---|---|---|
| Fear of hypoglycaemia (Hypo fear survey) – Behaviour – MD only given | 1 study (n=102) | Very serious | VERY LOW | MD 1.2 lower (4.2 lower to 1.9 higher) ;p=0.45 | |
| Depression (CES-D) - no SD given | 1 study (n=86) | Very serious | VERY LOW | Data provided: BGAT 15.5 and Control 15.4, p=0.19 | |
| PAID - no SD given | 1 study (n=86) | Very serious | VERY LOW | Data provided: BGAT 45.4 and Control 38.3, p=0.68 | |
| Knowledge, % of correct answers | 1 study (n=77) | Not serious | LOW | MD 7.50 higher (6.63 to 8.37 higher) | 64.9 |
| Knowledge of diabetes (GISED) | 1 study (n=56) | Not serious | LOW | MD 1.14 higher (1.04 to 1.23 higher) | 1.59 |

### 7.2.4 Economic evidence

**Published literature**

One study was included with the relevant comparison[399]. This is summarised in the economic evidence profile below (Table 36). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

In addition, NICE Technology Appraisal 60[505] recommends that *"structured patient education is made available to all people with type 1 diabetes at the time of initial diagnosis and then as required on an on-going basis, based on a formal, regular assessment of need of which the DAFNE programme may be a suitable option for individuals with type 1 diabetes"*. They also summarise that "given the relatively small costs associated with education programmes, only small improvements in terms of morbidity or health-related quality of life are needed to make educational interventions cost effective".

In the previous version of this guideline, one Health Technology Assessment identified only one study on type 1 diabetes and this has been selectively excluded[252]. Three new studies that met the inclusion criteria were selectively excluded due to the availability of a UK CUA.[162,190,700] One study[648] that met the inclusion criteria was selectively excluded as the included study[399] was its updated version. The excluded studies are listed in Appendix L.

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**Table 36:   Economic evidence profile: Structured training and treatment programme (STTP) (DAFNE) versus current practice**

| Study | Applicability | Limitations | Other comments | Increment al cost | Increment al effects | Cost effectivenes s | Uncertainty |
|---|---|---|---|---|---|---|---|
| Kruger 2013[399] (UK) | Directly applicable[a] | Potentially serious[b] | DAFNE vs. current practice HbA1c was the key surrogate outcome influencing long-term diabetes-related complications modelled through the Sheffield Type 1 Diabetes Policy Model. | £426 | 0.0294 QALYs | £14,475 per QALY | Probability DAFNE is cost-effective at £20,000 per QALY threshold: 54%.

DAFNE was dominant or still cost-effective when: 6-month HbA1c was predicted from RCT as 12-month, 4-year HbA1c maintained for lifetime, 6-month HbA1c predicted from RCT as 12-month and 4-year HbA1c maintained to 7 years, 12 month HbA1c maintained to year 7, 6-month HbA1c predicted from RCT as 12-month and maintained to year 7, 4-year HbA1c maintained to 7 years, 6-month HbA1c predicted from RCT as 12-month and HbA1c returns to baseline levels after 1 year, probabilities of severe hypoglycaemia and ketoacidosis differ between arms and linked to HbA1c based on research database.

If HbA1c returns to baseline levels after 1 year: ICER £78,227 per QALY gained |

*(a) CUA from the UK, NHS perspective. However the Sheffield Type 1 Diabetes Policy Model used published data from non-UK settings to define risk of long-term complications, some of which are now very old (for example DCCT). Old and non-UK data may not accurately represent the incidence of complications in the UK DAFNE population.*

*(b) It is possible not all the costs were included as PSS costs were not included. The study was only conducted over ten years where the full benefits of structured educational programmes are unlikely to be realised within ten years. The analysis used only HbA1c change to represent the clinical effectiveness of DAFNE. HbA1c was assumed to be equivalent between those individuals who had and had not received training. Health related quality of life data was unavailable for type 1 diabetes and so outcomes were estimated using multivariate statistical models developed for type 2 diabetes. In addition authors assumed that macro vascular complications have no impact on morbidity.*

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### 7.2.5    Evidence statements

**Clinical**

**Overall summary**

- Programmes examined were:
  - o  BGAT
  - o  BGAT-III
  - o  HyPOS
  - o  HAATT
  - o  DAFNE
  - o  BITES
  - o  De Weert et al.
  - o  Korhonen et al.
  - o  PRIMAS
  - o  Rossi et al., 2010
  - o  Rossi et al., 2013
  - o  Terent et al.
  - o  Trento et al., 2005
  - o  Trento et al., 2011
- Evidence was graded as moderate, low or very low for all the outcomes considered in the review.
- In a meta-analysis of RCTs comparing various programmes of structured education, there was no overall impact on HbA1c at 6 or 12 months of follow-up. The exception to this is DAFNE and PRIMAS, DAFNE resulted in a reduction in HbA1c difference of 1% (-1.42 to – 0.58%) at 6 months, and PRIMAS resulted in a reduction of 0.4% (-0.65 to -0.15), also at 6 months.
- Several programmes had a positive impact on severe hypoglycaemia when analysed individually. BGAT III, HAATT, Rossi 2013 and HyPOS showed a reduction in severe hypoglycaemia at 6 months, and BGAT and HAATT showed benefit also at 12months.
  - o  Of these three programmes, BGAT III encouraged the recruitment of people with severe hypoglycaemia (64% at baseline versus 47% in controls) while a history of severe hypoglycaemia was required of recruits to HAATT and HyPOS.
  - o  DAFNE, which did not recruit people specifically with problematic hypoglycaemia, did not demonstrate a significant reduction in severe hypoglycaemia in its RCT, although, there was no significant increase despite the fall in HbA1c.
  - o  BGAT III was also associated with improved hypoglycaemia awareness at 6 and 12 months, as did HyPOS at 6 months.
- Improved quality of life was demonstrated in DAFNE (ADDQoL- impact; DTSQ).
- When all the programmes are pooled together in meta-analysis, the studies showed no clinically significant benefit of structured education programmes versus control groups on all clinical and psychological outcomes except for:
  - o  At less than or equal to 6 months:
    - –  Severe hypoglycaemia – episodes every 6 months (favours structured education – evidence-based on BGATT III).
    - –  Severe hypoglycaemia – episodes per person, SD not given (favours structured education - evidence based on HAATT).

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- DTSQ total satisfaction (favours structured education – evidence based on ROSSI 2010)
- ADDQoL- impact (favours structured education – evidence based on ROSSI 2010
- Hypoglycaemia unawareness - % of patients with a greater recognition of low blood sugar (favours structured education – evidence based on BGATT III and HAATT)
- Hypoglycaemia unawareness - HAQ (favours structured education - evidence based on HYPOS)
- Knowledge - % of correct answers (favours structured education - evidence based on Korhonen)

o At 12 months:

- Severe hypoglycaemia – episodes every 6 months (favours structured education – evidence based on BGATT III)
- Severe hypoglycaemia – episodes per person, SD not given (favours structured education – evidence based on HAATT)
- Hypoglycaemia unawareness - % of patients with a greater recognition of low blood sugar (favours structured education – evidence based on BGATT III)
- Knowledge - % of correct answers (favours structured education – evidence based on Korhonen and Lennon)
- Knowledge - GISED (favours structured education – evidence based on Trento 2005 and Trento 2011)

- However, the quality of evidence for all of these outcomes (at both 6 and 12 months), was Low or Very low.

- However, when looking at the programmes individually, DAFNE and PRIMAS were the only programmes that showed some benefit on clinical outcome (HbA1c) which is clinically important versus a usual care control group DAFNE and PRIMAS show a difference, but the difference is lost when data from all the education programmes are pooled together.

o Subgroup analyses at 6 months and 12 months:

- When looking at the subgroup analyses of carbohydrate counting, the studies show that carbohydrate counting when combined with education is better for HbA1c at 6 months, but not at 12 months (the 12 months data was based on a small single study).
- Studies with CHO counting in education versus no CHO counting showed benefit of education on HbA1c
- Studies of education versus usual care showed benefit of education on HbA1c
- Studies recruiting not solely hypoglycaemic patients showed benefit of education on HbA1c, but there is significant heterogeneity.

**Economic**

One cost-utility analysis found that DAFNE was cost effective compared with no DAFNE (ICER: £14,475 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.

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### 7.2.6 Recommendations and link to evidence

12. Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose-adjustment for normal eating) programme. Offer this programme 6–12 months after diagnosis, at a time that is clinically appropriate and suitable for the person. [new 2015]

13. Explain to adults with type 1 diabetes that structured education is an integral part of diabetes care. [new 2015]

14. Provide an alternative of equal standard for a person unable or unwilling to participate in group education. [new 2015]

15. Ensure that any structured education programme for adults with type 1 diabetes includes the following components [i]:
   - It is evidence-based, and suits the needs of the person.
   - It has specific aims and learning objectives, and supports the person and their family members and carers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes.
   - It has a structured curriculum that is theory-driven, evidence-based and resource-effective, has supporting materials, and is written down.
   - It is delivered by trained educators who have an understanding of educational theory appropriate to the age and needs of the person, and who are trained and competent to deliver the principles and content of the programme.
   - It is quality assured, and reviewed by trained, competent, independent assessors who measure it against criteria that ensure consistency.
   - The outcomes are audited regularly. [new 2015]

16. Provide information about type 1 diabetes and its management to adults with type 1 diabetes at all opportunities from diagnosis onwards. Follow the principles in the NICE guideline on patient experience in adult NHS services. [new 2015]

17. Consider the Blood Glucose Awareness Training (BGAT) programme for adults with type 1 diabetes who are having recurrent episodes of hypoglycaemia (see also Section 11). [new 2015]

| Recommendations | |
|---|---|
| Relative values of different outcomes | The GDG were aware that in type 1 diabetes, as in many chronic diseases, education programmes can be shown to improve knowledge. They were particularly concerned with measures that produce benefit in terms of improved disease control. Not all of the educational programmes were designed with exactly the same aim in mind; for example, BGAT was designed specifically to combat major fluctuations in blood glucose, particularly episodes of hypoglycaemia, and did not incorporate some of the wider aspects of patient education which are featured in other programmes. The |

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i    Components of a structured education programme adapted from the NICE quality standard on diabetes in adults.

| | |
|---|---|
| | GDG felt that this had to be allowed for assessing the outcome measures. Overall, the GDG were interested in HbA1c as an objective measure of continuing glucose control and in improvements in quality of life.

It was noted that the outcome measures could not necessarily be taken in isolation. For example, superficially, anything which lowers HbA1c levels is valuable, but if this is achieved to the extent that episodes of hypoglycaemia also become more frequent, then it would become harmful.

Heterogeneity was noted in the outcome measures, which is readily apparent in the forest plots (Appendix J). Both the DAFNE and PRIMAS programmes produced statistically and clinically significant benefits in HbA1c which were not shown in any other individual study (except for Lennon 1990, which the GDG did not consider strongly because it was a very old study in only 74 people with an unusually high HbA1c of nearly 12%). This was apparent at the 6 month time point (and after 12 months in DAFNE when all patients in both arms of the trial continued on DAFNE - 12 month data only available for one arm). The DAFNE programme also showed benefits in some, but not all, components of the quality of life analysis.

The BGAT programme was shown to improve hypoglycaemia unawareness.

In a meta-analysis of RCTs comparing various programmes of structured education, there was no overall impact on HbA1c at the 6 or 12 month follow-up. The exception to this is DAFNE, which resulted in a reduction in HbA1c difference of 1% (-1.42 to 0.58%) at 6 months.

Several programmes had a positive impact on severe hypoglycaemia when analysed individually. BGAT III, HAATT, [605] and HyPOS showed a reduction in severe hypoglycaemia at 6 months, and BGAT and HAATT showed benefit also at 12 months. Of these three programmes, BGAT III encouraged the recruitment of people with severe hypoglycaemia (64% at baseline versus 47% in controls) while a history of severe hypoglycaemia was required of recruits to HAATT and HyPOS. DAFNE, which did not recruit people specifically with problematic hypoglycaemia, did not demonstrate a significant reduction in severe hypoglycaemia in its RCT. BGAT III is also associated with improved hypoglycaemia awareness at 6 and 12 months, as well as HyPOS at 6 months.

Improved quality of life was demonstrated in DAFNE (ADDQoL- impact; DTSQ). |
| Trade off between clinical benefits and harms | The studies did not report any direct harms of educational programmes, nor is it expected that there would be any. The GDG discussed whether the programmes might increase anxiety levels in some patients with type 1 diabetes, but there was no evidence of this. |
| Economic considerations | The GDG considered the cost-effectiveness analysis of an education programme based on the DAFNE programme. This was an update of a previous analysis which showed that the DAFNE programme was highly cost effective. Although the ICER is much higher in the more recent ScHARR analysis, this analysis is based on national audit outcome data rather than data from an RCT which informed the earlier analysis, and the HbA1c reductions have been less in the audit than had been anticipated from the RCT results. Nonetheless, the ICER is still below the conventional NICE threshold of £20,000 per QALY and the GDG could therefore conclude that the DAFNE programme is a cost effective intervention. The ScHARR analysis assumed no impact of DAFNE on hypoglycaemia.

Although there is no evidence for other education programmes, or for short or long courses, the GDG acknowledge that other courses of similar content, structure and criteria may also have the potential to be cost-effective. |
| Quality of evidence | GRADE analysis suggested that the data on structured education programmes is generally of Low or Very low quality. The main reasons for this were imprecision and also the heterogeneity between studies, but to some extent, this is understandable since the education programmes are all different, and in some cases have a particular primary focus, albeit there is overlap between the components. |

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| | |
|---|---|
| | It was noted that the studies were typically performed with people who have had diabetes for a number of years. In general, the GDG felt that education should be offered to patients at a much earlier stage of diagnosis (and indeed, this is now what happens in practice). There are surprisingly few data on the use of the intervention at this time-point. |
| Other considerations | There is a strong impression amongst healthcare professionals that education is of value in type I diabetes, and people with type 1 diabetes naturally have a strong desire to be able to control the condition, so it was disappointing that results across the range of educational programmes were not unequivocally positive. In the broader educational programmes, the results of the DAFNE and PRIMAS studies were superior to others. The GDG were aware that DAFNE was a programme already used widely in the UK, whereas PRIMAS was a specific programme in Germany, and thus, DAFNE (along with its greater improvement in HbA1c compared with PRIMAS) was considered to be the education programme of choice. The GDG debated whether their recommendation should specify that DAFNE alone could be employed. They were aware that there are other educational packages which appear to be useful but have not been formally studied. However, on the other hand, the results of the papers considered make it clear that educational programmes have been devised, which turn out to be of noaudit data on the DAFNE programme delivered in routine clinical practice.[328] This showed benefits on HbA1c, severe hypoglycaemia, hypoglycaemia awareness, well-being and psychological stress. The GDG were also aware of evidence pertaining to follow-up education programmes and the importance of sustaining and providing ongoing support to patients, although, this was not the remit of this review. However, such studies show sustained improvement in outcomes (for example the DAFNE programme.[179])

Taking all of this into consideration, as well as the RCT evidence, the GDG decided that they should stipulate that structured education programmes had to fulfil the criteria of the NICE quality standards.[510]

There was also a debate about when the programme should be offered. As already noted, the formal studies have been performed in patients with a relatively long duration of diabetes, but all members of the GDG felt that the programme should be offered earlier on. It was felt that the first few months post diagnosis are a period of considerable adjustment and that trying intensive education at this stage would be less worthwhile and even counter-productive. The overriding principal is that the programme should be undertaken when the person with diabetes feels ready to engage fully, but the consensus was that for most people it would be worthwhile enrolling in DAFNE (or similar) from a time point of 6-12 months post diagnosis. |

18. Carry out more formal review of self-care and needs annually in all adults with type 1 diabetes. Vary the agenda addressed each year according to the priorities agreed between the healthcare professional and the adult with type 1 diabetes. [2004, amended 2014]

Specific recommendations on patient education and information-giving in particular aspects of care are given in individual sections of this guideline.

### 7.2.7 Research recommendations

3. In adults with type 1 diabetes, what methods can be used to increase the uptake of structured education programmes and to improve their clinical outcomes (particularly achieving and sustaining blood glucose control targets)?

**Why this is important**

Structured education programmes in flexible insulin therapy have been shown to improve diabetes control (lower HbA1c and less hypoglycaemia) but achieving and sustaining optimal diabetes control for avoidance of complications remains challenging. Some people fail to achieve ideal targets for

glycaemic control; others achieve but cannot maintain them and still others do not access structured education at all. We therefore need to develop and test (1) more effective ways of engaging adults with type 1 diabetes in education; (2) improvements in the delivery of education to increase the number of people achieving targets for diabetes control and (3) enhanced support for adults with diabetes to sustain good diabetes control over time. If we can improve the uptake and delivery of clinically and cost effective education and support for adults with type 1 diabetes we will see a reduction in the short and long term complications of the condition.

4. **In adults with newly diagnosed type 1 diabetes, what is the optimal timing and method of delivering structured education in terms of clinical and cost-effectiveness?**

# 7.3 Dietary management

The 2015 GDG reviewed evidence in two areas that were not covered in 2004: Carbohydrate counting and GI diets. All other recommendations on dietary management from 2004 have been retained. The dietary management content from 2004 can be found in Appendix S.

## 7.3.1 Introduction to new evidence reviews on carbohydrate counting and GI diets [2015]

Carbohydrate is the macronutrient that has the greatest impact on glycaemic control. Carbohydrates include starches and sugars which are converted during the digestive process to glucose, the main purpose of which is to provide energy for the body. Starches are either oligosaccharides or polysaccharides, and are found in foods, such as bread, pasta, rice and potato. Sugars are either monosaccharides, such as glucose and fructose, or disaccharides, such as sucrose and lactose.

In the past it was largely assumed that sucrose-based carbohydrate foods had the largest impact on post-prandial blood glucose. It is now well established that the total carbohydrate or the glycaemic load is the main predictor of the rise in blood glucose levels postprandially.[368] Traditionally, people with diabetes were taught to estimate the carbohydrate content of food to be eaten, so that carbohydrate quantities could be prescribed for each meal to match insulin doses.

In modern diabetes management, insulin regimens, such as multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII), deliver basal (to control the body's own glucose production) and meal-related insulin replacement. For the latter, people with type 1 diabetes are taught to estimate or 'count' the carbohydrate in food to be eaten and adjust the insulin dose for the proposed meal accordingly, using individual insulin-to-carbohydrate ratios to estimate the insulin dose.[173] Accurate carbohydrate counting is key to the success of such flexible regimens, while for patients who are on fixed meal doses in a MDI regimen or still using twice-daily pre-mixed insulin, it is important to have consistent quantities of carbohydrate at every meal time. For the latter, it is also advantageous to keep the timings of meals consistent. In all these circumstances, people with diabetes need to be trained in carbohydrate counting. This is often incorporated into structured education programmes that aim to cover many aspects of insulin self-management, however, carbohydrate counting skills are often taught as a stand-alone topic. Carbohydrate counting can be taught in a one-to-one consultation by a Diabetes Specialist dietitian, by e-learning.[172,173] or by attending a structured education course (see Section 7.2).

Almost all current meal-related insulin regimens are based on matching insulin dose to quantities of carbohydrate eaten. It follows that, if less carbohydrate is consumed, with a larger part of the diet coming from protein and fat, less insulin will be required. There have been suggestions that even in today's era of "normalising", the diet for the adult with type 1 diabetes, restricting but not omitting carbohydrate intake, may improve diabetic control, particularly if the person with type 1 diabetes is overweight.

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Prandial insulin doses are given to maximise the match between the rise of insulin in the circulation and the rise in blood glucose after the meal. The blood glucose profile from carbohydrate consumed is influenced by the nature of the carbohydrate containing food to be eaten. The 'glycaemic index' or GI of a food describes the area under the blood glucose curve after its consumption in comparison to a standard unit, such as one slice of white bread. Foods with a low GI are thought to facilitate diabetes control as the blood glucose response is slower to rise and fall, and in theory, easier to control with injected insulin. However, the GI of a food varies with method of preparation and with other foods consumed at the same time in a mixed meal, making the value of GI estimation as a major dietary intervention less easy to predict.

**This chapter aims to address these questions:**

- In adults with type 1 diabetes, what is the clinical and cost-effectiveness of carbohydrate counting or restriction for optimal diabetic control?
- In adults with type 1 diabetes, what is the clinical and cost-effectiveness of a diet based on the GI for optimal diabetic control?

### 7.3.2 Review question: In adults with type 1 diabetes, what is the clinical and cost-effectiveness of carbohydrate counting or restriction for optimal diabetic control?

For full details see review protocol in Appendix C.

**Table 37: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
|---|---|
| Intervention/s | Carbohydrate counting/restriction (this may involve technology, such as a bolus calculator) |
| Comparison/s | • Placebo<br>• Usual care/no carbohydrate counting<br>• Manual carbohydrate counting (if the intervention is carbohydrate counting using a technology) |
| Outcomes | • HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Quality of life (continuous)<br>• Adverse events |
| Study design | RCTs, observational studies<br>• Unit of randomisation: individual patient |

### 7.3.3 Clinical evidence

**This review was divided into studies that compared:**

- Carbohydrate counting versus no carbohydrate counting
- Carbohydrate counting using technology (such as a bolus calculator) versus manual carbohydrate counting

Four studies were included in the first part of this review [176,413,623,627]. Three of the studies[413,623,627] were RCTs comparing patient carbohydrate counting with no carbohydrate counting. The fourth study[176] was an observational study (prospective case-series) of a prescribed diet and prescribed insulin doses and regime based on carbohydrate counting. Evidence from all the studies is summarised in Appendix G. Evidence from the three RCTs is summarised in the clinical GRADE

evidence in Appendix I. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

There were no data reported in any of the studies for the following outcomes:

- Nocturnal hypoglycaemia
- Adverse events.

Eight studies[54,87,222,374,383,464,627,770] were identified and included for the second part of the review which compared carbohydrate counting using technology (such as a bolus calculator) versus manual carbohydrate counting. Three of the studies[464,627,770] were RCTs comparing carbohydrate counting with the use of a bolus calculator with manual carbohydrate counting. Evidence from these three RCTs is summarised in the clinical GRADE evidence in Appendix I. See also the forest plots in Appendix J. The remaining 5 studies[54,87,222,374,383] were observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below.

For the comparison of bolus calculators versus manual carbohydrate counting there were no data reported in any of the studies for the following outcomes:

- Nocturnal hypoglycaemia
- Adverse events.

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**Table 38: Summary of studies included in the review: Carbohydrate counting versus no carbohydrate counting**

| Study | Intervention | Comparison | Population | Follow-up | Outcomes |
|---|---|---|---|---|---|
| RCTs | | | | | |
| SCHMIDT 2012<br><br>RCT | CarbCount | CarbCount Automated Bolus Calculator (CarbCount ABC)<br><br>and<br><br>control (no carb count) | Type 1 diabetes<br>n=63 (n=8 control, n=21, CarbCount; n=22, CarbCount Automated Bolus Calculator) | 16 weeks | ABC CarbCount and CarbCount were SS better than no carb counting for:<br>HbA1c (final values; ABC: 8.1±0.4%; CC: 8.4±0.9%; CHO alone 8.9±1.1%; ANOVA P=0.029)<br>DTSQ<br>There was NS difference between the groups for:<br>• Severe hypoglycaemia<br>• HFS score<br>• PAID score<br>• ADDQOL score |
| LAURENZI 2011<br><br>RCT | CHO counting | No CHO counting | n=61<br>Adults aged 18-65 years with Type 1 diabetes<br>SCII for >3 months<br>No previous training in CHO counting<br>**SCII (Glulisine, Lispro or Aspart)**<br>**SMBG 6-times daily** | 24 weeks (training during first 12 weeks in intervention group) | CHO counting group was SS better than no CHO counting group for:<br>DSQOLS diet restrictions score (change score; median 5.5 vs. 0)<br>There was NS difference between the groups for:<br>HbA1c (change from baseline; P=0.252) using ACA (Note: not enough data reported for forest plot).<br>Severe hypoglycaemia (no events observed during the study)<br>Frequency of mild hypoglycaemic events (BG 2.8 mmol/litre) using ACA (Note: not enough data reported for forest plot)<br>DSQOLS (social relations score, leisure-time score, physical complaints score, future worries score, daily hassles score, hypoglycaemia fears score) |
| SCAVONE 2010<br><br>RCT | CHO counting | No carb counting | n=256<br>Type 1 diabetes duration >5 years<br>No subjects had followed any dietetic or educational programme previously | 9 months (nutritional education programme and CHO count training 4 weeks | CHO counting group was SS better than no CHO counting group for:<br>HbA1c (change from baseline) using ACA<br>CHO: Baseline 7.8±1.3%; 9 months 7.4±0.9%<br>Control: Baseline 7.5±0.8%; 9 months 7.5±1.1%<br>Note: not enough data reported to present as change scores, presented as final values on forest plot. |

| Study | Intervention | Comparison | Population | Follow-up | Outcomes |
|---|---|---|---|---|---|
| | | | **Evening basal insulin and SA insulin at meal times** **SMBG 6-times daily** | preceding in intervention group) | Frequency of mild hypoglycaemic events (BG <3.9 mmol/litre; CHO: 4%; control: 7%) using ACA |
| Non-randomised trials | | | | | |
| DIAS 2010 Observational: prospective case-series | Diet and insulin doses prescribed based on CHO counting | Baseline | n=55 Mainly adults (10-60 years) Type 1 diabetes (ADA criteria) Evening basal NPH insulin and SA insulin at meal times **No SMBG during study** | 3 months | 3 month follow-up was SS better than baseline for: HbA1c (baseline 10.40±0.33%; 3 months 9.52±0.32%; P=0.0009) 38/51 patients had a reduction in HbA1c from baseline; 11/51 patients had an increase in HbA1c from baseline and 2/51 patients had no change. Note: patients not SMBG or carb counting themselves during study |

**Table 39: Carbohydrate counting using bolus calculator or other technology versus manual carbohydrate counting**

| Study | Intervention | Comparison | Population | Follow-up | Outcomes |
|---|---|---|---|---|---|
| Carbohydrate counting with bolus calculator | | | | | |
| MAURIZI 2011 RCT | Calsulin bolus calculator | CHO counting | n=40 Adults aged 16-65 Type 1 diabetes (ADA definition) Type 1 diabetes duration ≥1 year | 6 months | Calsulin group was SS better than CHO counting alone group for: HbA1c (6 months; change scores; calsulin -0.85%; CHO alone -0.07%) There was NS difference between the groups for: HbA1c (3 months; final values; calsulin 7.3±0.5%; CHO alone 7.7±1.0%) Frequency of hypoglycaemic events (Not enough data reported for forest plot and GRADE – only stated no SS difference between groups) |
| SCHMIDT 2012 (same as above) RCT | CarbCount Automated Bolus Calculator (CarbCountABC) | CarbCount and control (no carb count) | Type 1 diabetes n=63 (n= n=8 control, n=21, CarbCount; n=22, CarbCount Automated Bolus Calculator) | 16 weeks | ABC CarbCount and CarbCount were SS better than no carb counting for: HbA1c (final values; ABC: 8.1±0.4%; CC: 8.4±0.9%; CHO alone 8.9±1.1%; ANOVA P=0.029) DTSQ There was NS difference between the groups for: • Severe hypoglycaemia • HFS score • PAID score |

| | | | | | • ADDQOL score |
|---|---|---|---|---|---|
| ZIEGLER 2013<br><br>RCT | Carb counting (BG meter with bolus calculator) | Manual carb count (standard BG meter with manual bolus calculation) | Type 1 diabetes and type 2 diabetes (93% Type 1 diabetes) on MDI treatment<br>n=218 | 26 weeks | Bolus calculator was SS better than manual CHO counting group for:<br>QOL (DTSQ; 8 questions of 7-point scale; BC 11.4±6.0; CHO alone 9.0±6.3)<br>Manual CHO counting group was SS better than bolus calculator group for:<br>Mild Hypoglycaemia (no. of patients <70 mg/dl; BC 43/105, CHO alone 31/113)<br>There was NS difference between the groups for:<br>HbA1c (change scores; BC -0.7±0.7%; CHO alone -0.5±0.7%)<br>Severe hypoglycaemia (no. of patients <36 mg/dl or 3rd party; BC 11/105, CHO alone 7/113) |
| KLUPA 2008<br>Observational retrospective cohort study | Bolus calculator | No BC (trained in CC) | n=18<br>Type 1 diabetes<br>Treated with CSII<br>Trained in food counting (including carb, protein and lipid counting and GI estimation) | Bolus calculator provided 9 months previously | There was NS difference between the groups for:<br>HbA1c (final values; BC 6.8%; CHO alone 7.0%).<br>Hypoglycaemic episodes/day (CMBG n=3 in each group; BC 1.4; CHO alone 1.6) |
| FRANC 2009<br><br>Observational prospective case-series | Phone bolus calculator for FIT CHO counting | CHO counting using FIT | n=35<br>Type 1 diabetes duration ≥1 year<br>Use of CHO counting using flexible intensive insulin therapy (FIT) for at least 6 months<br>**SCII or MDI** | 4 months | Use of bolus calculator was SS better than baseline (CHO counting alone) for:<br>HbA1c (change scores; baseline 7.8±0.9%; 4 months 7.3±0.6%)<br>There was NS difference from baseline for:<br>Mild hypoglycaemic events at 12 weeks (BG<3 mmol/litre; events/individual/week; Baseline 1.4; 12 weeks 0.8)<br>Patients reported to vary CHO content from one day to the next and enjoy dietary freedom |
| Carbohydrate counting using other technologies | | | | | |
| BAO 2011<br><br>RCT crossover | FII algorithm + CHO counting to calculate insulin dose (lab test meal) | CHO counting alone to calculate insulin dose (lab test meal) | • n=31<br>• Adults aged ≥18 and ≤70<br>• Type 1 diabetes duration ≥1 year<br>• HbA1c ≤9% | 3 hours after each test meal | • FII group was SS better than CHO counting alone group for:<br>   ○ Time within normal BG (4-10mmol/l) in 3 hour post-prandial period<br>• There was NS difference between the groups for:<br>   ○ Severe hypoglycaemia (3 hour post-prandial period; no events in either group)<br>   ○ Mild hypoglycaemic episodes (3 hour post-prandial period; FII 6 episodes; |

| | | | Use of SCII (including bolus calculator) for ≥2 months and reliable SMBG 4-times daily | | CHO alone 1 episode) |
|---|---|---|---|---|---|
| KILBRIDE 2011<br><br>Cohort study (prospective) | CHO counting algorithm developed considering exercise (lab test exercise session) | self-management (patients experienced in CHO counting; lab test exercise session) | • n=14<br>• Adults (20-50 years)<br>• Type 1 diabetes duration > 2 years<br>• HbA1c <10%<br>• Experienced in CHO counting by education<br>**Basal-bolus insulin regime** | 2 weeks (week 1: self-management; week 2: CHO/exercise algorithm | • Exercise algorithm + CHO counting was SS better than CHO counting alone for:<br>  ○ Duration of hypoglycaemia during 40 exercise session (<4mmol/l)<br>  ○ Duration of hypoglycaemia during 6-hour post exercise period (<4mmol/l)<br>• Mild hypoglycaemic episodes (episodes/week; self-reported)<br>  ○ Algorithm: 2; CHO counting alone: 18 (on exercise days)<br>  ○ Algorithm: 27; CHO counting alone: 34 (on non-exercise days)<br>• There was NS difference between the treatments for:<br>Severe hypoglycaemic episodes (no events during either treatment) |
| BRAZEAU 2013<br><br>Cross-sectional study (accuracy of patient CHO estimates in CHO counting) | Patient estimate of CHO | Dietitian assessment of CHO | • n=50<br>• Adults ≥18 years<br>• Type 1 diabetes duration >6 months<br>• Had worn a CGM for 72 hours and had concomitantly assessed CHO content in food diary in >75% meals<br>• SCII (n=10), basal insulin and MDI (n=39), intermediate NPH bedtime insulin (n=1)<br>SA insulin at meal times | 72 hours (patient estimates of CHO content and dietitian assessment of CHO content from food diary compared over 72 hours) | • Lower accuracy of patient CHO content estimates was a predictor of shorter time spent within normal BG range (4-10mmol/L) and longer time spent in hyperglycaemia (>10mmol/L). |

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**Table 40:   Clinical evidence summary: Carbohydrate counting versus no carbohydrate counting**

| Outcome | No. of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000) | Control group mean |
|---|---|---|---|---|---|---|
| **HbA1c** | | | | | | |
| >6 months | 1 | None | LOW | MD 0.1 lower (0.41 lower to 0.21 higher)<br>**MD 0.4 lower (change score[a])** | - | 7.5±1.1% (final value)<br>**0% change score[a]** |
| ≤6 months | 1 | Serious | MODERATE | MD 0.5 lower (1.35 lower to 0.35 higher)[b] | - | 8.9±1.1% |
| **Mild hypoglycaemia** | | | | | | |
| >6 months | 1 | Very serious | VERY LOW | 30 fewer per 1000 (from 59 fewer to 73 more) | 71 per 1000 | - |
| **Severe hypoglycaemia** | | | | | | |
| ≤6 months | 2 | Very serious | LOW | 15 fewer per 1000 (from 58 fewer to 393 more) | 63 per 1000 | - |
| **DSQOLS ≤6 months** | | | | | | |
| Diet restrictions | 1 | Serious | LOW | SS higher (p=0.008 reported; median change score 5.5 vs. 0) | - | Median change score (IQR) 0 (-2 to 3.5) |
| Social relations; Leisure-time flexibility; Physical complaints; Worries about future; Daily hassles | 1 | Serious | LOW | NS difference between groups | - | |
| **Hypoglycaemia fear survey (transformed onto 0-100 scale; higher scores indicate more fear)** | | | | | | |
| ≤6 months | 1 | Very serious | VERY LOW | MD 1.7 lower (15.62 lower to 12.22 higher) | - | 24.5±18.2 |
| **Problem areas in diabetes questionnaire (transformed onto 0-100 scale; higher scores indicate more problems)** | | | | | | |
| ≤6 months | 1 | Very serious | VERY LOW | MD 0.8 higher (14.6 lower to 16.2 higher) | - | 27.2±18.8 |
| **Audit of Diabetes Dependent QOL questionnaire (range of scores -9 to 9; higher values indicate better QOL)** | | | | | | |
| ≤6 months | 1 | Very serious | VERY LOW | MD 0.4 lower (1.33 lower to 0.53 higher) | - | -1.4±0.9 |
| **Diabetes Treatment Satisfaction Questionnaire (range of scores: 0-36; Better indicated by higher values)** | | | | | | |
| ≤ 6 months | 1 | Serious | LOW | MD 2.1 lower (6.47 lower to 2.27 higher) | - | 28.5±5.1 |

*(a)  Reported as SS difference (p<0.01) between groups for change score (not enough data provided to report change score and CI in meta-analysis and GRADE)*

(b) HbA1c change scores reported as NS different between groups for Laurenzi 2011 but not enough data reported from Laurenzi 2011 to include data in meta-analysis. Observational before and after study (Dias 2010) 3 month follow-up was SS better than baseline (baseline 10.40±0.33%; 3 months 9.52±0.32%; p=0.0009)

**Table 41:   Clinical evidence summary: Bolus calculator versus manual carbohydrate counting**

| Outcome | No. of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000) | Control group mean |
|---|---|---|---|---|---|---|
| HbA1c | | | | | | |
| ≤6 months | 3 | No serious imprecision | MODERATE | MD 0.25 lower (0.41 to 0.08 lower)[a] | - | 8.1% |
| Mild hypoglycaemia | | | | | | |
| ≤6 months | 1 | Serious | LOW | 134 more per 1000 (from 5 more to 323 more) | 274 per 1000 | - |
| Severe hypoglycaemia | | | | | | |
| ≤6 months | 2 | Very serious | VERY LOW | 41 more per 1000 (from 26 fewer to 192 more) | 79 per 1000 | - |
| Hypoglycaemia fear survey (transformed onto 0-100 scale; higher scores indicate more fear) | | | | | | |
| ≤6 months | 1 | Very serious | VERY LOW | MD 0.2 lower (9.34 lower to 8.94 higher) | - | 22.8 |
| Problem areas in diabetes questionnaire (transformed onto 0-100 scale; higher scores indicate more problems) | | | | | | |
| ≤6 months | 1 | Serious | LOW | MD 2.4 lower (12.81 lower to 8.01 higher) | - | 28.0 |
| Audit of Diabetes Dependent QOL questionnaire (range of scores -9 to 9; higher values indicate better QOL | | | | | | |
| ≤6 months | 1 | Very serious | VERY LOW | MD 0 higher (0.96 lower to 0.96 higher) | - | -1.8 |
| Diabetes Treatment Satisfaction Questionnaire (range of scores: 0-36; Better indicated by higher values) | | | | | | |
| ≤6 months | 1 | Serious | LOW | MD 5.10 higher (2.19 to 8.01 higher) | - | 26.4 |

(a) Klupa 2008 observational cohort study reported a NS difference between groups for HbA1c. Franc 2009 observational before and after study reported HbA1c was SS lower at 4 months after using bolus calculator (baseline 7.8±0.9%; 4 months 7.3±0.6%)

### 7.3.4 Economic evidence

**Published literature**

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix C.

**Unit costs**

**Table 42: Cost of hospital dietitians**

| Cost | Band 5 | Band 6 | Band 7 |
|---|---|---|---|
| Cost per hour[a] | £34[b] | £43[c] | £55[c] |

(a) Including qualification costs
(b) PSSRU 2012[148]
(c) Calculated using NHS Staff Earning Estimates in PSSRU 2012[148]

**Table 43: Cost of 'stand-alone carbohydrate counting' course**

| Staff costs[a] | Number of patients on course | Incremental cost per patient[b] | Incremental QALY gain required[b] |
|---|---|---|---|
| £343 | 4 | £86 | 0.00429 |
| | 8 | £43 | 0.00214 |
| | 12 | £29 | 0.00143 |

(a) Assuming 3.5 hours (3 hours to deliver course; 0.5 hours of preparation, set up and take down) of a band 6 and a band 7 dietitian.
(b) Compared with no carbohydrate counting course.
(c) To be cost-effective at a £20k per QALY threshold.

### 7.3.5 Evidence statements

**Clinical**

**Carbohydrate counting versus no carbohydrate counting**

Moderate, Low and Very low quality evidence, mainly from single studies, showed a clinical benefit of carbohydrate counting for HbA1c (change from baseline) at up to 6 months and over 6 months, and mild hypoglycaemia at over 6 months. There was also a clinical benefit for severe hypoglycaemia and the DSQOLs domain of diet restrictions both at up to 6 months .

Low and Very low quality evidence from single studies showed no clinical benefit of carbohydrate counting for HbA1c (final values) at over 6 months, and for the QoL scores of DSQOLs (other domains), PAID, ADDQOL, Hypoglycaemia fear survey, and DTSQ all up to 6 months

Low quality evidence from a single observational study (case-series/before and after study) showed that compared with baseline, there were improvements in HbA1c after patients used carbohydrate counting.

**Carbohydrate counting using a bolus calculator versus manual carbohydrate counting**

Low quality evidence from a single study showed a clinical benefit of bolus calculators for DTSQ at up to 6 months.

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Moderate quality evidence from three studies showed a borderline clinical benefit of bolus calculators for HbA1c at up to 6 months.

Low and Very low quality evidence from a single study and from two studies showed clinical harm of bolus calculators for mild hypoglycaemia, and severe hypoglycaemia at up to 6 months.

Low and Very low quality evidence from single studies showed no clinical benefit of bolus calculators for mild hypoglycaemia, and severe hypoglycaemia at up to 6 months; and for the QoL scores of Hypoglycaemia fear survey, PAID, ADDQOL, and DTSQ at up to 6 months.

Low quality evidence from a single observational study (retrospective cohort) showed no difference between using a bolus calculator to assist carbohydrate counting and manual counting for HbA1c, and number of hypoglycaemic episodes/day (at more than 6 months).

Low quality evidence from an observational study (a case-series/before and after study) which showed that compared with baseline (manual carbohydrate counting), using a bolus calculator to assist with carbohydrate counting led to improvements at 12 weeks in HbA1c, but no improvement in the number of mild hypoglycaemic events experienced /individual/week.

**Economic**

No relevant economic evaluations were identified.

### 7.3.6    Recommendations and link to evidence

| Recommendations | 19. Offer carbohydrate-counting training to adults with type 1 diabetes as part of structured education programmes for self-management (see Structured Education, section 7.2).[new 2015]<br><br>20. Consider carbohydrate-counting courses for adults with type 1 diabetes who are waiting for a more detailed structured education programme or are unable take part in a stand-alone structured education programme.[new 2015] |
|---|---|
| Relative values of different outcomes | The GDG determined the impact of carbohydrate counting regimens and bolus calculators on clinical outcomes in adults with type 1 diabetes, by assessing their impact on the following clinical outcomes:<br>• Improvement in glycaemic control; assessed by reduction in HbA1c.<br>• Incidence of hypoglycaemia, with particular focus given to:<br>• Incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a third party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes.<br>• Incidence of nocturnal hypoglycaemia.<br>• Quality of life: the evidence was reviewed to look at the impact of carbohydrate counting and bolus calculator use on quality of life outcomes.<br>• Adverse events: the literature was reviewed for any adverse events related to teaching and use of carbohydrate counting and bolus calculators. |
| Trade off between clinical benefits and harms | **Carbohydrate counting regimens**<br>The evidence for the use of carbohydrate counting regimens outside of structured education courses was reviewed.<br><br>**Impact on glycaemic control** |

Update 2015

| | |
|---|---|
| | **19.Offer carbohydrate-counting training to adults with type 1 diabetes as part of structured education programmes for self-management (see Structured Education, section 7.2).[new 2015]** |
| | **20.Consider carbohydrate-counting courses for adults with type 1 diabetes who are waiting for a more detailed structured education programme or are unable take part in a stand-alone structured education programme.[new 2015]** |
| **Recommendations** | |

One study [623] reported a 0.4% reduction in HbA1c at >6 months with the intervention of carbohydrate counting, but it was noted that the HbA1c of the control group was lower at the start of the study compared with the intervention group (7.5 % versus 7.8 %). A second study with <6 months follow-up did report a significant reduction in HbA1c with carbohydrate counting .[627]

**Impact on frequency of hypoglycaemia**

One study showed that mild hypoglycaemic episodes were reduced with the introduction of carbohydrate counting.[623] For severe hypoglycaemic episodes, an absolute difference of 15 fewer episodes per 1000 patient-years was thought to be of clinical significance, although, statistical significance was not attained and numbers within the individual studies were small. One small study reported that the frequency of severe hypoglycaemia episodes was reduced in the carbohydrate counting group.[627] A third study[413] reported no episodes of severe hypoglycaemia in both the educated and non-educated groups. There were no data available from any of the studies about the impact of carbohydrate counting regimens on the incidence of nocturnal hypoglycaemia.

**Impact on quality of life**

One study reported that individuals with the ability to carbohydrate count felt less restricted in their daily dietary intake [413], but other studies indicated no impact of carbohydrate counting on the Hypoglycaemia Fear Survey (HFS), Problems Areas In Diabetes (PAID), Audit of Diabetes-Dependent Quality of Life (ADDQoL) and Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores.

**Impact on adverse events**

There were no data available for non-hypoglycaemia adverse events from any of the studies assessing the impact of carbohydrate counting regimens on clinical outcomes.

**Use of bolus calculators:**

The evidence for the use of bolus calculators used with self-monitoring of blood glucose levels was reviewed.

**Impact on glycaemic control**

Three studies reported a reduction in HbA1c with use of a bolus calculator in place of manual counting ([464,627,770]). However, the mean reduction in HbA1c achieved at <6 months (0.25 %) was <0.3 % and not felt to be significant by the GDG.

**Impact on frequency of hypoglycaemia**

For studies assessing the impact of bolus calculator use on the incidence of hypoglycaemia, the mean incidence of mild and severe hypoglycaemia was higher with bolus calculator use compared with manual counting. There were no data

Update 2015

| | |
|---|---|
| **Recommendations** | **19. Offer carbohydrate-counting training to adults with type 1 diabetes as part of structured education programmes for self-management (see Structured Education, section 7.2).[new 2015]**<br><br>**20. Consider carbohydrate-counting courses for adults with type 1 diabetes who are waiting for a more detailed structured education programme or are unable take part in a stand-alone structured education programme.[new 2015]** |
| | available from any of the studies about the impact of bolus calculators on the incidence of nocturnal hypoglycaemia.<br><br>**Impact on quality of life**<br>One study reported that bolus calculator use improved DTSQ scores.[627] However, other studies indicated no impact of bolus calculator use on HFS, PAID and ADDQoL scores.<br><br>**Impact on adverse events**<br>There were no data available for non-hypoglycaemia adverse events from any of the studies assessing the impact of bolus calculators on clinical outcomes.<br>From a review of all of the available evidence, the GDG concluded that there was evidence to suggest a benefit of carbohydrate counting regimens taught outside of structured education courses for the management of type 1 diabetes. However, the GDG also recognised that evidence available from structured education programme reviews indicated that the effectiveness of carbohydrate counting teaching was likely to be improved when incorporated into structured education courses for the management of type 1 diabetes, with greater and more sustained improvements in glycaemic control, incidence of hypoglycaemia and quality of life.<br><br>The use of bolus calculators was associated with an improvement in glycaemic control, but an increased incidence of hypoglycaemia. The GDG recognised that the current evidence base for bolus calculators referred to trials where participant numbers were small; therefore a research recommendation was made requesting further evidence for the assessment of bolus calculators in adults with type 1 diabetes. |
| Economic considerations | No economic evaluations about the use of carbohydrate counting regimens outside of structured education courses or bolus calculators in the management of adults with type 1 diabetes was available for review.<br>Consultation amongst healthcare professionals within the GDG concluded that a three and a half hour education session from a dietitian could be reasonably recognised as sufficient time to educate adults with type 1 diabetes on carbohydrate counting regimens (half an hour for course set-up followed by three hours education). Dietitian costs for a three and a half hour education session were calculated to be £343 per session, based on a band 6 and a band 7 dietitian. Cost per patient per session was reduced with increasing numbers of patient per session (£86 for 4 adults, £43 for 8 adults and £29 for 12 adults). The GDG believed that education could be reasonably delivered to 8 adults at a single session; groups larger than this could result in a detriment in the quality of the education and time available for each course attendee. Cost per attendee per session was therefore calculated at £43 per individual: at this level of cost, the improvement in quality of life per individual achieved by the education session would only have to be small to be cost-beneficial. The GDG concluded that carbohydrate-counting courses were cost-beneficial for |

Update 2015

| | |
|---|---|
| **Recommendations** | **19. Offer carbohydrate-counting training to adults with type 1 diabetes as part of structured education programmes for self-management (see Structured Education, section 7.2).[new 2015]**<br><br>**20. Consider carbohydrate-counting courses for adults with type 1 diabetes who are waiting for a more detailed structured education programme or are unable take part in a stand-alone structured education programme.[new 2015]** |
| | adults with type 1 diabetes. |
| Quality of evidence | The impact of carbohydrate counting regimens used outside of structured education courses for adults with type 1 diabetes were assessed in the evidence review. Three studies ([627], [413], [623]) were randomised controlled trials (RCTs) comparing the impact of carbohydrate counting on outcomes versus no carbohydrate counting, and one study was a before and after observational study ([176]) assessing the clinical impact of a prescribed diet and prescribed insulin doses regimen based on carbohydrate counting. <br><br>Eight studies ([87], Ziegler 2013,[627] , [54],[374], Maurizi 2011, [222]Franc 2009, [383]) did not compare carbohydrate counting with a control group but reported methodologies (technologies or additional algorithms) to assist patient carbohydrate counting and they were therefore included in the evidence review for carbohydrate counting. Three of these studies (Ziegler 2013, [627], Maurizi 2011) were RCTs comparing carbohydrate counting with the use of technology (a bolus calculator) vs. manual carbohydrate counting (without technology). This evidence was also used to assess the impact of bolus calculators on clinical outcomes in adults with type 1 diabetes. <br><br>The GRADE quality of the assessed studies ranged from Moderate to Very low, and the potential for risk of bias was considered to be serious to very serious. The GDG noted that many of the available studies were small in size (largest study [623]; 256 participants) and of short duration (longest follow-up [623]; 9 months). |
| Other considerations | The available evidence for the use of bolus calculators in the management of type 1 diabetes had a substantial overlap with that of the use of carbohydrate counting, and therefore the GDG considered the impact of each in a single set of recommendations, as the evidence for bolus calculators was inextricably linked with that of carbohydrate counting outcomes. The GDG also recognised that correct use of bolus calculators was likely to be highly dependent on the level of education delivered to an individual from a preceding carbohydrate counting course. <br><br>The evidence reviewed by the GDG for the use of bolus calculators did not include evidence for their use in conjunction with insulin pump therapies, and only considered their impact on clinical outcomes when used with self-monitoring of blood glucose levels in adults with type 1 diabetes using multiple daily injections of insulin. The GDG noted that any recommendations made about the use of bolus calculators should not stop individuals on continuous subcutaneous insulin infusions using bolus calculators built into insulin pump devices. <br><br>The GDG found no evidence about when carbohydrate counting education should occur in individuals with type 1 diabetes. Members of the GDG recognised that ideally some carbohydrate-counting education should be provided soon after a diagnosis of type 1 diabetes, so that the individual understand the relationship between bolus insulin and carbohydrate intake. However, the GDG also recognised that some individuals may be overwhelmed by carbohydrate-counting education whilst coming to terms with a new diagnosis of type 1 diabetes. In addition, some of the benefits of carbohydrate counting education may not be fully realised if education was provided during the honeymoon period, when good glucose control |

Update 2015

| | |
|---|---|
| **Recommendations** | **19.** Offer carbohydrate-counting training to adults with type 1 diabetes as part of structured education programmes for self-management (see Structured Education, section 7.2).[new 2015]<br><br>**20.** Consider carbohydrate-counting courses for adults with type 1 diabetes who are waiting for a more detailed structured education programme or are unable take part in a stand-alone structured education programme.[new 2015] |
| | might be achieved even without accurate carbohydrate counting. The GDG concluded that there was insufficient evidence to make a recommendation as to when carbohydrate counting education should take place, and that timing and depth of education was likely to be based on an individual's personality and needs.<br>The GDG recommended that carbohydrate counting be given as part of a structured education course, as carbohydrate counting education delivered in this way was more likely to have greater benefit to an individual with diabetes than carbohydrate counting education on its own. However, the GDG also recognised that there may be circumstances where access to a structured education course might be limited or delayed, and that early carbohydrate counting education alone could be of benefit to adults with type 1 diabetes willing to make lifestyle changes. The GDG therefore made an additional recommendation to provide guidance on providing carbohydrate counting education outside of structured education courses in these circumstances.<br><br>Bolus calculators can be a useful addition to a patient's own carbohydrate-counting. They remove much of the burden of dose and correction calculation, especially for patients using more varied or more precise ratios. Additionally bolus calculators can assist patients who have difficulty with mental arithmetic. However the GDG felt that it is important to recognise that a bolus calculator's effectiveness relies on carefully adjusted settings, ratios and blood glucose targets, and ability to carbohydrate count accurately. These are usually established with the help of skills learned in structured education, or in intensive one-to-one consultation with a suitably trained healthcare professional. It is also important for patients to realise that these settings should be regularly reviewed and updated to take account of changing circumstances. |

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### 7.3.7 Research recommendation

5. **In adults with type 1 diabetes, what is clinical and cost effectiveness of bolus calculators used in conjunction with self-monitoring blood glucose meters?**

### 7.3.8 Review question: In adults with type 1 diabetes, what is the clinical effectiveness of a diet based on the glycaemic index for optimal diabetic control?

For full details see review protocol in Appendix C.

**Table 44: PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults with type 1 diabetes |
| **Intervention(s)** | High GI diet |
| **Comparison(s)** | Low GI diet |
| **Outcomes** | • HbA1c<br>• Severe hypoglycaemia |

| Population | Adults with type 1 diabetes |
|---|---|
| | • Nocturnal hypoglycaemia<br>• Quality of life<br>• Patient satisfaction<br>• Adherence |
| Study design | RCTs |

### 7.3.9 Clinical evidence

Five studies (one non-randomised crossover study and four crossover randomised controlled trials) were included in the review[102,219,408,472,719] and these are summarised in Table 45 below. Evidence from these studies is summarised as a GRADE table in Appendix I. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, and excluded studies list in Appendix K.

Update 2015

**Update 2015**

**Table 45:   Summary of studies included in the review**

| Study | Intervention versus comparison | Study design; Population | Critical outcomes reported | Comments |
|---|---|---|---|---|
| Calle-Pascual 1988[102] | Low GI diet (GI range: 29 – 36) vs. High GI diet (GI range: 50 – 02) | Non-randomised crossover study 4 weeks treatment Type 1 diabetes mean age = 25.6 ± 4.3 years Type 1 diabetes (n=16) and type 2 diabetes (n=18) Baseline insulin regimen: 2 daily doses (fast and delayed action) Mean insulin dose - unit per day (SD): 40 ± 16 | HbA1c | The results for type 1 diabetes participants were reported separately from those of type 2 diabetes participants. The relatively low mean age implies that the population may include children and young people (<18 years old) but this is not stated. |
| Fontvieille[219] 1992 | Low GI diet (GI mean ± SD: 38 ± 5) vs. High GI diet (GI mean ± SD: 64 ± 3) | Crossover RCT 5 weeks treatment Type 1 diabetes mean age = 42.7 ± 10.3 years Type 1 diabetes (n=12) and type 2 diabetes (n=6) Baseline insulin regimen: 2 – 3 injections per day (type 1 diabetes only) Mean insulin dose - unit per day (SD): 40.9 ± 12.8 | HbA1c | The results were of both the type 1 diabetes and type 2 diabetes participants combined, but it is noted that there were no statistically significant differences between the two groups for any of the outcomes. |
| Lafrance[408] 1998 | Low GI (GI <60) vs. Intermediate GI (GI 60 – 90) vs. High GI (GI >90) | Crossover RCT 12 days treatment Mean age not reported Type 1 diabetes only (n=9) Baseline insulin regimen: Intensive insulin therapy for ≥3 months with either multiple subcutaneous insulin injections (n=5) or continuous subcutaneous insulin infusion | Severe hypoglycaemia | The participants are said to be highly motivated and had well-controlled diabetes. |

| Study | Intervention versus comparison | Study design; Population | Critical outcomes reported | Comments |
|---|---|---|---|---|
| | vs.<br>High fibre<br>(GI 60 – 90 + ≥40 g fibre/day) | with multiple basal rates and pre-meal boluses (n=4)<br>Mean insulin dose – unit per day (SD): not reported | | |
| McCulloch[472] 1985 | New diet (ND)<br>(high carb + high fibre + low fat)<br>vs.<br>Continuation of current diet (CD) | RCT<br>>6 months treatment<br>Mean age = 35 years (Range 17 – 64)<br>Type 1 diabetes only (n=40)<br>Baseline insulin regimen: short and intermediate acting insulin given 30 minutes before breakfast and 30 minutes before the evening meal<br>Mean insulin dose – unit per kg per day: ND 0.67 ± 0.03 vs. CD 0.88 ± 0.08 | HbA1c<br>Adherence to treatment | The final values were measured at different time points (intervention group at 10 months and control group at 6 months) and therefore caution should be taken when comparing the outcomes. |
| Venhaus[719] 1998 | Unrefined carbohydrate diet (fibre-rich = low GI)<br>vs.<br>Refined carbohydrate diet (fibre-depleted = high GI) | Crossover RCT<br>6 weeks treatment<br>Mean age = 27 ± 9 years<br>Type 1 diabetes only (n=10)<br>Baseline insulin regimen: continuous subcutaneous insulin infusion for >1 year<br>Mean insulin dose – unit per day: 41.7 ± 6.9 | HbA1c<br>Severe hypoglycaemia | It was reported that the overall intake of carbohydrate and hence, energy was lower in the intervention group than in the comparison group. The difference in daily energy intake between the two groups was significant (p=0.04). The mean age is also relatively low, and there may have been children or young people, but this is not clearly stated. |

**Update 2015**

**Table 46: Evidence summary table: Low GI diet versus high GI diet**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference Low GI diet | Final value for control group High GI diet |
|---|---|---|---|---|---|
| HbA1c at ≤6 months (Non-RCT) | 1 study (n=24) | Serious | VERY LOW | MD 0.25 higher (from 0.09 to 0.59 higher) | 9.02 |
| HbA1c at ≤6 months (RCT) | 2 studies (n=56) | No serious imprecision | LOW | MD 0.36 higher (from 0.14 lower to 0.86 higher) | Study 1 = 8.3 Study 2 = 5.8 |
| HbA1c at >6 months (follow-up at different time points) | 1 study (n=22) | Serious | VERY LOW | MD 0.5 higher (from 0.08 to 0.92 higher) | 9.5 |
| Severe hypoglycaemia ≤6 months | 2 studies (n=38) | No serious imprecision | VERY LOW | No difference | 0 event |
| Adherence to treatment at >6 months (Coefficient of variation based on patient's food diary) | 1 study (n=22) | Not applicable | VERY LOW | 1.7% higher | 28.1% |

### 7.3.10 Economic evidence [2015]

**Published literature**

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

### 7.3.11 Evidence statements

#### 7.3.11.1 Clinical evidence statements [2015]

- Low and Very low quality evidence from RCTs showed a clinically important harm in terms of HbA1c at less than or equal to 6 months and at more than 6 months for a low GI diet compared with a high GI diet.
- Very low quality evidence mostly from single studies showed no clinically important difference between low GI diet and high GI diet for HbA1c and severe hypoglycaemia at less than or equal to 6 months, and for adherence to treatment at more than 6 months. The HbA1c data in this case was from a non-randomised controlled trial.

#### 7.3.11.2 Economic [2015]

No relevant economic evaluations were identified.

### 7.3.12 Recommendations and link to evidence

| Recommendations | 21.Do not advise adults with type 1 diabetes to follow a low glycaemic index diet for blood glucose control.[new 2015] |
|---|---|
| Relative values of different outcomes | The GDG determined the impact of high GI diets in comparison to low GI diets on clinical outcomes in adults with type 1 diabetes by assessing the impact of each intervention on the following outcomes: |
| | **Improvement in glycaemic control -** Assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular and macrovascular complications. A diet comprising low GI foods, which are individually associated with a low post-prandial blood glucose peak, may be associated with better overall glycaemic control than a diet of high GI foods, which are associated with a more rapid release of glucose into the circulation |
| | **Hypoglycaemia, including severe hypoglycaemia -** A low GI diet might theoretically reduce the incidence of hypoglycaemia in an individual with type 1 diabetes by providing a more sustained release of glucose into the bloodstream over a longer period of time in comparison to a high GI diet. Particular focus was given to: |
| | Incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a third party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. |
| | Incidence of nocturnal hypoglycaemia. |
| | **Quality of life** – The evidence was reviewed to look at the impact of each diet on |

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quality of life outcomes. An intervention that reduces the frequency of severe hypoglycaemia episodes and improves glycaemic control should increase quality of life. However, the need to adhere to a strict diet may also impact on quality of life.

**Adverse events** – A diet aiming to achieve a GI target may produce gastro-intestinal side-effects; the evidence was reviewed to assess any reported adverse events associated with adherence to diets.

| | |
|---|---|
| Trade-off between clinical benefits and harms | The GDG considered evidence from available randomised controlled trials (RCTs) and observational studies assessing the impact of high and low GI diets on clinical outcomes in adults with type 1 diabetes.<br><br>**Impact on glycaemic control**<br>The GDG reviewed the impact of GI diets on glycaemic control, with glycaemic control assessed by HbA1c (%) at <6 months in three studies (Calle-Pascual 1998, Venhaus 1988, Fontvielle 1992), and at >6 months in one study (McCulloch 1985). No difference in HbA1c outcome was noted with low or high GI diets at <6 months or >6 months.<br><br>I**mpact on incidence of hypoglycaemia**<br>One study (LaFrance 1998) reported no significant difference in frequency of hypoglycaemia in nine participants who were alternated between low, medium and high GI diets; none of the participants experienced severe hypoglycaemia events during the study, which lasted a total of 48 days.<br><br>A second crossover study (Venhaus 1988) compared 10 participants on a high GI diet with 10 participants on a low GI diet, with participants switching over diets after six weeks. No difference in incidence of hypoglycaemia was reported when outcomes were compared for high and low GI diets.<br><br>None of the other studies reported outcomes on incidence of hypoglycaemia.<br><br>I**mpact on quality of life**<br>None of the reviewed studies commented on the impact of high and low GI diets on quality of life.<br><br>**Adverse events**<br>None of the available evidence reviewed by the GDG reported any adverse events as a consequence of adhering to a diet aimed at maintaining a fixed GI at mealtimes, with no adverse side-effects and no instances of diabetic ketoacidosis reported in the studies. |
| Economic considerations | No cost effectiveness studies assessing the impact of GI diets on clinical outcomes in adults with type 1 diabetes were available for review.<br><br>As GI diets did not show any significant impact on clinical outcomes, they are unlikely to be cost effective in the management of adults with type 1 diabetes. |
| Quality of evidence | Five studies met the inclusion criteria for review by the GDG: one non-randomised crossover study [102] and four crossover RCTs [219,408,472,719].<br><br>The GDG noted that the available evidence for review was from more than a decade ago, that the number of participants in each study was small (the largest study was undertaken in 40 adults with type 1 diabetes [472], and that the duration of the trials was short (the longest duration of a dietary intervention in the studies was four months [472] making it difficult to assess the impact on glycaemic control by |

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| | |
|---|---|
| | HbA1c measurement).<br><br>The quality of the evidence was GRADE assessed, and ranged from Low to Very low, with a serious to very serious risk of bias. |
| Other considerations | The GDG noted that there were no recent studies assessing the impact of GI diets on clinical outcomes in adults with type 1 diabetes. Many of the previous studies used only small numbers of participants over a short duration of time and few used modern insulin treatment regimens.<br><br>The GDG recognised that there are theoretical reasons why a low GI diet might lead to improved blood glucose control, and that post-prandial glucose levels might be reduced with a low GI diet. There are currently no long-term trials assessing the impact of low GI diets which is low in fat (low GI foods can be those which are high in fat, such as, chocolate and cakes) on the incidence of microvascular complications.<br><br>Given that no adverse events were reported from adherence to a diet aimed at achieving a target GI, the GDG decided that a research recommendation be made for further assessment of following a low GI diets (also low in fat) in adults with type 1 diabetes. |

*Update 2015*

22. **Provide nutritional information sensitive to personal needs and culture from the time of diagnosis of type 1 diabetes. [2004]**

23. **Provide nutritional information individually and as part of a diabetes education programme (see Section 8.2). Include advice from professionals with specific and approved training and continuing accredited education in delivering nutritional advice to people with health conditions. Offer opportunities to receive nutritional advice at intervals agreed between adults with type 1 diabetes and their advising professionals. [2004]**

24. **Discuss the hyperglycaemic effects of different foods an adult with type 1 diabetes wishes to eat in the context of the insulin preparations chosen to match those food choices. [2004]**

25. **Make programmes available to adults with type 1 diabetes to enable them to make:**
    - **optimal choices about the variety of foods they wish to consume**
    - **insulin dose changes appropriate to reduce glucose excursions when taking different quantities of those foods. [2004, amended 2015]**

*Update 2015*

26. **Agree the choice of content, timing and amount of snacks between meals or at bedtime available to the adult with type 1 diabetes, based on informed discussion about the extent and duration of the effects of eating different food types and the insulin preparations available to match them. Modify those choices based on discussion of the results of self-monitoring tests. [2004]**

27. **Make information available on:**
    - **effects of different alcohol-containing drinks on blood glucose excursions and calorie intake**
    - **use of high-calorie and high-sugar 'treats'. [2004, amended 2015]**

*Update 2015*

28. Make information available about the benefits of healthy eating in reducing arterial risk as part of dietary education in the period after diagnosis, and according to need and interest at intervals thereafter. Include information about fruit and vegetables, types and amounts of fat, and ways of making the appropriate nutritional changes. [2004, amended 2015]

29. Modify nutritional recommendations to adults with type 1 diabetes to take account of associated features of diabetes, including:
- excess weight and obesity
- underweight
- eating disorders
- hypertension
- renal failure. [2004]

30. Be aware of appropriate nutritional advice on common topics of concern and interest to adults living with type 1 diabetes, and be prepared to seek advice from colleagues with more specialised knowledge. Suggested common topics include:
- body weight, energy balance and obesity management
- cultural and religious diets, feasts and fasts
- foods sold as 'diabetic'
- sweeteners
- dietary fibre intake
- protein intake
- vitamin and mineral supplements
- alcohol
- matching carbohydrate, insulin and physical activity
- salt intake in hypertension
- comorbidities including nephropathy and renal failure, coeliac disease, cystic fibrosis, or eating disorders
- use of peer support groups. [2004, amended 2015]

31. Offer dietary advice to adults with type 1 diabetes about issues other than blood glucose control, such as weight control and cardiovascular risk management, as indicated clinically. [new 2015]

7.3.13   Research Recommendations

6. In adults with type 1 diabetes, what is the clinical and cost effectiveness of different types of diet and dietary constituents, particularly in terms of the effect on insulin requirement and blood glucose control?

# 7.4   Physical activity [2004]

Physical activity was not within the scope of the 2015 update. The content presented here is from 2004.

### 7.4.1 Rationale

Many people wish to perform varying amounts of physical exercise, but this can interact to disturb blood glucose levels in people on insulin therapy. Physical exercise is usually recommended to the general population as part of a package of lifestyle measures to improve future health, in particular reduction of arterial risk, which is markedly elevated in people with Type 1 diabetes.

### 7.4.2 Evidence statements

**Aerobic exercise**

One small randomised controlled trial was identified that assessed the effect of a 16-week aerobic exercise programme on fitness and lipid profile in young men with Type 1 diabetes.[403] There were significant differences in $VO_{2max}$ and serum total cholesterol compared with no training. There were no significant changes in outcomes of HbA1c and plasma glucose. The study was not blinded due to the nature of the intervention (**Ib**).

A small cross-sectional study evaluating the effect of three months of individualised aerobic exercise in altering blood pressure and lipid profile found that HbA1c, fructosamine, and total blood glucose did not change significantly from baseline levels.[435] The design of the study would not represent a sound basis for supporting a recommendation for advocating exercise as therapy (**IIa**) .

Another study with a similar intervention found that four months of aerobic training provided no changes in terms of HbA1c or total cholesterol, although there were benefits of exercise compared to control in terms of peak oxygen uptake (**IIb**).[403]

A prospective non-randomised study with a before and after design found that steady-state plasma glucose was significantly decreased compared to baseline as was plasma insulin with supervised exercise program (at least 135 minutes/week) for three months compared to no exercise.[424] Also cholesterol decreased significantly, however there were no reported significant changes in fasting blood glucose, HbA1c and microalbuminuria (**IIb**).

**Education and exercise**

A medium-sized randomised controlled trial of intensive advice and lifestyle programme with specified diet and exercise prescriptions compared to conventional care found that HbA1c decreased from baseline measurements significantly over six months in the control group but remained relatively stable in the intervention group, but no between-group comparison was made.[555] Also HDL cholesterol and triglycerides were not significantly different between groups at any phase of the study. However exercise sessions were not standardised in the study and a lack of blinding limited the validity of the trial (**Ib**).

A small before and after study found that an intervention of 10 hours of education and physical training three or four times a week produced no metabolic response at three months with fasting plasma glucose levels and serum cholesterol not changing significantly.[628] Without blinding or randomisation this evidence is not sufficient to support the use of a mixed education and exercise intervention for people with type 1 diabetes (**IIb**).

**Other exercise**

A non-randomised prospective controlled study to assess whether exercise is related to better diabetes control was reviewed.[435] There was no significant correlation between the exercise expenditure and HbA1c in all Type 1 diabetes patients, nor was there any relationship to the frequency of mild hypoglycaemic events (**IIa**).

**Guidelines on exercise**

The ADA guidelines present recommendations based on a good evidence-based review.[29]They recommend that a thorough evaluation be undertaken of patients before exercise is initiated. General recommendations for how to exercise safely include:

- metabolic control before activity
- blood glucose monitoring before and after physical activity
- food intake to be considered with added carbohydrate as necessary (**Ia**).

### 7.4.3   Health economic evidence

No evidence was found on the cost-effectiveness of programmes encouraging physical activity for Type 1 diabetes.

### 7.4.4   Consideration

The group noted that the evidence for an improved arterial risk profile in people with Type 1 diabetes was consistent with that for other diabetic and non-diabetic people. Evidence of a consistent effect in improving blood glucose control was absent, although by analogy with people with Type 2 diabetes the overweight/insulin-resistant person might benefit form an exercise programme as part of a lifestyle improvement initiative. Some people will undertake significant exercise by choice and would benefit from support in so doing.

### 7.4.5   Recommendations

**32.Advise adults with type 1 diabetes that physical activity can reduce their enhanced arterial risk in the medium and longer term. [2004]**

**33.Give adults with type 1 diabetes who choose to integrate increased physical activity into a more healthy lifestyle information about:**
- **appropriate intensity and frequency of physical activity**
- **role of self-monitoring of changed insulin and/or nutritional needs**
- **effect of activity on blood glucose levels (likely fall) when insulin levels are adequate**
- **effect of exercise on blood glucose levels when hyperglycaemic and hypoinsulinaemic (risk of worsening of hyperglycaemia and ketonaemia)**
- **appropriate adjustments of insulin dosage and/or nutritional intake for exercise and post-exercise periods, and the next 24 hours**
- **interactions of exercise and alcohol**
- **further contacts and sources of information. [2004]**

## 7.5   Cultural and individual lifestyle [2004]

Cultural and individual lifestyle was not within the scope of the 2015 update. The content presented here is from 2004.

### 7.5.1   Rationale

Cultural and genetic differences between ethnic groups are known to affect health and response to healthcare for many diseases. In regard of Type 1 diabetes this is particularly true of eating habits,

while arterial risk is known to differ for the general population and people with Type 2 diabetes. Other care issues seem likely.

### 7.5.2    Consideration

The group were aware of a systematic review designed to detect issues of relevance (rather than trials of interventions) identified papers concerning differences in incidence, attitudes to complications, degree of response to education programmes, blood glucose control, religious fasting and feasting, and hospitalisation.

The group noted that cultural and genetic issues affected diabetes healthcare delivery in the areas of:

* patient education and self-care
* nutritional advice
* insulin therapy (including religious feasts and fasts)
* arterial risk
* blood pressure management
* hospitalisation.

In some areas there was overlap with social/deprivation issues. The group's recommendations addressed cultural/religious issues in the appropriate sections of this guideline, emphasising the primacy of the individual in this regard.

### 7.5.3    Recommendations

34. Regard each adult with type 1 diabetes as an individual, rather than as a member of any cultural, economic or health-affected group (see also recommendations 22, 30 and 65 about the cultural preferences of individual adults with type 1 diabetes). [2004, amended 2015]

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# 8 Blood glucose control

The evidence and text from the 2004 guideline, CG15, that has been superseded by this update is included in Appendix S.

## 8.1 Optimum target HbA1c level and frequency of HbA1c monitoring

### 8.1.1 Introduction

One of the main objectives of care for people with type 1 diabetes is to keep the risk of microvascular and macrovascular complications of diabetes to a minimum. Optimising glycaemic control is an obvious tool and one measure of glycaemic control is the glycated haemoglobin, or HbA1c, which is formed by an interaction between the red cell pigment, haemoglobin, and the circulating blood glucose. HbA1c measurements reflect time-averaged blood glucose concentrations during the previous 2 to 3 months and are used worldwide as the gold standard assessment of glycaemic control in people with type 1 diabetes. Lowering the HbA1c towards the non-diabetic range with intensified insulin therapy was proven to reduce the risk of microvascular complications in the randomised controlled Diabetes Control and Complications Trial (DCCT) [687] and was associated with a reduction in macrovascular disease in the DCCT follow-up studies ([498 405]). Of various measures of glucose control, only HbA1c was associated with risk of both microvascular and cardiovascular disease.[274]

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has standardised HbA1c measurements across the world, providing a reference method for calibration purposes. Local laboratories should report results that are reproducible in other laboratories, using the IFCC standards. The IFCC reference method reports HbA1c in mmol/mol. Previously, results were reported as a percentage of total haemoglobin (%) as in the DCCT assay standard and dual reporting of both values has been encouraged. [501]

In DCCT, the attainment of lower HbA1c was associated with a greater risk of severe hypoglycaemia (low blood glucose concentration that impaired function so that the person was unable to self-treat and required treatment from a third party). [1,687] Subsequently, many groups have been able to support adults with type 1 diabetes reduce risk of severe hypoglycaemia at the same time as lowering HbA1c, (for example, [616],[328]) but there remain concerns that targets for glycaemic control need to take into account individual ability to achieve them without increasing severe hypoglycaemia risk. Adults with type 1 diabetes need information on the blood glucose control targets they need to achieve if they wish to minimise vascular risk

**The GDG therefore addressed the following questions:**

- In adults with type 1 diabetes, what is the optimum target HbA1c level that should be achieved to reduce the risk of complications?
- In adults with type 1 diabetes, what is optimum frequency of HbA1c monitoring for effective diabetic control?

For full details see review protocol in Appendix C.

### 8.1.2 Review question: In adults with type 1 diabetes, what is the optimum target HbA1c level that should be achieved to reduce the risk of complications?

**Table 47: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
|---|---|

_Update 2015_

| | |
|---|---|
| | • Adult is defined as aged ≥18 years |
| **Intervention/s** | HbA1c target values |
| **Comparison/s** | • Other target values (RCTs and comparative observational studies)<br>• No targets (prognostic studies) |
| **Outcomes** | Outcomes<br>• Number of people reaching target HbA1c (dichotomous)<br>• Final HbA1c value (continuous)<br>• Hypoglycaemia (dichotomous or continuous outcome at a particular target<br>• Severe hypoglycaemia (dichotomous or continuous outcome, depending how it is reported)<br>• Nocturnal hypoglycaemia (dichotomous or continuous outcome, depending how it is reported)<br>• Complications/avoidance:<br>    o CV events (MI, IHD, Stroke, cardiac and peripheral revascularisation, major amputation)<br>    o Retinopathy<br>    o Low-level (micro) albuminuria/proteinuria<br>    o Renal replacement therapy/end-stage renal failure<br>    o Neuropathy<br>    o Sudden death<br>• Quality of life – (dichotomous/continuous) |
| **Study design** | RCTs, observational studies |

### 8.1.3 Review question: In adults with type 1 diabetes, what is optimum frequency of HbA1c monitoring for effective diabetic control?

For full details see review protocol in Appendix C.

**Table 48:   PICO characteristics of review question**

| | |
|---|---|
| **Population** | Adults with type 1 diabetes<br>• Adult is defined as aged ≥18 years |
| **Intervention/s** | HbA1c monitoring |
| **Comparison/s** | • HbA1c monitoring (the same as the intervention but at a different frequency or delivery time)<br>• Standard care<br>• No comparison (non-comparative studies) |
| **Outcomes** | • Number of people reaching target HbA1c (dichotomous)<br>• Final HbA1c value (continuous)<br>• Hypoglycaemia (dichotomous or continuous outcome at a particular target<br>• Severe hypoglycaemia (dichotomous or continuous outcome, depending how it is reported)<br>• Nocturnal hypoglycaemia (dichotomous or continuous outcome, depending how it is reported)<br>• Complications/avoidance:<br>    o CV events (MI, IHD, Stroke, cardiac and peripheral revascularisation, major amputation)<br>    o Retinopathy<br>    o Low-level (micro) albuminuria/proteinuria<br>    o Renal replacement therapy/end-stage renal failure |

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| | |
|---|---|
| | ○ Neuropathy |
| | ○ Sudden death |
| | • Quality of life – (dichotomous/continuous) |
| **Study design** | RCTs, observational studies |

### 8.1.4 Clinical evidence

Forty three studies were identified for the optimum HbA1c target review.[2,3,5,21,24,41,89,175,185,221,270,307,315,344,377-380,401,420,425,437,448,492,493,498,527,533,534,553,586-588,606,644,675,687,715,734,738,743,744,771] Five studies reported from the Diabetes Control and Complications (DCCT) RCT.[3-5,24,687,739] Three studies were post-intervention follow-ups of DCCT (DCCT/EDIC).[344,498,738] Two studies reported from the Pittsburgh Epidemiology of Diabetes Complications study (Pittsburgh EDC).[533,534] Three studies reported from Stockholm Diabetes Intervention Study (SDIS)[586-588], two at 94 months [586,587], and one 3 years later[588] Seven studies reported from the Wisconsin Epidemiology Study of Retinopathy (WESDR).[377-380,420,492,493] Two studies reported from a Swedish cohort.[743,744]

Four studies reported glycated haemoglobin as HbA1, which includes non-enzymatic binding of several carbohydrate moieties to HbA) [377-379,492,493], while the remaining studies measured HbA1c (binding of glucose specifically).

Two studies were identified for the frequency of monitoring HbA1c review.[208,411] Both these studies measured HbA1c.

Most of the studies were observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below. A summary of the included studies is provided in Table 49, Table 50, Table 51 and Table 52. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

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**Table 49:   Summary of studies included on optimum HbA1c target level**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| Agardh 1997[21] | Prospective case-series | n=442 with type 1 diabetes Sweden | 5 years | Retinopathy<br>Urinary albumin concentration<br>Death<br>MI<br>CV disease | Regression analysis |
| ARASKIEWICZ[41] | Prospective case series | n=88 with type 1 diabetes Poland | 6 years | Retinopathy<br>Low-level (micro) albuminuria<br>Severe hypoglycaemia<br>QoL | Regression analysis |
| Brinchmann-Hansen 1992[89] | Prospective case-series of patients originally enrolled in Oslo 1985 RCT[152] | n=45 with type 1 diabetes Norway | 7 years | Retinopathy | Regression analysis<br>Oslo 1985 RCT; insulin pumps versus multiple injections versus conventional retreatment treatment (regular insulin and isophane insulin twice daily) |
| DCCT 1993[264,687]<br>DCCT 1995[3]<br>DCCT 1996[4]<br>DCCT 1997[5]<br>DCCT end of follow-up[24] | RCT<br>Intensive therapy;<br>≥3 insulin injections daily or external<br>insulin pump use<br>Conventional therapy<br>1-2 daily insulin injections | n=1441 IDDM USA | 6.5 years | Progression to retinopathy<br>Macular oedema<br>Severe non-proliferative or proliferative retinopathy<br>Nephropathy<br>Neuropathy (5 years)<br>Mortality<br>Hypoglycaemia requiring assistance | Intensive therapy; glucose target of 70 to 120 mg/dl (3.9 to 6.7 mmol/litre) before meals<br>Conventional therapy; no target<br><br>Population<br><20% 13-18 year olds |
| DCCT/EDIC 2005[498]<br>DCCT/EDIC | Prospective case-series | DCCT; n=1441 EDIC; n=1421 USA | 17 years | CVD events; non-fatal MI, stroke, CVD death, angina<br>Retinopathy | Proportional hazards model<br>Prospective case series (EDIC ending 2004) from patients originally enrolled in DCCT (Baseline |

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| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| 2008[738]<br>DCCT/EDIC 2013[344] | | | | DQoL | 1983–1989, end of DCCT 1993) |
| Diamante 1997[175] | Cross-sectional observational study | n=1822<br>Spain; 18 centres | NA | Nephropathy | Regression analysis |
| EEG-OLOFSSON 2010[185] | Retrospective case-series | n=7,454 with type 1 diabetes<br>Sweden | 5 years | Mortality<br>CV outcomes | Regression analysis |
| FORREST 2000[221] | Prospective case-series | n=658 with type 1 diabetes<br>USA | 6 years | Mortality<br>CHD<br>LEAD (lower extremity arterial disease) | Regression analysis |
| GUERCI 1999[270] | Cross-sectional study | n=341 with type 1 diabetes<br>France | n/a | Retinopathy<br>Proliferative retinopathy | Regression analysis |
| HIETALA 2013[307] | Prospective case-series | n=2019 with type 1 diabetes<br>Finland | Mean 5.2 years | Mortality<br>Retinopathy<br>Nephropathy | Regression analysis |
| Hislop 2008[315] | Prospective case series | n=92<br>Australia | 6 months | Quality of life<br>CES-D<br>ASR | ANOVA statistical analyses |
| KULLBERG 1994[401] | Retrospective case series | n=90 with type 1 diabetes<br>Sweden | 9.2 years (average) | Retinopathy | Regression analysis |
| Lehto 1999[425] | Prospective case series | n=177 with type 1 diabetes<br>Finland | 7 years | CHD mortality<br>Combined outcome; CHD mortality<br> or non-fatal MI | Regression analysis |

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| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|-------|--------------------------|------------|-----------|----------|----------|
| LIND 2011[437] | Prospective case series | n=20,985 with type 1 diabetes Sweden | 9 years (mean) | Heart failure | Regression analysis |
| Lustman 2005[448] | Cross-sectional observational study | n=188 with type 1 diabetes USA | NA | Quality of life SCL-90 SDSCA | Regression analysis |
| NORDWALL 2009[527] | Case-series (retrospective and prospective elements) | n=269 with type 1 diabetes Sweden | Between 14 to 28 years | Retinopathy Nephropathy | Regression analysis |
| Pirez Mendez 2007[553] | Prospective case series | n=59 with type 1 diabetes Spain | 7 years | HbA1c Severe hypoglycaemia Mild hypoglycaemia | Regression analysis Patient switched to multiple insulin dose regime with target of HbA1c <6.2% at start of study |
| Pittsburgh EDC 2002[533] | Prospective case series | n=586 with type 1 diabetes USA | 10 years | Lower extremity arterial disease (claudication, foot ulceration or lower extremity amputation) | Regression analysis |
| Pittsburgh EDC 2003[534] | Prospective case series | n=603 with type 1 diabetes USA | 10 years | CAD death, non-fatal MI, angina, revascularisation, ECG ischaemia | Regression analysis |
| ROSSING 1996[606] | Prospective case series | n=939 with type 1 diabetes Denmark | 10 years | Mortality CV mortality | Regression analysis |
| SDIS 1995[586-588] | RCT/cohort follow-up | n=89 with type 1 diabetes Sweden | 94 months/10 years | Retinopathy Nephropathy Neuropathy | Incidence of outcomes according to HbA1c levels Regression analysis Patients originally randomised to either intensified conventional insulin treatment (insulin with education to ensure constant monitoring and treatment) or standard therapy (2 to 3 insulin injections/day) |
| Shaban 2006[644] | Cross-sectional | n=273 with type | NA | Quality of life | Regression analysis |

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| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | observational study | 1 diabetes UK | | HADS | |
| Tabaei 2004[675] | Cross-sectional observational study USA | n=634 with type 1 diabetes USA | NA | Quality of life QWB-SA | Regression analysis |
| Van Tilburg 2001[715] | Cross-sectional observational study | n=30 with type 1 diabetes USA | NA | Quality of life BDI | Regression analysis |
| WDRS 2013[420] | Prospective case series | n=305 with type 1 diabetes USA | 20 years | Retinopathy and proliferative retinopathy | Regression analysis |
| WEINSTOCK 2013[734] | Cross-sectional study/retrospective case-series | n=7012 with type 1 diabetes USA | n/a and previous 12 years data | Severe hypoglycaemia | Regression analysis |
| WESDR 1994[493] | Prospective case series | n=2990 with type 1 diabetes USA | 10 years | CHD death | Regression analysis 2 subgroups of WESDR; n=1210 subjects with diabetes diagnosis <30 years n=1780 subjects with diabetes diagnosis ≥30 years |
| WESDR 1995[378,379] | Prospective case series | n=2990 with type 1 diabetes USA | 10 years | Retinopathy Nephropathy Neuropathy | Nephropathy; incidence at 6 year follow-up 2 subgroups of WESDR; n=12101 subjects with diabetes diagnosis <30 years n=1780 subjects with diabetes diagnosis ≥30 years |
| WESDR 1998[377] | Cross-sectional observational study | n=987 with type 1 diabetes USA | 14 years | Quality of life SF-36 | Regression analysis 2 subgroups of WESDR; n=654 subjects with diabetes diagnosis <30 years |

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | | | | | n=333 subjects with diabetes diagnosis ≥30 years |
| WESDR 1998a [380] | Prospective case series | n=634 With type 1 diabetes USA | 14 years | Retinopathy | Regression analysis 1 subgroup of WESDR; n=654 subjects with diabetes diagnosis <30 years |
| WESDR 1999[492] | Prospective case series | n=1890 with type 1 diabetes USA | 14 years | Lower extremity amputations | Regression analysis Incidence of outcomes according HbA1c 2 subgroups of WESDR; n=906 subjects with diabetes diagnosis <30 years n=984 subjects with diabetes diagnosis ≥30 years |
| WESDR 2013[420] | Prospective case series | n=583 with type 1 diabetes USA | 20 years | Retinopathy and proliferative retinopathy | Regression analysis |
| Wikblad 1991[744] | Retrospective case series | n=185 with type 1 diabetes Sweden | 9 years | Retinopathy Nephropathy (proteinuria) | Incidence of outcomes according to HbA1c levels |
| Wikblad 1996[743] | Retrospective case series | n=108 with type 1 diabetes Sweden | 10 years | Quality of life SWEDQUAL Hypoglycaemia | ANOVA statistical analyses |
| ZOFFMANN 2014[771] | Cross-sectional study | n=710 with type 1 diabetes Norway | n/a | PAID score | Regression analysis |

Abbreviations: ANOVA, Analysis Of Variance; ASR, Adult-Self-Report Scale; BDI, Beck Depression Inventory; CAD, coronary artery disease; CES-D, Centre for Epidemiological Studies-Depression Scale; CHD, coronary heart disease; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; HADS, Hospital Anxiety and Depression Scale; MI, myocardial infarction; NA, not applicable; NR, not reported; Pittsburgh EDC, Pittsburgh Epidemiology of Diabetes Complications; QWB-SA, Quality of Well-Being Self-Administered; SDIS, Stockholm Diabetes Intervention Study; SCL-90, Symptom Checklist-90; SDSCA, Summary of Diabetes Self-Care Activities; SF-36, Short Form 36; SWEDQUAL, Swedish quality of life questionnaire; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy

**Table 50:** **Summary of studies included on frequency of HbA1c monitoring**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| Eid Fares 2010[208] | Retrospective case series | n=117 with type 1 diabetes USA | 5 years | Fluctuations in HbA1c Nephropathy | Regression analysis Age range; 9–33 years |
| Larsen 1990[411] | RCT Monitored group; HbA1c levels available to staff, used with blood or urine glucose values to adjust treatment, target NFBG <9mmol/(162 mg/dl) Control group; HbA1c levels (including the randomisation values) not entered into the patients' records during study period, staff treated patients on blood or urine glucose values, target NFBG <9 mmol/(162 mg/dl) Second year; HbA1c levels in both groups available to healthcare professionals | n=240 with IDDM Denmark | 1 year (followed for 2nd year post intervention) | HbA1c | Analysis of HbA1c levels between groups Unclear if patients were type 1 diabetes or type 2 diabetes 8% patients lost to follow-up at 1 year, 22% patients lost to follow-up at 2 years |

*Abbreviations: IDDM, insulin dependent diabetes mellitus; NFBG, non-fasting blood glucose*

**Table 51: Study details and results for optimum HbA1c target**

| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Measure of glycosylated haemoglobin and results |
|---|---|---|---|---|---|---|
| Agardh 1997[21] | 442 | Prospective case series 5 years | NR | 8.5±1.6 (HbA1c) | Mean±SD; 16±5 times/patient | Measured; HbA1c<br>Retinopathy (n=121 follow-up data available for patients without retinopathy at entry);<br>Any retinopathy (n=64); HbA1c; 8.2±1.1% versus no retinopathy (n=57); HbA1c; 7.5±1.1%, p<0.0)<br>Cumulative frequency for retinopathy at 5 years;<br>50% patients who still had no signs of retinopathy, the mean HbA1c levels were <7.5% during the observation period versus<br>50% patients who developed any type of retinopathy, the mean HbA1c levels were >8.3% (p<0.0002)<br>50% patients who progressed to severe retinopathy mean HbA1c levels were >8.9%, (p<0.001) compared with patients without retinopathy at follow-up or those who developed any type of retinopathy<br>Increase UAC associated with mean HbA1c levels (p<0.01)<br>MI, CV disease, death not associated with mean HbA1c levels |
| ARASKIEWICZ[41] | 88 | Prospective case series 6 years | Intensive functional insulin therapy | 8.1 ± 1.9 (HbA1c) | Not reported | Measured; HbA1c<br>• Patients with retinopathy had higher values of HbA1c (p=0.04) than those without<br>• HbA1c <7.0% versus >7.0%: OR = 1.35 (95% CI 0.21 to 8.52), p = 1.0<br>• Patients with low-level (micro) albuminuria had higher values of HbA1c (p=0.04) than those without<br>• HbA1c <7.0% versus >7.0%: OR = 4.25 (95% CI 0.50 to 35.5), p=0.27<br>• Final HbA1c value:<br>  ○8.8 ± 1.3 (with retinopathy) versus 8.1 ± 1.4 (without retinopathy)<br>  ○ 8.8 ± 1.3 (with low-level (micro) albuminuria) versus 8.8 ± 1.3 (without low-level (micro) albuminuria) |
| Brinchmann- | 45 | Prospective | 10 patients; | 11.2±2.2 | Every 2 | Measured; HbA1 |

| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Measure of glycosylated haemoglobin and results |
|---|---|---|---|---|---|---|
| Hansen 1992[89] | | case-series 7 years | insulin pumps 29 patients; multiple injections delivered by an insulin pen 6 patients; conventional treatment (regular insulin and isophane insulin twice daily) | (HbA1) | months | Retinopathy<br>Mean±SD; number of microaneurysms and haemorrhages according to mean HbA1;<br><9.0% (n=20); baseline 11.8(14.8), 7 years 25.5(43.1), change 13.8(39.5)<br>9.1 to 10.0% (n=13); baseline 24.7(40.8), 7 years 41.1(58.7), change; 16.4(56.6)<br>>10.1% (n=12); baseline; 17.6(16.2), 7 years 80.5(66.7), change 62.8(65.8)*<br>*p= 0.014 compared with patients with HbA1 <10.0%<br>Multivariate regression analysis<br>Severity of retinopathy not correlated to age, BP, or kidney function, patients with retinopathy at baseline were more likely to have more severe retinopathy at 7 years (r = 0.41; p=0.005)<br>Independent variables; baseline HbA1, change HbA1, duration diabetes, baseline retinopathy<br>Regression coefficient(95%CI); baseline HbA1 r=0.36(0.06 to 0.66) p=0.027, change Hb1A r=-0.35(-0.068 to -0.02) p=0.041 duration diabetes r=0.009(0 to 0.018) p=0.44, baseline retinopathy r=0.35(0.02 to 0.68) p=0.046 |
| DCCT 1993[264,687] DCCT 1995[3] DCCT 1996[4] DCCT 1997A[5] DCCT end of follow-up[24] | 1441 Primary cohort; n=726<br><br>Secondary cohort; n=715 | RCT 6.5 years | Intensive therapy; ≥3 insulin injections daily or external insulin pump use<br>Conventional therapy | Primary cohort Intensive therapy; 8.8±1.6 Conventional therapy; 8.8±1.7<br>Secondary cohort | 4 times/year | Measured; HbA1c<br>Progression of retinopathy;<br>Primary prevention cohort; intensive versus conventional RR (95%CI) 0.73 (0.62 to 0.85)<br>Secondary prevention cohort; intensive versus conventional RR(95%CI) 0.54 (0.39 to 0.66)<br><br>ARR per 100 patient-years (95%CI)<br>Progression of retinopathy<br>Primary cohort; |

| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Measure of glycosylated haemoglobin and results |
|---|---|---|---|---|---|---|
| | | | | Intensive therapy; 8.9±3.8 Conventional therapy; 8.6±3.7 (HbA1c) | | Conventional; 4.7 versus intensive; 1.2 risk reduction 76 (95%CI 62 to 85) Secondary cohort Conventional; 7.6 versus intensive; 3.7 risk reduction 54 (95%CI 39 to 66) Macular oedema Secondary cohort Conventional; 3.0 versus intensive; 2.0 risk reduction 54 (95%CI -13 to 48) Severe non-proliferative or proliferative retinopathy Secondary cohort Conventional; 2.4 intensive; 1.1 risk reduction 47 (95%CI 14 to 68) UAE ≥40 mg/24 hours Primary cohort Conventional; 3.4 versus intensive; 2.2 risk reduction 34 (95%CI 2 to 56) Secondary cohort Conventional; 5.7 versus intensive; 3.6 risk reduction 43 (95%CI 21 to 58) UAE ≥300 mg/24 hours Primary cohort Conventional; 0.3 versus intensive; 0.2 risk reduction 44 (95%CI -124 to 86) Secondary cohort Conventional; 1.4 versus intensive; 0.6 risk reduction 56 (95%CI 18 to 76) Clinical neuropathy at 5 years |

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| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Measure of glycosylated haemoglobin and results |
|---|---|---|---|---|---|---|
| | | | | | | Primary cohort<br>Conventional; 9.8 versus intensive; 3.1<br>risk reduction 34 (95%CI 2 to 56)<br>Secondary cohort<br>Conventional; 16.1 versus intensive; 7.0<br>risk reduction 57 (95%CI 29 to 73)<br>Mortality; conventional 7 patients died versus intensive 4 patients died<br><br>Regression model estimates of the effect of 10% higher mean HbA1c on the change in risk of other outcome<br>Retinopathy; ≥3 microaneurysms (primary cohort only)<br>Conventional therapy<br>%change in risk; 56, 95%CI 39 to 74<br>Intensive therapy<br>%change in risk; 66, 95%CI 39 to 96<br><br>Neuropathy at 5 years; confirmed<br>Conventional therapy<br>%change in risk; 41, 95%CI 19 to 66<br>Intensive therapy<br>%change in risk; 43, 95%CI 9 to 87<br><br>Nephropathy; AER ≥300 mg/24 hours<br>Conventional therapy<br>%change in risk; 71, 95%CI 32 to 121<br>Intensive therapy<br>%change in risk; 57, 95%CI 7 to 133 |

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| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Measure of glycosylated haemoglobin and results |
|---|---|---|---|---|---|---|
| | | | | | | Hypoglycaemia requiring assistance<br><br>HbA1c at eligibility screening subgroups; intensive versus conventional therapy<br><br><7.825%; intensive n=189, conventional n=171 RR(95%CI) 2.098 (1.37 to 3.19)<br><br>7.825-8.819%; intensive n=185, conventional n=175 RR(95%CI) 3.12(2.15 to 4.51)<br><br>8.820-10.099%; intensive n=166, conventional n=192 RR(95%CI) 4.13(2.79 to 6.13)<br><br>>10.100%; intensive n=190, conventional n=173 RR(95%CI) 4.89 (3.05 to 7.83)<br><br>Relative risk reductions associated with a 10% lower mean HbA1c among HbA1c values ≤8 versus values >8% estimated from a segmented (change point) model<br><br>Sustained retinopathy progression, %risk reduction (95%CI)<br><br>Intensive<br><br>≤8%; 49 (27 to 65) versus >8%; 37 (17 to 53), p=0.46<br><br>Conventional<br><br>≤8%; 69 (29 to 87) versus >8%; 37 (26 to 41), p=0.055<br><br>Sustained low-level (micro) albuminuria, %risk reduction (95%CI)<br><br>Intensive<br><br>≤8%; 43 (2 to 67) versus >8%; 44 (17 to 62), p=0.97<br><br>Conventional<br><br>≤8%; 58 (-50 to 87) versus >8%; 33 (17 to 45), p=0.47<br><br>Confirmed clinical neuropathy, %risk reduction (95%CI)<br><br>Intensive<br><br>≤8%; 30 (-19 to 58) versus >8%; 35 (-17 to 64), p=0.87<br><br>Conventional |

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| | | | | | | ≤8%; 32 (-70 to 56) versus >8% ; 29 (13 to 42), p=0.90<br><br>• **Retinopathy:** Higher values of HbA1c were all associated with higher rate of retinopathy progression. For each 10% decrease in HbA1c (for example, 9.0-8.1): 44% decreased risk of progression. |
| DCCT/EDIC 2005[498]<br>DCCT/EDIC 2008[738]<br>DCCT/EDIC 2013 [344] | 1441 | Prospective case series study<br>DCCT 17 years and 23 years = EDIC 10 years and 17 years | DCCT Intensive therapy 3 insulin injections or external insulin pump<br>Conventional therapy; 1-2 daily insulin injection<br>EDIC follow-up, percentage on intensive; conventional group; 94% intensive group; 97% | DCCT; Intensive group (n=711); 27±7<br>Conventional group therapy (n=730); 27±7<br>Start of EDIC; Intensive group(n=698); 34±7<br>Conventional group (n=723); 33±7 | DCCT 4 times/year<br>EDIC; every year | Measured; HbA1c<br>CVD event (non-fatal MI, stroke, CVD death, angina) at 17 years (DCCT/EDIC) (EDIC; 10 years);<br>Intensive therapy; 0.38 events/100 patient-years<br>Conventional therapy; 0.80 events/100 patient-years (p=0.007 versus intensive therapy)<br>Cumulative incidence 1st CVD event<br>Intensive versus conventional therapy ; RR (95%CI) 0.59 (0.9 to 0.63), p=0.02<br>Cumulative incidence 1st non-fatal MI, stroke or CVD death<br>Intensive versus conventional therapy; RR (95%CI) 0.57 (0.12 to 0.79), p=0.02<br>HbA1c; per 10% increase (adjusted for HbA1c, age, cholesterol, smoking status at baseline);<br>HR (95%CI) 1.25 (1.10 to 1.43)<br>HbA1c; per 10% decrease (adjusted for HbA1c, age, cholesterol, smoking status at baseline);<br>HR (95%CI) 0.8 (0.70 to 0.91)<br>Higher HbA1c levels (9.5% versus 9.0%), at DCCT baseline associated with occurrence of the CV events independent of treatment assignment (p=0.014)<br><br>Progression to retinopathy from DCCT closeout to EDIC at 10 years (n=1211) |

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| | | | | | | Risk reduction (95%CI) with intensive versus conventional therapy; 53% (43% to 61%), p<0.001<br><br>HbA1c intensive versus conventional therapy; 87.07% versus 7.98% p=ns<br><br>• Higher values of HbA1c were all associated with a sustained drop of ≥5 points in DQOL score (multivariate: HR 1.12, 95% CI 1.06 to 1.19; p<0.01).<br>• Higher values of HbA1c were all associated with a sustained drop of ≥5 points in DQOL score (multivariate: HR 1.12, 95% CI 1.06 to 1.19; p<0.01). |
| Diamante 1997[175] | 1822 | Cross-sectional observational study | Insulin treatment (%)<br>1 dose; 1.1<br>2 doses; 35.7<br>3 doses; 46.3<br>4 doses; 16.4 | 7.5±1.6 (HbA1c) | Not reported | Measured; HbA1c<br>Logistic regression analysis<br>HbA1c correlated with ESRF versus no ESRF (p<0.00005)<br>HbA1c correlated with low-level (micro) albuminuria versus normoalbuminuria (p<0.00005)<br>HbA1c levels<br>Normoalbuminuria; 7.3±1.6%<br>Low-level (micro) albuminuria; 8.0±1.6%<br>Macroalbuminuria + ESRF; 7.7±1.9%<br>HbA1c (diabetes <5 years evolution)<br>Normoalbuminuria; 7.3±1.6%<br>Low-level (micro) albuminuria; 8.0±1.6%<br>Macroalbuminuria + ESRF; 7.7±1.9% |
| EEG-OLOFSSON 2010[185] | 7,454 | Retrospective case-series 5 years | Not reported | 8.0 (1.2 to 0.01) (HbA1c) | Not reported | • Mean HbA1c and baseline HbA1c were SS predictors of: all CVD, and all CHD<br>• Mean HbA1c and baseline HbA1c were not SS predictors of: all stroke, and all mortality.<br>• The risk of all CVD with baseline HbA1c categories was: |

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| | | | | | | o HbA1c 5.0 to 7.9%: HR 1.0<br>o HbA1c 8.0 to 11.9%: HR = 1.59 [95% CI 1.13 to 2.24]<br>• The risk of all CHD with baseline HbA1c categories was:<br>o HbA1c 5.0 to 7.9%: HR 1.0<br>o HbA1c 8.0 to 11.9%: HR 1.71 [95% CI 1.18 to 2.48]<br>• The risk of all stroke with baseline HbA1c categories was:<br>o HbA1c 5.0 to 7.9%: HR 1.0<br>o HbA1c 8.0 to 11.9%: HR = 1.40 [95% CI 0.70 to 2.79] |
| FORREST 2000 [221] | 658 | Prospective case-series 6 years | Not reported | 10.75 (HbA1c) | Not reported | • HbA1c level was not a SS predictor of CV mortality or of total CHD.<br>• HbA1c was a SS predictor of LEAD (lower extremity arterial disease) |
| GUERCI 1999 [270] | 341 | Cross-sectional study n/a | Intensive conventional insulin therapy (split and mixed insulin regimens) | 7.57 (HbA1c) | Not reported | • HbA1c was a SS predictor of retinal status in all subjects, and in those who had had diabetes for ≥20 years |
| HIETALA 2013 [307] | 2019 | Prospective case-series 5.2 years | Not reported | 8.4±1.2 (HbA1c) | Not reported | • The estimated 5-year cumulative incidence of laser treatment for retinopathy increased significantly with increasing HbA1c quartile (p<0.0001)<br>• Mean HbA1c was higher with worse severity of retinopathy:<br>o No retinopathy = 8.2 ± 1.2<br>o Non-proliferative retinopathy = 8.5 ± 1.2<br>o Proliferative retinopathy = 8.7 ± 1.3<br>• Risk of proliferative retinopathy increase with higher HbA1c quartile |

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|---|---|---|---|---|---|---|
| | | | | | | o 1st Q: HR = 1; p = 0.003<br>o 2nd Q: HR = 1.3 [0.97 to 1.8]; p = 0.07<br>o 3rd Q: HR = 1.5 [1.1 to 2.0]; p < 0.001<br>o 4th Q: HR = 1.7 [1.3 to 2.2] |
| Hislop 2008[315] | 92 | Prospective case series 6 months | 17/92 patients on continuous subcutaneous insulin infusion | 8.7±1.8 (HbA1c) | Not reported | Measured; HbA1c<br>Quality of life<br>CES-D<br>Patients with worse quality of life (higher CES-D score ≥16) had higher HbA1c compared with those with normal CES-D (9.4% versus 8.4%, p=0.01)<br>No correlation between HbA1c and CES-D in total cohort (r=0.2, p=0.14)<br>Controlling for CSII use, higher CES-D score and HbA1c correlated (r=0.3, p=0.02)<br>Patients on CSII versus patients not on CSII; lower HbA1c (7.9 versus 8.9%, p=0.03)<br>ASR-T<br>No difference in glycaemic control between patients with normal ASR-T scores (≤ 59) and psychologically distressed ASR-T scores (≥60) |
| KULLBERG 1994[401] | 90 | Retrospective case series 9.4 years | Not reported | 7.2 ± 1.3 (HbA1c) | Mean 31.7 times/whole measurement period (mean of 9.4 years); measured regularly every 3-4 months at the | • Patients with mean HbA1c >8% had higher RRs for all kinds of background retinopathy compared with patients with HbA1c ≤ 7%<br>• Mean HbA1c for the preceding year did not contribute further to any regression model.<br>• The impact of long-term HbA1c concentration was significant for all sets of retinopathy scores. |

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|---|---|---|---|---|---|---|
| | | | | | clinic visit. | |
| Lehto 1999[425] | 177 | Prospective case-series 7 years | Not reported | Men without CHD 9.5±0.21 Men with CHD 10.5±0.4 Women without CHD 10.1 ±0.2 Women with CHD 11.1±0.4 (HbA1) | Not reported | Measured; HbA1 CHD death Univariate Cox regression model; HbA1 associated with risk of CHD death (p<0.001) and all CHD events (p<0.01) Poor Glycaemic control (10.4% versus ≤10.4%) was associated with the incidence of CHD death (p<0.05) High HbA1 (>10.4%) associated with all CHD events Multivariate analysis (adjustment CV factors; age, gender, area of residence, previous MI, smoking, BMI, hypertension, total cholesterol, total triglycerides, and HDL cholesterol); High HbA1 (>10.4%), HR 5.4 [1.4 to 20.4]) associated with the incidence of CHD death (p=0.013) High HbA1 (>10.4%), HR 2.8 [1.2 to 6.9]) associated with the incidence of all CHD events (p=0.021) RR (95% CI) for HbA1 (per 1–percentage point increase) and incident coronary heart disease event (CHD death + non-fatal MI); 1.55 (1.05 to 2.30) |
| LIND 2011[437] | 20,985 | Prospective case series | Not reported | 8.8±1.34 | Not reported | **Incidence of HF** increased monotonically with HbA1c, with a range of 1.42 -5.20 per 1000 patient-years in the lowest (<6.5%) and highest (≥10.5%) categories of HbA1c **Risk of HF per 1% increase in HbA1c:** HR 1.30 (95% CI 1.21 to 1.40; p<0.0001). **Risk of HF at intervals of HbA1c (multivariate\*):** <br>• **6.5 to <7.5%:** HR 1.26 (0.76 – 2.07) <br>• **7.5 to <8.5%:** HR 1.47 (0.91 – 2.38) <br>• **8.5 to <9.5%:** HR 1.75 (1.07 – 2.85) <br>• **9.5 to <10.5%:** HR 2.58 (1.54 – 4.34) |

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| | | | | | | • **≥10.5%:** HR 3.98 (2.23 – 7.14) |
| Lustman 2005 [448] | 188 | Cross-sectional observational study | Use of insulin pump; 55/188(29%) Total daily insulin dose, units mean(±SD); 37.2±20.9 | 7.7±1.3 (HbA1c) | NA | Measured; HbA1c Quality of life Multiple regression SDSA; HbA1c levels positively correlated with depression symptoms on SDSA (t=0.44, p<0.02) HbA1c levels were higher in the depressed than in the non-depressed patients (covariate-adjusted means±standard error of mean=8.8%±0.3% versus 7.6%±0.1%, F=10.1, p<0.0001) SDSCA composite score; Addition of SDSCA composite score to regression analysis, the parameter estimate for depression effect on HbA1c level was attenuated minimally (parameter estimate 0.50, t =3.3, p<0.001), SDSCA score had no effect within the model (p=0.40) SCL-90; Scores on SCL-90 depression subscale were 2.3±0.4 in the depressed group versus 0.6± 0.4 in the non-depressed group HbA1c levels correlated to severity depression symptoms within depressed group (p<0.02, across subgroups) |
| NORDWALL 2009 [527] | 269 | Case-series (retrospective and prospective elements) 14-28 years | Not reported | 8.55 (HbA1c) | 3-4 times/year | • HbA1c showed a SS correlation to any retinopathy (OR 4.1 [95% CI 1.8 to 9.2]; p = 0.001).<br>• Patients with low-level (micro) albuminuria had a mean HbA1c of 8.7 ± 0.9<br>• Patients with severe laser-treated diabetic retinopathy had higher mean HbA1c levels versus those with background retinopathy, and those with no retinopathy (9.0 ± 1.0 versus 8.5 ± 0.8 versus 7.8 ± 0.8) |

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| Pirez Mendez 2007[553] | 59 | Prospective case series 7 years | Multiple Dose Insulin (MDI); MID 2 or 3 daily injection of NPH insulin with short-acting analogue lispro as a pre-meal bolus The goal of HbA1c values was <6.2%. | Not reported | Every 3 months | Measured; HbA1c Mean values of HbA1c: 7.5±1.5%, 7.2±1.8%, 7.6±1.6%, 7.1±1.7%, 7±1.4,6.6,±1.6% and 6.8±1.4% for first, second, third, fourth, fifth, sixth and seventh year of follow-up, respectively  Percentage of patients reaching target HbA1c <6.2% for the first, second, third, fourth, fifth, sixth and seventh year of follow-up: 16%, 27.5%, 15.7%, 33.3%, 28.6%, 42% and 33%  Severe hypoglycaemic episodes (episodes/patient-year) Year before study; 0.32±0.2 During study; 0.28±0.1 (ns compared with before study)  Mild/moderate hypoglycaemia episodes (episodes/patient-month) Year before study started; 17.7±6 During study; 16.5±4 to 21.7±5 (NS compared with before study value) |
| Pittsburgh EDC 2002[533] | 586 | Prospective case series | Not reported | Without LEAD; 10.3±1.8 With LEAD; 10.9±1.9 (HbA1) | Not reported | Measured; HbA1 HR(95%CI) for 10 year incident LEAD (men and women); 1.53(1.22 to 1.92), p<0.001 HR(95%CI) for 10 year incident LEAD (men); 1.70(1.27 to 2.29), p<0.001 |
| Pittsburgh EDC 2003[534] | 603 | Prospective case series 10 years | Insulin dose/kg BW; Patients without CAD; 0.81±0.25 Patients with | Patients without CAD; 10.4±1.8 Patients with CAD; 10.3±1.8 (HbA1) | Not reported | Measured; HbA1 HbA1 not association with subsequent CAD events RR (95% CI) for HbA1 (per 1–percentage point increase) and incident coronary heart disease event (CAD death, non-fatal MI, ECG ischaemia, revascularisation, angina); 0.97 (0.86 to 1.09) |

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|---|---|---|---|---|---|---|
| | | | CAD; 0.75±0.31 | | | |
| ROSSING 1996[606] | 939 | Prospective case-series 10 years | Not reported | 9.17 (HbA1c) | Not reported | HbA1c was a SS predictor of all-cause mortality: RR 1.11 (95% CI 1.03 to 1.20); p<0.02 HbA1c was not a SS predictor of CV mortality. |
| SDIS 1995[586-588] | 89 | Prospective cohort study 94 months | Intensified conventional insulin treatment (insulin with education to ensure constant monitoring and treatment) Standard therapy (2 to 3 insulin injections/day) | 9.5±1.3 (HbA1) | Not reported | Measured; HbA1c Retinopathy Cumulative frequency of serious retinopathy; increased with higher HbA1c levels only in patients with mild retinopathy at baseline, no increase in patients with moderate retinopathy (shown graphically) Patients with mild retinopathy with HbA1c below 7% did not develop serious retinopathy Nephropathy; patients with HbA1c <9% did not develop nephropathy 5/10 patients with HbA1c ≥9% developed nephropathy 0/12 patients with mild initial retinopathy and HbA1c ≥9% during the study had nephropathy Urinary albumin excretion (microgram/minute), mean±SD; HbA1c <7%; 87±40 HbA1c 7%-7.99%; 21±5 HbA1c 8%-8.99%; 55±19 HbA1c 9%-0.9%; 308±123 HbA1c ≥9; 266±150 Neuropathy (patients without neuropathy at baseline) HbA1c <7% (6.5±0.1%); 2/20 patients HbA1c 7%-7.99% (7.5±0.1%); 8/24 patients HbA1c 8%-8.99% (8.4±0.1%); 7/18 patients HbA1c ≥9% (9.6±0.2%); 3/7 patients Multivariate analysis |

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| | | | | | | Development of serious retinopathy at any time during follow-up; Related to HbA1c at baseline [OR(95%CI) 1.70 (1.0 to 2.8)] and during first 6 to 60 months of follow-up [OR(95%CI) 2.4 (1.4 to 4.3)], not after 60 months OR for HbA1c during the study Serious retinopathy; 2.70 (1.55 to 4.69) Nephropathy; 3.33 (1.66 to 7.56) Neuropathy; 3.13 (1.56 to 6.28) |
| Shaban 2006[644] | 273 | Cross-sectional observational study | Not reported | 8.8±1.5 (HbA1c) | NA | Measured; HbA1c Quality of life HADS (maximum score 21-higher scores indicate worse outcome); HbA1c positively correlated with HADS scores (anxiety r=0.2, p=0.001, depression r=0.14, p=0.02) Patients 'moderate to severe levels' of anxiety demonstrated poorer glycaemic control than those reporting 'none to mild' Anxiety score ≥11: HbA1c 9.4%; anxiety score <8, HbA1c 8.5%, p=0.001) No difference in HbA1c for patients reporting different symptom severity for depression (depression ≥11: HbA1c 8.7%; depression <8, HbA1c 8.9% p=0.5) |
| Tabaei 2004[675] | 634 | Cross-sectional observational study | Not reported | Median (range); 8.3(4.7-14.1) (HbA1c) | NA | Measured; HbA1c Linear regression Quality of life HbA1c not associated with QWB-SA derived utility score Multivariable regression analysis (adjustments; hypoglycaemia, gender, complications) HbA1c not associated with QWB-SA derived utility score (partial R2= -0.05, p=0.25) |
| Van Tilburg | 30 | Cross- | Insulin pump; | 8.3±1.2 | NA | Measured; HbA1c |

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| 2001[715] | | sectional observational study | 9/30(30%) Insulin 1 to 2 injections per day; 5/30(17%) Insulin ≥3 injections per day; 16/30(53%) | (HbA1c) | | Linear regression Quality of life; HbA1c levels positively correlated with BDI scores with (r=0 .44, p<0.02) |
| WDRS 2013[420] | 305 | Prospective case series 20 years | 93% on intensive insulin management (MDI or CSII) | 8.0 ± 1.5 (HbA1c) | Not reported | % of patients who had HbA1c <7% with diabetic retinopathy at different severity grades: • None to minimal =34% • Mild to moderate = 18.5% • Vision threatening = 18.2% |
| WEINSTOCK 2013[734] | 7012 | Cross-sectional study/retrospective case-series n/a and previous 12 years data | Not reported | 7.7 ± 1.2 (HbA1c) | Not reported | Frequency of SH event, with HbA1c levels: • <6.5: OR 1.95 [1.40 to 2.72] • 6.5 - 6.9: OR 1.64 [1.18 to 2.72] • 7.0 - 7.4: OR 1.0 • 7.5 - 7.9: OR 1.47 [1.09 to 2.00] • 8.0 - 8.9: OR 1.62 [1.21 to 2.17] • 9.0 - 9.9: OR 1.01 [0.66 to 1.52] • ≥10.0: OR 1.25 [0.80 to 1.97] |
| WESDR 1994[493] | 2990 | Prospective case series 10 years | Not reported | Younger onset; 12.6±2.6 Older onset; 11.1±2.4 (GHb) | Not reported | Measured; states 'glycosylated hemoglobin' Younger onset; HR (95% CI) for ischaemic heart disease mortality for a 1–percentage point increase in GHb; 1.18 (1.00 to 1.40) Older onset; HR (95% CI) for ischaemic heart disease mortality for a 1–percentage point increase in GHb; 1.18 (1.04 to 1.17) |

| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Measure of glycosylated haemoglobin and results |
|---|---|---|---|---|---|---|
| WESDR 1995[378,379] | 2990 | Prospective case series | Not reported | Younger onset; 10.8 Older onset; 10.2 (GHb) | Not reported | Measured; states 'glycosylated hemoglobin' Retinopathy Younger onset patients; <30 OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of progression to proliferative retinopathy; 0.58 (0.48 to 0.72) Older onset patients OR of (95%CI) 2% difference in HbA1c from baseline to 6 year follow-up on the incidence of progression to proliferative retinopathy; 0.69 (0.47 to 1.04) Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of macular oedema; 0.53 (0.43 to 0.66) Older onset patients OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of macular oedema; 1.06 (0.67 to 1.69) Nephropathy Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of gross proteinuria; 0.71 (0.59 to 0.86) Older onset patients OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of gross proteinuria; 0.81 (0.61 to 1.09) Neuropathy Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of tactile sensation; 0.81 (0.67 to 0.98) |

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| | | | | | | Older onset patients; |
| | | | | | | OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of tactile sensation; 0.77 (0.54 to 1.06) |
| | | | | | | Younger onset patients; |
| | | | | | | OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of self-reported loss of temperature sensitivity; 0.84 (0.67 to 1.04) |
| | | | | | | Older onset patients; |
| | | | | | | OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of self-reported loss of temperature sensitivity; 0.84 (0.61 to 1.16) |
| | | | | | | |
| | | | | | | Younger onset; any retinopathy |
| | | | | | | GHb 5.6-9.4% (n=52), incidence; 82.1%, RR 1.0 |
| | | | | | | GHb 9.5-10.5% (n=61), incidence 86.4%, RR(95%CI) 1.1 (0.8 to 1.4) |
| | | | | | | GHb 10.6-12.0% (n=71) incidence 93.1%, RR(95%CI) 1.3 (1.0 to 1.7) |
| | | | | | | GHb 12.1-19.5% (n=64) incidence 96.9%, RR(95%CI) 1.6 (1.3 to 2.1) |
| | | | | | | Younger-onset; progression to proliferative retinopathy |
| | | | | | | GHb 5.6-9.4% (n=52), incidence; 6.2%, RR 1.0 |
| | | | | | | GHb 9.5-10.5% (n=61), incidence 11.6%, RR(95%CI) 1.9 (0.8 to 4.5) |
| | | | | | | GHb 10.6-12.0% (n=71) incidence 34.4, RR(95%CI) 5.9 (3.0 to 11.6) |
| | | | | | | GHb 12.1-19.5% (n=64) incidence 96.9, RR(95%CI) 9.9 (5.4 to 18.0) |
| | | | | | | Older onset; any retinopathy |
| | | | | | | GHb 5.6-9.4% (n=40), incidence; 65.9%, RR 1.0 |
| | | | | | | GHb 9.5-10.5% (n=40), incidence 85.0%, RR(95%CI) 1.1 (0.9 to 2.1) |
| | | | | | | GHb 10.6-12.0% (n=32) incidence 78.8%, RR(95%CI) 1.2 (0.7 to 1.9) |
| | | | | | | GHb 12.1-19.5% (n=23) incidence 100.0%, RR(95%CI) 2.1 (1.4 to 3.2) |
| | | | | | | Older onset; progression to proliferative retinopathy |

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|---|---|---|---|---|---|---|
| | | | | | | GHb 5.6-9.4% (n=40), incidence; 10.7%, , RR 1.0 |
| | | | | | | GHb 9.5-10.5% (n=40), incidence 13.1%, RR(95%CI) 1.1 (0.4 to 2.8) |
| | | | | | | GHb 10.6-12.0% (n=32) incidence 27.6%, RR(95%CI) 1.3 (1.2 to 5.5) |
| | | | | | | GHb 12.1-19.5% (n=23) incidence 37.9%, RR(95%CI) 1.6 (1.6 to 7.3) |
| WESDR 1998[377] | 987 | Retrospective case-series | Not reported | NA | NA | Measured; states 'glycosylated hemoglobin'<br>Multiple linear regression age mean<br>Younger onset subgroup; GHb variable for negatively associated general health coefficient (r= -1.6, p<0.005), no association with physical functioning or physical role<br>Older onset subgroup; GHb variable no association with general health, physical functioning or physical role |
| WESDR 1998a[380] | 634 | Prospective case series | Not reported | 10.6±2.0 (HbA1) | Not reported | Measured; HbA1<br>Retinopathy<br>After controlling for baseline retinopathy, duration of diabetes and gender, each percentage point of lower glycosylated haemoglobin at baseline was associated with increased odds of improvement of retinopathy (OR; 1.41; 95% CI 1.19, 1.67)<br>Progression to retinopathy<br>HbA1 5.1-9.4% (n=187); 75.4%, RR 1.00<br>HbA1 9.5 to 10.5% (n=153); 79.5%, RR (95%CI) 1.37 (1.12 to 1.68)<br>HbA1 10.6 to 12.0%( n=174); 95.2%, RR (95%CI) 1.99 (1.67 to 2.38)<br>HbA1 12.1 to 19.5% (n=168); 95.0%, RR (95%CI) 2.64 (2.18 to 3.20)<br>Incidence of macular oedema<br>HbA1 5.1-9.4% (n=187); 12.7%, RR 1.00<br>HbA1 9.5 to 10.5% (n=153); 22.6%, RR (95%CI) 1.90 (1.12 to 3.25)<br>HbA1 10.6 to 12.0% (n=174); 33.9%, RR (95%CI) 3.11 (1.95 to 4.95)<br>HbA1 12.1 to 19.5% (n=168); 36.8%, RR (95%CI) 3.37 (2.12 to 5.34) |
| WESDR 1999[492] | 1890 | Prospective case series | Not reported | Younger onset; | Not reported | Measured; states 'glycosylated hemoglobin'<br>Univariate analysis; lower extremity amputation |

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| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Measure of glycosylated haemoglobin and results |
|---|---|---|---|---|---|---|
| | | 14 years | | 10.8±2.1 Older onset; 9.6±2.0 (GHb) | | Younger onset<br>GHb 5.6–9.4% (n=223); incidence=2.5%, RR 1.00<br>GHb 9.5–10.5% (n=206); incidence= 6.7%, RR (95%CI) 2.93 (1.10 to 7.83)<br>GHb 10.6–12.0% (n=220); incidence=7.6%, RR (95%CI) 3.21 (1.24 to 8.33)<br>GHb 12.1–19.5% (n=216); incidence=13.4%, RR (95%CI) 5.64 (2.43 to 13.10)<br>Older onset<br>GHb 5.4–8.1% (n=244); incidence= 4.4%, RR 1.00<br>GHb 8.2–9.4% (n=218); incidence=8.5%, RR (95%CI) 1.98 (0.78 to 4.99)<br>GHb 9.5–10.8% (n=223); incidence=12.6%, RR (95%CI) 2.68 (1.15 to 6.24)<br>GHb 10.9–20.8% (n=225); incidence=14.6%, RR (95%CI) 3.79 (1.72 to 8.35)<br>Multivariable analyses (linear logistic model)<br>Younger onset<br>GHb associated with a higher incidence of amputations; OR 1.39 (1.21 to 1.59), p<0.0001<br>Older onset<br>GHb associated with a higher incidence of amputations; OR 1.25 (1.09 to1.43), p<0.005 |
| WESDR 2013[420] | 583 | Prospective case series 20 years | 21% on intensive insulin management (MDI or CSII) | 9.3 ± 1.7 (HbA1c) | Not reported | • Odds of Diabetic retinopathy severity by HbA1c (per 1%): OR = 1.34 [1.23 to 1.47]<br>• % of patients who had HbA1c <7% with diabetic retinopathy at different severity grades:<br>  o None to minimal =11.1%<br>  o Mild to moderate = 9.5% |

| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Measure of glycosylated haemoglobin and results |
|---|---|---|---|---|---|---|
| | | | | | | o Vision threatening = 4.2% |
| Wikblad 1991[744] | 185 | Retrospective case series 9 years | ≥20 U insulin daily at recruitment | 8.7±1.3 (HbA1c) | Not reported | Measured; HbA1c Patients without retinopathy changes HbA1c ≤7.5%; 53% HbA1c 7.6-8.4%; 28% HbA1c 8.5-9.4%; 30% HbA1c ≥9.5%; 29% Patients without proteinuria; HbA1c ≤7.5%; 88% HbA1c 7.6-8.4%; 77% HbA1c 8.5-9.4%; 58% HbA1c ≥9.5%; 47% |
| Wikblad 1996[743] | 108 | Retrospective case series | ≥ 20 U insulin daily at recruitment | 7.7±1.0 (HbA1c) | Not reported | Measured; HbA1c Patient grouping according to mean values for HbA1c (during 1 year); Good; HbA1c ≤7.0, n=35 Acceptable; HbA1c = 7.1–8.0%, n=23 Unsatisfactory; HbA1c = 8.1 – 9.0%, n=24 Quality of life; SWEQUAL (high score indicates better health/more favourable health state; scale 0 to 100) Physical functioning; Good; 88.1 ±2.9 Acceptable; 91.0±2.4 Unsatisfactory; 78.2±5.5 Satisfaction with physical health; Good; 71.5±4.8 Acceptable; 72.8±5.8 Unsatisfactory; 61.6±6.1 Role limitation due to emotional health; |

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| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Measure of glycosylated haemoglobin and results |
|---|---|---|---|---|---|---|
| | | | | | | Good; 92.2±3.0 <br> Acceptable; 89.4±5.8 <br> Unsatisfactory; 85.9±4.6 <br><br> Groups comparable for; Satisfaction with family life, Marital functioning, Sexual functioning, General health, Positive feelings, Negative feelings, Pain, Mobility <br><br> Patients who reported episodes of hypoglycaemia had significantly lower HbA1c mean values when compared with patients without severe hypoglycaemia (6.9%±1.0 versus 7.9%±1.2; F= 5.7, p=0.01) |
| ZOFFMANN 2014[771] | 710 | Cross-sectional study n/a | 13.3% on CSII | 8.2 ± 1.5 (HbA1c) | Not reported | • **PAID score:** SS higher prevalence of diabetes distress (PAID ≥30) among patients with HbA1c ≥8% (Score 48.3, 95% CI 41.4-55.3) versus those with lower HbA1c (score 35.7, 95% CI 29.0 – 42.9), p<0.01. <br> • **HbA1c was positively correlated with:** lack of motivation, and the PAID score (both p<0.001). <br> • **HbA1c was negatively correlated with:** perceived competence, self-esteem, well-being, and autonomy index (all p<0.001). |

*Abbreviations: ARR, absolute rate reduction; ASR, Adult-Self-Report Scale; BDI, Beck Depression Inventory; CES-D, Centre for Epidemiological Studies-Depression Scale; CSII, continuous subcutaneous insulin infusion; ESRF, end-stage renal failure; GHb, glycosylated haemoglobin; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; CVD, cardiovascular disease; MI, myocardial infarction; NA, not applicable; NPH, neutral protamine Hagedorn; NR, not reported; LEAD, lower extremity arterial disease; OR, odds ratio; QWB-SA, Quality of Well-Being Self-Administered; RR, relative risk; SCL-90, Symptom checklist-90; SDSCA, Summary of Diabetes Self-Care Activities; UAC, urine albumin concentration*

**Table 52: Study details and results for frequency of HbA1c monitoring**

| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Result |
|---|---|---|---|---|---|---|
| Larsen 1990[411] | 240 | RCT | See results | Monitored group; 10.1±1.9 | Every 3 months for monitored | Measured HbA1c <br> 1 year follow-up; HbA1c mean(±SD) <br> Monitored group; decreased 10.1 ± 1.8% to 9.5 ± 1.3%(p<0.005) |

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| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Result |
|---|---|---|---|---|---|---|
| | | | | Control group; 9.9±1.8 (HbA1c) | group | Control group; no difference<br>Mean(±)HbA1c in monitored (n=98) versus control group (n=99)<br>Baseline; monitored group 10.1±1.9% versus control 9.9±1.8%<br>3 months; monitored group 9.9±1.9% versus control; 10.1±1.6%<br>6 months; monitored group 9.8±1.7% versus control; 10.2±1.7%<br>9 months; monitored group 9.9±1.6% versus control; 10.2±1.7%<br>12 months; monitored group 9.4±1.4% versus control; 10.0±1.7%, p<0.02<br>18 months; monitored group 9.6±1.4% versus control; 10.1±1.5%<br>24 months; monitored group 9.3±1.2% versus control; 9.5±1.5%<br>At 12 months<br>Proportion patients in monitored group with HbA1c >10.0% decreased (46% to 30%, p<0.01), proportion of patients with values above 9.0% fell from 69% to 56% (p <0.05), proportion patients in control group with HbA1c > 9.0% remained at 69%<br><br>Treatment changes during 1 year<br>Control group (n=107)<br>1 daily injection; at entry 14.0% versus 11.2% at 12 months<br>2 daily injections; at entry 80.4% versus 67.7% at 12 months<br>3 or 4 daily injections; at entry 5.6% versus 27.1% at 12 months<br>Monitored group (n=115)<br>1 daily injection; at entry 10.4% versus 4.3% at 12 months<br>2 daily injections; at entry 80.0% versus 55.7% at 12 months<br>or 4 daily injections; at entry 9.6% versus 40.0% at 12 months (p<0.05 for comparison between groups)<br><br>Significant improvement in glycaemic control was achieved after 12 months care if clinicians and patients had access to HbA1c results, rather than being blinded to the results at 3 monthly consultations |
| Eid Fares 2010[208] | 117 | Retrospective case-series 5 years | NR | NR | Every 3 months | Measured HbA1c<br>Nephropathy |

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| Study | Number of patients | Study type/ follow-up | Diabetes therapy | Baseline HbA1c level, mean %±SD | Frequency of HbA1c monitoring | Result |
|---|---|---|---|---|---|---|
| | | | | | | 18/117 (15.4%) developed nephropathy |
| | | | | | | HbA1c in patients with; |
| | | | | | | Neuropathy; 9.4±1.6% |
| | | | | | | No neuropathy; 8.5±1.1% |
| | | | | | | Fluctuations in HbA1c; |
| | | | | | | Present with nephropathy; 15/18(83%) |
| | | | | | | Present without nephropathy; 54/117(54%) |
| | | | | | | Absent with nephropathy; 3/18(17%) |
| | | | | | | Absent without nephropathy; 45/117(45%) |
| | | | | | | Fluctuations and incidence of nephropathy in 77 patients $HbA_{1C}$ ≤8%; |
| | | | | | | With nephropathy, fluctuations present; 15(26%) |
| | | | | | | With nephropathy, fluctuations absent; 5(1%) |
| | | | | | | Without nephropathy; fluctuations present; 42(74%) |
| | | | | | | Without nephropathy, fluctuations absent 19(95%) |
| | | | | | | Multivariate analysis |
| | | | | | | Mean HbA1c only significant predictor for development of diabetic nephropathy (adjustment for fluctuations) |
| | | | | | | Average mean of HbA1c; |
| | | | | | | OR (95%CI) 1.66 (1.03 to 2.68) [Model 1], 1.55 (1.01; 2.38) [Model 2], 1.75 (1.18; 2.59) [Model 3] |
| | | | | | | Model 1; all risk covariates (average mean of HbA1c, Fluctuations in HbA1c, gender, family history, age at onset, time between diabetes onset to clinic admission, baseline BMI) |
| | | | | | | Model 2; mean and fluctuations HbA1c |
| | | | | | | Model 3; mean HbA1c |
| | | | | | | Model 4; fluctuations HbA1c |

*Abbreviations: NA, not applicable; NR, not reported; OR, odds ratio*

### 8.1.5 Economic evidence for optimal HbA1c

**Published literature**

No relevant economic evaluations were identified.

**New economic analysis**

New economic analysis was prioritised for this question. A summary is included here. The full analysis can be found in Appendix O.

**a) Model overview and methods**

An HbA1c target of 6.5% was compared with 7.5% in the model; however we did not estimate an ICER as the outputs of the model were only the costs and QALYs accrued by a cohort of patients reaching the target level, that is, the model did not compare actual strategies or interventions aimed at obtaining the set HbA1c target. For this reason, it would have been incorrect to conclude that the difference in costs and QALYs estimated in the model represent the incremental cost and effectiveness of setting a lower target, as this could be achieved through different strategies which have a cost that was not included in the calculations. This model simply estimates the potential cost savings and QALY gain in a hypothetical cohort of patients achieving the same set target. Even if a threshold analysis was conducted to estimate the maximum cost that we would be willing to pay (based on the cost-effectiveness threshold of £20,000per QALY) this would rely on the assumption that interventions provided to achieve the lower threshold are 100% effective (ie all the patients to whom the interventions are provided achieve a target of 6.5%). For this reasons it would be misleading to estimate an incremental cost effectiveness ratio or to conduct a threshold analysis. The analysis was undertaken using a validated, internet-based model (IMS CORE Diabetes Model (CDM). IMS CDM is an interactive computer model developed to determine the long-term health outcomes and economic consequences of interventions for type 1 or type 2 diabetes mellitus. Separate transition probabilities and management strategies are used for each type where data exist, facilitating running diabetes type-specific analysis. IMS CDM has been widely used and validated against real-life clinical and epidemiological data.

A cohort of type 1 diabetes patients with defined demographic characteristics reflecting the young adult type 1 diabetes population in the UK was used in the base case analysis. A lifetime horizon was used in the analysis. Health outcomes and costs were discounted at an annual rate of 3.5%. The analysis was undertaken from the perspective of the UK NHS and PSS.

**b) Results**

The mean costs and health outcomes associated with each strategy are reported in Table 53 below. Achieving a target of 6.5% HbA1c compared with a 7.5% target is associated with a gain of 0.554 quality adjusted life-years (QALYs) and a reduction in healthcare costs of £3,524, when only the consequences of the lower HbA1c in terms of reduction of complications are considered. The actual costs of strategies that have to be implemented to achieve this target have not been considered and could in theory offset the cost savings.

**Table 53: Probabilistic results (mean per patient)**

| | HbA1c 6.5% | | HbA1c 7.5% | | Difference |
|---|---|---|---|---|---|
| | Mean | SD (low – high 95% CI) | Mean | SD (low – high 95% CI) | |
| Life expectancy - undiscounted | 31.627 | 12.669 (30.842 - | 29.752 | 12.658 (28.967 - | 1.875 |

| | HbA1c 6.5% | | HbA1c 7.5% | | Difference |
|---|---|---|---|---|---|
| years (SD, low 95% CI – high 95% CI) | | 32.412) | | 30.536) | |
| Life expectancy - discounted years (SD, low 95% CI – high 95% CI) | 16.952 | 4.305 (16.685 - 17.218) | 16.308 | 4.472 (16.031 - 16.586) | 0.644 |
| QALYs undiscounted (SD, low 95% CI – high 95% CI) | 22.799 | 9.367 (22.218 - 23.38) | 21.314 | 9.359 (20.734 - 21.894) | 1.485 |
| QALYs discounted (SD, low 95% CI – high 95% CI) | 12.429 | 3.335 (12.223 - 12.636) | 11.875 | 3.462 (11.66 - 12.089) | 0.554 |
| Direct Costs discounted (£) (SD, low 95% CI – high 95% CI) | 29,908 | 18,739 (28,746 – 31,069) | 33,432 | 20,272 (32,176 – 34,689) | -3,524 |

The undiscounted values are quite high compared with the discounted outcomes as many of the benefits of the 6.5% strategy are experienced later in the patient's life through averted diabetes-related complications and subsequent deaths.

The analysis has some major limitations: the cost of any additional intervention(s) used to achieve the lower target is not included. Therefore this analysis does not give information about which interventions would be cost-effective in the achievement of a lower HbA1c target, and it does not conclude whether the lower target is cost-effective at all.

This original economic analysis is based on many parameters that are not specific to a type 1 diabetes population but utilises data on the type 2 population as well. It also utilises reduction in HbA1c as one of two main clinical outcome measures which is an intermediate outcome measure; but this is considered to be a reliable proxy measure of disease progression and complications outcomes. Its link to the most important clinical outcomes for diabetes patients is already well established and validated.

Disutility due to fear of hypoglycaemia was not explicitly included in the model. However, it was believed that the utility value associated with suffering a major hypoglycaemic event already incorporates this disutility.[146] Also the potential increased risk of hypo events associated with a lower target level has not been taken into account in the analysis. This could have led to an overestimation of the QALY gain and cost savings associated with the lower target.

### 8.1.6 Evidence statements

**Clinical**

**Optimal HbA1c target**

Overall, Low quality evidence from 43 studies (mostly observational and mostly case-series but including 3 randomised controlled trials), showed that with lower HbA1c values, the risk and incidence of clinical outcomes was significantly reduced. The main outcomes assessed by the evidence included mortality, CVD, CHD, stroke, retinopathy, low-level (micro) albuminuria, severe

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hypoglycaemia, nocturnal hypoglycaemia, and QoL). Of these outcomes, all but hypoglycaemia rates were improved with lower HbA1c and/or intensive insulin therapy.

**Frequency of HbA1c monitoring**

Two studies (one RCT and one case series) examined frequency of monitoring HbA1c and one RCT (Cagliero et al., 1999) examined the benefits of having the HbA1c available at the consultation which was done 3 monthly. The last mentioned study showed significantly lower HbA1c in the group where the HbA1c result was available during the consultation.

**Economic**

Our analysis indicates that achieving a target of 6.5% HbA1c compared with a 7.5% target is associated with a gain of 0.554 quality adjusted life-years (QALYs) and a reduction in healthcare costs of £3,524. The analysis was assessed as partially applicable with potentially serious limitations.

### 8.1.7 Recommendations and link to evidence

| | |
|---|---|
| | 35. Measure HbA1c levels every 3-6 months in adults with type 1 diabetes. [new 2015] |
| | 36. Consider measuring HbA1c levels more often if the person's blood glucose control is suspected to be changing rapidly; for example, if the HbA1c level has risen unexpectedly above a previously sustained target. [new 2015] |
| | 37. Calibrate HbA1c results according to International Federation of Clinical Chemistry (IFCC) standardisation. [new 2015] |
| | 38. Inform adults with type 1 diabetes of their HbA1c results after each measurement and ensure that their most recent result is available at the time of consultation. Follow the principles in the NICE guideline on patient experience in adult NHS services about communication. [new 2015] |
| | 39. Support adults with type 1 diabetes to achieve and maintain a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications. [new 2015] |
| | 40. Agree an individualised HbA1c target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia. [new 2015] |
| | 41. Ensure that achieving, or attempting to achieve, an HbA1c target is not accompanied by problematic hypoglycaemia. [new 2015] |
| **Recommendations** | 42. Diabetes services should document the proportion of adults with type 1 diabetes in a service who achieve an HbA1c level of 53 mmol/mol (7%) or lower. [new 2015] |

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| Relative values of different outcomes | **Optimal glycosylated haemoglobin (HbA1c) target**<br><br>Inadequate glycaemic control has been linked to microvascular and macrovascular complications. The evidence was reviewed to look at the range of glycosylated haemoglobin values at which the following complications occurred, in order to determine the optimal glycosylated haemoglobin target:<br><br>• Mortality and sudden death<br><br>• Macrovascular complications, including Myocardial infarction/Ischaemic heart disease; Stroke; Cardiac and peripheral revascularisation; Major amputations<br><br>• Microvascular complications, including Retinopathy; Nephropathy, including low-level (micro) albuminuria, macroalbuminuria, proteinuria, end-stage renal failure, and renal replacement therapy<br><br>• Neuropathy<br><br>Hypoglycaemia is a regular occurrence in the treatment of type 1 diabetes and has been associated with a reduction in quality of life for people with diabetes, and an obstacle to improved control. The benefits of a glycaemic target that achieves an improvement in glycaemic control must be weighed up against the risk of producing an increase in the frequency of hypoglycaemia events. The following outcomes were therefore considered:<br><br>Incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a third party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes.<br><br>Incidence of nocturnal hypoglycaemia.<br><br>Loss of awareness of hypoglycaemia (episodes detected only by co-incidental blood glucose testing or recognised by someone other than the patient), as this increases risk of severe hypoglycaemia six-fold loss of awareness of hypoglycaemina was reported in the study but not prioritised by the GDG as a main outcome).[243]<br><br>The evidence was reviewed to look at the impact of different HbA1c targets on quality of life outcomes. Setting HbA1c targets high may result in decreased quality of life by producing an increase in the incidence of vascular complications and/or worry about such complications. However, low HbA1c targets may be associated with an increase in the incidence of hypoglycaemia, which may also impact on quality of life.<br><br>**Optimal frequency of glycosylated haemoglobin (HbA1c) monitoring**<br><br>The evidence for HbA1c monitoring was reviewed to determine the following:<br><br>• The frequency of HbA1c measurement required to achieve improvement in blood glucose control<br><br>• The cost of HbA1c monitoring<br><br>• Patient quality of life issues as a consequence of HbA1c monitoring |
| Trade off between clinical benefits and harms | **Mortality and macrovascular disease**<br><br>The available evidence showed that the incidence of macrovascular disease increased with increasing HbA1c. Poor glycaemic control was associated with an increased incidence of coronary heart disease (fatal and non-fatal)[425], WESDR 1999). Outcomes from the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that intensive treatment (mean HbA1c achieved 7.4 %) compared with conventional treatment (mean HbA1c 9.1 %) over 6 years reduced the risk of any predefined cardiovascular disease outcome by 42 % over a 17 year follow-up; each 10 % reduction in HbA1c was associated with a 20 % reduction in the risk of a cardiovascular event (DCCT/EDIC 2005, 2008). A further report has shown improved |

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surrogate markers in the intensively treated group and a risk reduction of cardiovascular events of 42% (95% CI 9 to 63%, p=0.016) [405] although epidemiological data on the risk at any given mean HbA1c are still awaited.

Reduced glycosylated haemoglobin levels have been shown to be associated with a reduction in the incidence of lower limb extremity amputations (WESDR 1999). However, not all cohort studies reported an association between glycaemic control and the incidence of macrovascular disease (Pittsburgh EDC, 2003)[534].

One observational study divided people with type 1 diabetes into quartiles of HbA1c at recruitment into the study and followed them for 30 years.[666].Mortality increased in each successive quartile, being lowest in the quartile with an initial HbA1c <6.5%.

**Microvascular disease**

**Retinopathy**

The DCCT showed that intensive treatment and improved glycaemic control reduced the risk of developing retinopathy by 76 % in those without retinopathy; whilst in those with mild retinopathy, development of severe non-proliferative retinopathy was reduced by 47 % (DCCT 1993, 1995, 1996). Inspection of the plot of 3-step deterioration of retinopathy against achieved HbA1c in these data showed flattening of the relationship at lower HbA1c values, with minimal deterioration when HbA1c was 6.5% or less. Retinopathy was reported not to occur at a level <7.5 % in one observational study [21], whilst in a randomised controlled trial, no serious retinopathy developed in individuals with an HbA1c <7 % over 94 months (SDIS 1995).

**Nephropathy**

In the DCCT, intensive control reduced the risk of low-level (micro) albuminuria (>40 mg/day) by 39 %, and reduced the risk of albuminuria (>300 mg/day) by 54 % (DCCT 1993, 1995, 1996). An increase in glycosylated haemoglobin was associated with increases in the urine/albumin creatinine ratio and the incidence of proteinuria in other studies.[744], WESDR 1995, [21] Individuals with a mean HbA1c of <9 % were shown not to develop nephropathy in one study (SDIS 1995), whilst logistic regression analysis in another study showed that increased HbA1c correlated with the incidence of end-stage renal failure (Diamante et al., 1997). In the 30 year follow-up of patients divided into quartiles of HbA1c at enrolment, frequency of renal replacement therapy was significantly increased in each quartile, being lowest in the quartile with initial HbA1c <6.5%.[666]

**Neuropathy**

The DCCT showed that intensive therapy and improved HbA1c reduced the incidence of clinical neuropathy by 60 % and abnormal nerve conduction by 44 % (DCCT 1993, 1995, 1996), a finding supported by outcomes from other studies (SDIS 1995, WESDR 1995). One study showed that mean HbA1c was 8.5 +/- 1.1 % in those without neuropathy and 9.4 +/- 1.6 % in those with neuropathy.[208]

Hypoglycaemia

The DCCT reported that patients receiving intensive therapy for improved glycaemic control were two to three times as likely to experience severe hypoglycaemia in comparison to those receiving conventional therapy (DCCT 1997), Another study reported that in a cohort of patients aiming to improve HbA1c to a target of 6.2 %, no increase in the incidence of hypoglycaemia events was recorded with improvements in HbA1c (Pirez-Mendez 1997). There have been a series of studies of intensified insulin therapy in which HbA1c is reduced at the same time as severe hypoglycaemia rate falls (see Chapter 7 on education).

**Quality of life**

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Measures assessing quality of life were found to be negatively associated with glycaemic control, with individuals with a higher HbA1c more at risk of depression and anxiety (Wikblad et al., 1996, WESDR 1998, [715], [448] [644] [315] Audit of structured education programmes such as DAFNE[328] show improved quality of life and/or reduced anxiety and depression after intensified insulin therapy associated with lower HbA1c, and the DCCT/EDIC follow-up[344] showed deterioration of HbA1c (as well as serious diabetes complications, their symptoms and development of psychiatric illness) to be associated with deterioration in quality of life measures. However, the GDG noted that the studies did not indicate whether having a good HbA1c resulted in an improvement in quality of life or whether reduced mood led to deterioration in glycaemic control.

**Frequency of monitoring**

The available evidence showed that a significant improvement in glycaemic control was achieved after 12 months care if clinicians and patients had access to HbA1c results, rather than being blinded to the results at 3 monthly consultations.[411]

A further study showed that immediate access to HbA1c results from a bench top analyser available in clinic led to an improvement in glycaemic control in comparison to groups where no immediate HbA1c result was available. (Cagliero et al., 1997).

Although the evidence available showed that a knowledge of HbA1c at clinic appointments led to improvements in clinical outcomes, no data were available on the optimal frequency of HbA1c monitoring. The GDG recognised that if an HbA1c was checked, patients should be informed of the result and that ideally the result should be discussed at a clinic appointment to optimise therapeutic interventions.

The GDG recognised that there was no new evidence to suggest a change in practice for the frequency of HbA1c monitoring originally suggested in the 2004 NICE Guideline. Patient members of the GDG expressed concern that increasing the frequency of HbA1c monitoring may result in difficulties making arrangements to attend appointments, particularly if a visit to a healthcare member was required to for a blood test in the week preceding a clinic appointment. The GDG therefore decided to leave the recommendation for the routine frequency of HbA1c monitoring unchanged from the NICE 2004 recommendation of 3-6 monthly, advising that an increase in the frequency of HbA1c checks might be considered if an individual's therapies had been recently altered.

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| Economic considerations | **Economic considerations for optimal HbA1c target**<br><br>No relevant economic evaluations regarding optimum HbA1c target were identified. An original economic analysis was conducted to estimate the consequences in terms of costs and health outcomes associated with achieving a HbA1c target of 6.5% compared with 7.5%. This analysis showed that achieving a target of 6.5% HbA1c compared with a 7.5% target is associated with a gain of 0.554 quality adjusted life-years (QALYs) and a reduction in healthcare costs of £3,524 over a lifetime, when only the consequences of the HbA1c reduction in terms of reduction of complications are considered. The actual costs of strategies that have to be implemented to achieve this target have not been considered in the analysis. Interventions that could be used to achieve a lower target HbA1c would include the use of insulin pumps, higher doses of insulin but also education programmes and more frequent monitoring. Since different interventions could be provided to achieve the lower target, it would not be possible to estimate this cost. Even if a threshold analysis was conducted to estimate the maximum cost that we would be willing to pay (based on the cost-effectiveness threshold of £20,000per QALY) this would rely on the assumption that interventions provided to achieve the lower threshold are 100% effective (that is, all the patients to whom the interventions are provided achieve a target of 6.5%). For this reasons it would be misleading to estimate an incremental cost effectiveness ratio or to conduct a threshold analysis. The GDG believed that the cost of interventions required to reach the target could |

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| | be offset by the improvement in the quality of life. This analysis, however, was limited as it does not explicitly identify the most cost effective threshold and it does not confirm whether providing an intervention or some interventions to achieve a lower target is cost effective.<br><br>**Economic considerations for optimal frequency of HbA1c monitoring**<br>No relevant economic evaluations regarding optimum frequency of HbA1c monitoring were identified, and again the GDG made a qualitative judgment on cost-effectiveness for frequency of monitoring.<br><br>Whilst an availability of HbA1c results to clinicians and individuals with type 1 diabetes was shown to improve glycaemic control outcomes (Larsen et al., 1990), there was no evidence to suggest an optimum frequency of HbA1c monitoring.<br><br>The previous 2004 NICE Guideline had suggested that HbA1c should be monitored 3-6 monthly. The GDG recognised that increasing the frequency of monitoring would have cost implications (investigation costs, appointment costs for blood tests and subsequent clinic appointments for review), with no evidence to suggest that an increase in the frequency of monitoring was required. Additionally, patient representatives within the GDG expressed concern that an increase in the frequency of monitoring may have an impact on quality of life, and the possibility of an increase in the frequency of missed clinic appointments. The GDG therefore decided to leave the frequency of routine HbA1c monitoring unchanged from the NICE 2004 recommendation of 3-6 monthly, thus resulting in no increase in HbA1c monitoring costs. |
| Quality of evidence | The methodological quality of each study was assessed by the GDG. Studies assessing populations with type 1 diabetes where ≥50 % of study participants were >18 years were considered for review. Studies with mixed populations of type 1 and type 2 diabetes were only considered if data were reported for the subgroup of type 1 diabetes patients, or if the assessed population contained ≥70 % of type 1 diabetes patients<br><br>Randomised controlled trial data evidence was insufficient when considered alone, and therefore evidence from prospective case series studies and cross-sectional observational studies were identified by the GDG and included in the evidence review. This meant that the available evidence could not be GRADE assessed, and the GDG evaluated the quality of each individual study before making recommendations.<br><br>**Evidence for optimum HbA1c target**<br>Randomised controlled trials, prospective case series studies and cross-sectional observational studies were identified by the GDG for the HbA1c target review: 29 studies were identified as suitable for review.<br><br>Four studies were reported from the Diabetes Control and Complications randomised control Trial (DCCT), with two further prospective case series studies reporting post-intervention follow-up of DCCT participants (DCCT/EDIC).<br><br>Six studies were reported from the Wisconsin Epidemiology Study of Retinopathy (WESDR), a cross-sectional observational study.<br><br>Three studies reported from the Stockholm Diabetes Intervention Study (SDIS), a randomised controlled trial with outcomes were reported at 94 months and a further cohort follow-up study three years later.<br><br>Two studies reported from the Pittsburgh Epidemiology of Diabetes Complications Study, a prospective case series study. |

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Two studies reported from a Swedish cohort looking at retrospective and prospective case series (Wikblad et al., 1991, 1996).

Further prospective cohort studies from Norway (Brinchmann-Hansen et al., 1992), Sweden (Agardh et al., 1997), Finland (Lehto et al., 1999), Spain (Pirez-Mendez et al., 2007) and Australia (Hislop et al., 2008) and two further cross-sectional observational studies from Spain (Diamante et al,. 1997) and the US (Lustman et al,. 2005) were also reviewed when determining optimum HbA1c target.

**Evidence for optimum frequency of HbA1c monitoring**

Two studies were available for review of the optimal frequency of monitoring of HbA1c. The first study was a Very low quality randomised controlled trial investigating whether HbA1c outcomes improved when clinicians and patients were made aware of HbA1c results, with the control group blinded to HbA1c results (Larsen et al,. 1990). The second study was a Very low quality case series in adults with type 1 diabetes and nephropathy (Eid Fares et al,. 2010).

The economic evidence was based on an original economic analysis which was assessed as partially applicable and with minor limitations.

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| Other considerations | In selecting an HbA1c target for the management of individuals with type 1 diabetes, the GDG recognised that individuals should achieve a target that minimised the risk of developing complications from glycaemia. Retinopathy is often the first microvascular complication to develop from inadequate glycaemic control, and particular attention was paid to the risk of retinopathy at varying levels of glycaemia reported by the Diabetes Control and Complications Trial. The GDG selected an HbA1c target of 6.5 % on the grounds that a minimal risk of retinopathy was achieved at this level, with further improvements in HbA1c not achieving any further significant reduction in retinopathy risk.

The GDG also acknowledged the importance of the DCCT data as a large RCT of intensified therapy. It noted that the study design was intended to compare the outcomes of intensive versus conventional therapy, rather than identify an HbA1c value associated with minimal complication risk and that the target for the intensive therapy group was an HbA1c of 6.05%. This was achieved at least once during the study by 44% of participants using intensive therapy; but sustained there by only 5%. The mean HbA1c achieved over the trial by the intensive therapy group was just under 7% and this achieved value has support from other studies as being associated with reduced microvascular risk. The GDG therefore selected a target HbA1c value that is lower than the achieved HbA1c of the DCCT, as the one the evidence supports as associated with meaningful reduction in risk of complications, recognising that achieving the value of 7%, as done in the DCCT, was more likely if the target was set lower than this.

The GDG recognised that aiming for an HbA1c of 6.5 % might lead to an increase in the frequency of hypoglycaemia events. The GDG believed that recent advances in treatments for type 1 diabetes mean that improvements in HbA1c might be achieved without necessarily increasing the risk of hypoglycaemia. The GDG agreed that if diabetes care was optimised with currently available therapeutic interventions, then a target HbA1c of 6.5 % could be achieved by some people with minimally increased risk of hypoglycaemia frequency and that adults with type 1 diabetes should be supported in achieving such a target, where this could be done without problematic hypoglycaemia.

The GDG recommended that where such tight glycaemic control might not be |

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desired by certain individuals (for example, those working at heights, those required to drive for a living), then healthcare professionals should be allowed to agree individualised targets of glycaemic control with patients, so that a glycaemia target allowing desired daily activities could be achieved.

When determining the optimal frequency of HbA1c monitoring, the GDG agreed that HbA1c results should be readily available at consultation for discussion with patients attending clinic. The GDG therefore discussed whether site of care testing for HbA1c should be used in preference to laboratory testing. It was recognised that laboratory testing was likely to provide the most accurate measurement of HbA1c, although this was likely to require a patient to attend a pre-clinic appointment to have bloods taken and sent to the laboratory so that results were available at the time of clinic attendance. Site of care testing might allow HbA1c results to be made available whilst a patient attended clinic, allowing testing and discussion of results within a single visit. The GDG recognised that there was no evidence available on comparison of laboratory analysis and site of care HbA1c testing to determine which might be the most cost-effective, and which might have the greatest impact on improvement in glycaemic control in adults with type 1 diabetes. The GDG therefore made the research recommendation that this be investigated to determine which form of testing should be employed in clinics to improve clinical outcomes in the type 1 diabetes population.

43. If HbA1c monitoring is invalid (because of disturbed erythrocyte turnover or abnormal haemoglobin type), estimate trends in blood glucose control using one of the following:

- fructosamine estimation

- quality-controlled plasma glucose profiles

- total glycated haemoglobin estimation (if abnormal haemoglobins). [2004, amended 2015]

### 8.1.8 Research recommendations

7. **What methods and interventions are effective in increasing the number of adults with type 1 diabetes who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?**

**Why this is important**

The evidence that sustained near-normoglycaemia substantially reduces risk of long-term complications in adults with type 1 diabetes is unequivocal. Current methods for achieving such glycaemic control require skills in glucose monitoring and insulin dose adjustment, injection technique and site management, and the ability to use such self-management skills on a day-to-day basis life-long. Fear of hypoglycaemia and of weight gain are major barriers to success, as is fitting diabetes self-management into busy lifestyles. Everyone struggles to meet optimised targets and some are more successful in achieving them than others. Research into new interventions ranging from more effective education and support, through improved technologies in terms of insulin replacement and glucose monitoring, and including use of cell-based therapies, are urgently needed. It is also important to ensure that adults with type 1 diabetes are able to engage with such methodologies

8. **Can a risk stratification tool be used to aid the setting of individualised HbA1c targets for adults with type 1 diabetes?**

**Why this is important**

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Strict glycaemic control early in the history of type 1 diabetes has been shown to reduce the development and progression of long term complications but we are unable to determine who is at particular risk of glucose-driven poor outcomes. Furthermore, there is a dearth of evidence of the risk:benefit ratio of strict glycaemic control in people who already have diabetes complications. As achieving and maintaining near-normal plasma glucose concentrations is complicated, a risk stratification tool to calculate the modifiable individual risk of complications will allow us to tailor glycaemic targets for each individual and provide appropriate support.

9. **In adults with type 1 diabetes, is HbA1c measurement by laboratory analysis more cost-effective compared to site of care HbA1c testing?**

## 8.2 Self-monitoring of blood glucose

### 8.2.1 Introduction

Self-monitoring of blood glucose (SMBG) is central to the self-management of type 1 diabetes. A small sample of capillary blood, achieved by skin puncture, is obtained by the person with diabetes and the plasma glucose concentration of the sample is measured using a glucose meter. People with diabetes may use SMBG to check their plasma glucose when they feel unwell, to detect or confirm hypo- or hyper-glycaemia, but the ability of the person with diabetes to use SMBG to optimise blood glucose control longer term is dependent on their skills at interpreting blood glucose data and responding to them. Helping people with diabetes develop these skills is fundamental to structured education programmes supporting insulin self-management with the aim of optimising outcomes (see structured education, Chapter 7.2).

Self-monitoring of blood glucose can be used in different ways. A person with diabetes can use the result immediately to determine whether to take any action to change it, for example, to eat if the result is low or take additional insulin if high. This is something many patients, at least after structured education in insulin therapy, find useful and relatively easy to do. [415]Recording SMBG over a period of time, usually by writing in a diary either at the time of the test, and sometimes accompanied by notes on food eaten, insulin taken or other relevant activity, or downloaded from the meter memory later (see SMBG technology, Section 10) may inform a decision to change an insulin regimen prospectively, for example, increase bedtime background insulin if pre-breakfast SMBG readings are consistently over target. This is reported by patients to be less easy.[415]Records may also be shown to healthcare professionals intermittently, who may use them to advise on treatment change, but the utility of this may be limited by the infrequency of the contacts.

The person with diabetes needs to know the range of plasma glucose readings he or she should aim to achieve. In people with type 1 diabetes, the range of possible plasma glucose concentrations is much greater than in health. Plasma glucose will be affected by such factors as the nutritional state (fasted versus fed); the speed of absorption of glucose from food or drink ingested; the amount of exercise taken, both in absolute terms and relative to the individual's norm; other drugs and substances, including alcohol, being taken and levels of emotional and physical stress. In the largest randomised controlled trial of intensified insulin therapy conducted in people with type 1 diabetes, the Diabetes Control and Complications Trial (DCCT), the targets for pre-meal, post-meal and 3 am plasma glucose were chosen to reflect the non-diabetic state (3.9-6.7; less than 10 and more than 3.6 mmol/litre, respectively).[687] However, the values achieved by people in the trial associated with reduced diabetes complications is not clear and the impact of hyperglycaemia at different times of day (particularly comparing fasting and pre-meal with post-prandial glucose excursions) on risk for diabetes complications remains uncertain. Indeed, the evidence suggests that only glycated haemoglobin predicts both micro- and macro-vascular disease[500] and SMBG may best be considered as a tool to achieve target HbA1c.

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There are down-sides to SMBG. Although there have been major advances in the technology, such as reduced blood volume required per test, allowing less traumatic skin pricking devices, and much faster results from the meters, there remain issues. Use of the finger tip for sampling, which is recommended as having the closest approximation to a formal blood sample [192] can cause discomfort; the procedure is messy and obtaining a result that is outside target is distressing. Another issue is timing. Plasma glucose concentrations can change very rapidly after eating carbohydrate, and post-prandial testing may pick up a value that is very high but which may be only transiently so. Applying algorithms designed to correct pre-meal insulin doses for a pre-meal plasma glucose that is over target increases the risk of hypoglycaemia. (Reference for post meal corrections associated with hypoglycaemia)

**The GDG therefore considered the questions:**

- In adults with type 1 diabetes, what is the optimum frequency and timing to self-monitor blood glucose for effective diabetic control?
- In adults with type 1 diabetes, what is the optimum glucose target or profile for self-monitoring of blood glucose for effective diabetic control?

### 8.2.2 Review question: In adults with type 1 diabetes, what is the optimum timing and frequency to self-monitor blood glucose for effective diabetic control?

For full details see review protocol in Appendix C.

**Table 54: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
| --- | --- |
| | • Adult defined as aged >18 years |
| Intervention/s | SMBG (finger pricks) |
| Comparison/s | • SMBG (finger pricks) – the same as the intervention but at a different frequency or delivery time |
| | • No comparison (non-comparative study) |
| Outcomes | • Adherence |
| | • Adverse events |
| | • Diabetic ketoacidosis (DKA) |
| | • HbA1c |
| | • Hypoglycaemia |
| | • Nocturnal hypoglycaemia |
| | • Quality of life |
| | • Severe hypoglycaemia |
| | • Time within range (blood glucose) |
| | • Unscheduled care use |
| Study design | RCTs, observational studies |

### 8.2.3 Review question: In adults with type 1 diabetes, what is the optimum glucose target or profile for self-monitoring of blood glucose for effective diabetic control?

**Table 55: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
| --- | --- |
| | • Adult defined as aged >18 years |
| Intervention/s | SMBG (finger pricks) – blood glucose target/profile values/glucose variability |
| Comparison/s | • Other target values (RCTs and comparative observational studies) |

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| | |
|---|---|
| | • No targets (prognostic studies) |
| **Outcomes** | • HbA1c value |
| | • Quality of life |
| | • Risk of complications |
| | • Risk of hypoglycaemia |
| | • Risk of nocturnal hypoglycaemia |
| | • Risk of severe hypoglycaemia |
| **Study design** | RCTs, observational studies |

### 8.2.4 Clinical evidence

For the review on self-monitoring of blood glucose targets and timing in people with type 1 diabetes we searched for randomised control trials or observational studies that reported on one of the following three topics: 1) the relationship between frequency of self-monitoring of blood glucose (SMBG) levels and diabetic control 2) the timing of measuring blood glucose levels and diabetic control and 3) the optimal target blood glucose value to prevent hypoglycaemia.

For topic one (frequency) we found 35 relevant studies. These included 2 RCTs, 31 observational studies, and 2 post-hoc analysis of RCTs. [12,42,63,65,82,84,89,95,109,138,201,258,259,282,366,381,442,470,480,483,484,499,515,626,634,657,658,687,694,715,735,749,767-769] Some of these studies were not an exact match to the review protocol, but considered useful by the GDG. A summary of these papers can be found in Table 11.

For topic two (timing) we found 4 relevant studies. These included 3 observational studies and one post-hoc analysis of an RCT. [309,643,650,745]

For topic three (targets) we found seven relevant studies all of which were observational. [137,395,495,642,721,733,739]

Most of the studies were non-comparative observational studies (mainly case-series), and therefore were not able to be combined in a meta-analysis or GRADE profile (as GRADE is not designed for this type of study), and were graded as Low quality (due to their study design). However, a summary of the methodological limitations of each of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below. A summary of the included studies is provided inTable 49,Table 50, Table 51 and Table 52. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

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**Table 56:   Summary of studies included in the review for frequency and timing**

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| Frequency | | | | | |
| ABDELGADIR2006 [12] | Cross-sectional study SMBG: Fasting blood glucose using portable glucose meters Accutrend sensor | n=193 consecutive type 2 diabetes (n=143 [74%]) and type 1 diabetes (n=50 [26%]) | Cross-sectional | HbA1c Blood glucose (mmol/litre) | Included type 1 and type 2 diabetes. Data from only the type 1 diabetes patient subgroup was used for the analysis in this review. |
| BOTT 1994 [82] | Prospective case-series. SMBG: Patients advised to measure blood glucose before main meals and at bed time and to inject NPH-insulin in the morning and at bedtime and regular insulin before meals | n=697 type 1 diabetes patients. Type 1 diabetes patients, age 15-40 years Free of advanced diabetic late complications | 3 years | HbA1c Severe hypoglycaemia | type 1 diabetes taking part in an in-patient treatment and teaching programme (TTP) for intensified insulin treatment (IIT) |
| BRAGD 2003 [84] | No intervention Prospective case-series. | n=178 with type 1 diabetes | Same cohort followed up 14 years later | Severe hypoglycaemia | Prediction of severe hypoglycaemia based on SMBG |
| COX 2007 [138] | No intervention. Prospective case-series. | n=90 type 1 diabetes | 4 months | Severe hypoglycaemia | Prediction of severe hypoglycaemia based on SMBG |
| EVANS 1999 [201] | Retrospective case-series. Registry data | n=258 with type 1 diabetes | 2 years data | Frequency of SMBG and HbA1c | Regression analysis |
| GORDON 1991 [259] | Cross-over trial BG reading 3 times before each meal and at 22h on any two non-consecutive days per week. BG reading 3x before each | n=25 with type 1 diabetes | 3x12 week periods | Patient preference Frequency of SMBG and HbA1c | Regression analysis |

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| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | meal and at 22 hours on any day of the week<br><br>Two blood glucose measurements on each day for 7 days per week | | | | |
| KARTER 2001 [366] | Retrospective case-series. | n=1159 TIDM | 1 year of data | Frequency of SMBG and HbA1c | Regression analysis |
| KLEIN 1992 [381] | Prospective case-series.<br>SMBG:<br>Self-monitoring of blood glucose at least once a day or more.<br>Two or more insulin injections per day.<br>Combination of intermediate and short-acting insulin | n=1210 eligible patients with IDDM<br>n=996 participated in the baseline examination.<br>n=891 participated in the follow-up examination. | Participants followed up over 4 years | HbA1c | |
| MINDER 2013[484] | Cross-sectional study | n=150 type 1 diabetes | n/a | Association between frequency of SMBG and HbA1c | Results show HbA1c declines by approximately 0.2% for each additional measurement of SMBG, up to 4 times per day. After 4 times per day each additional mmt leads to a 0.02% decrease in HbA1c. HbA1c graphs show there is a decline until approximately 10 times per day and then HbA1c slowly increases again. |
| NATHAN 1996 [499] | Prospective case-series data | n=94 IDDM and n=137 | 1 year | Association | Insulin dependent and |

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| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | taken from a cohort study | NIDDM | | between frequency of SMBG and HbA1c | non-insulin dependent patients |
| SCHIFFRIN 1982 [626] | Cross over trial of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII)<br>CSII 4x/d<br>CSII 2x/d<br>MSI 4x/d<br>MSI 2x/d | n=21<br>IDDM | 21 months | HbA1c | |
| SCHUTT 2006 [634] | Prospective case-series<br>SMBG 4.4 times a day<br><br>• Intensified conventional (≥4 daily injections) or continuous subcutaneous insulin infusion therapy (CSIIT)<br>• Conventional (1-3 daily injections) therapy (CT) | n=24,500 participants with 19,491(80%) type 1 diabetes. For each patient the most recent complete year of diabetes care was evaluated. | 1 year | HbA1c | On average type 1 diabetes performed 4.4 blood glucose measurements per day. This number increased continuously with the following years (1995: 3.1 values/day and 2004: 4.9 values/day; p<0.0001). |
| SKEIE 2009 [658] | RCT<br>SMBG:<br>Focussed, structured 9-month SMBG<br>regular care SMBG | n=134 adults with type 1 diabetes.<br>n=65, control group; n=69, intervention | 9 months | HbA1c | |
| TILDESLEY 2004 [694] | Prospective case-series<br>SMBG:<br>The majority of patients used 2 injections of insulin per day, with a treatment goal of | n=934 TID using insulin therapy | 10-year observation period with an average of 4.7 visits | HbA1c<br>Hypoglycaemia | The number of insulin injections per day increased during the 10-year observation period. |

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | A1C<8.0% (normal range: 4.0% to 6.0%) | | | | |
| WEITGASSER 1994 [735] | Prospective case-series. SMBG: At baseline (year one) and five years SMBG was done ≤2 per day by 51% versus 12%, >2 but <4/day in 20% versus 21%, and ≥4/day by 29% versus 67% of the patients. | n=57; on intensive insulin therapy (IIT) requiring SMBG | 5 years | HbA1c Hypoglycaemia Retinopathy Neuropathy | |
| ZIEGLER1993 [768] | Cross-sectional study SMBG: Blood glucose measured 4 times a day (1 + 1 + 2 in a 3-injection regimen, 2 + 2 in a 2-injection-split and mixed regimen) before each meal and at bed-time. | n=80 insulin dependent diabetic patients chosen at random among diabetic patients treated by intensive insulin therapy (IIT) | At least 6 months | HbA1c | Fewer than 2 daily blood glucose determination was considered as incompatible with proper use of SMBG |

**Table 57: Summary of papers that were not fully extracted but included in the evidence statements**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| Frequency | | | | | |
| ANON 1993[687] | RCT – conventional once a day SBMG versus intensive ≤4 times a day | n=1441 IDDM (<20% 13-18 year olds) | 6.5 years | Mortality Hypoglycaemia Diabetic Ketoacidosis Quality of life | Included <20% adolescents. McCARTER2006 is post-hoc analysis |
| ARASZKIEWICZ 2008 | Prospective case-series. | n=86 | 7.1±1.5 years | Association between risk of | |

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| [42] | No intervention. Only logistic regression model was used to estimate RR for diabetic retinopathy and low-level (micro) albuminuria events | Type 1 diabetic patients | | retinopathy and SMBG | |
| BELL 1994 [63] | Prospective case-series. | n=211 Insulin dependent diabetes | Questionnaire | Severe hypoglycaemia and glucose tests and insulin injections | |
| BELL1984 [65] | Prospective case-series. | n=34 Diabetic patients | 3-4 months. | Association between frequency of testing and HbA1c | |
| BRUTTOMESSO 1992 [95] | No intervention. Retrospective case-series. | n=17 Type 1 diabetes | 23.6 months (3-83mo) | Association between frequency of testing and HbA1c and blood glucose level | |
| BRINCHMANN-HANSEN 1992 [89] | Prospective case-series. Insulin pumps (continuous subcutaneous insulin infusion) versus Multiple injections (4-6 times a day) and conventional insulin (2 times a day) | n=45 Insulin dependent diabetes | 7 years | HbA1c readings | |
| CHAN 2009 [109] | Prospective case-series. No intervention. | n=1898 Type 1 diabetes | 5 years, this includes a 2-week cross-sectional and a 9-month longitudinal survey. | Association between frequency of testing and achieving HbA1c of <7% | |
| GONDER 1988 [258] | Prospective case-series. Use of memory meters versus record test results in diaries | n=30 Adults with insulin dependent diabetes of at least 1 year | 2 weeks | Association between frequency of SMBG and HbA | |

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| HARTEMANN2001 [282] | Cross-sectional study Good glycaemic control. HbA <7.5% versus poor glycaemic control HbA >8.5% | n=122 Adults with type 1 diabetes | Cross-sectional study | Association between frequency of SMBG and complications | |
| LLOYD 1993 [442] | Cross-sectional No intervention. Multiple regression analysis to assess which factors are independent correlates of glycaemic control (as measured by GHb). | n=592 type 1 diabetes | Cross-sectional | Association between daily injections or tests and glycaemic control | |
| MERIMEE 1984 [480] | Prospective case-series. Glucose monitored initially daily, later 2 times a week | n=15 diabetic patients (unclear if type 1 or type 2 diabetes) with normal IGF-I and IGF-II values | 6 months | Change in HbA1c | |
| MCCLEAN 2005 [470] | Cross-sectional study. No intervention. Logistic regression analysis was used to identify characteristics associated with the presence of complications. | n=290 Type 1 and type 2 diabetes | Cross-sectional | Association between HbA1c and risk of retinopathy and neuropathy | |
| MILLER 2013 [483] | Cross-sectional study. No intervention. General linear relationship between HbA1c levels and SMBG | n=8914 Type 1 diabetes (adult data only) | Cross-sectional registry study | Association between frequency of SMBG and HbA1c | |

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| NAYAK 2011[515] ABSTRACT | Cross-sectional study. No Intervention. | n=127 Type 1 diabetes 61.4% | Cross-sectional study | Predictors of HbA1c. | |
| SJOBERG 1988 [657] | Cross-sectional study. No intervention. Pearson correlation analysis. | n=44 Insulin dependent diabetes. Excretors of C-peptide versus non-excretors | Cross-sectional analysis | Association between frequency of SMBG and HbA1c | |
| VAN TILBURG 2001[715] | Cross-sectional study. No intervention. Linear regression analysis. | n=30 Type 1 diabetes | Cross-sectional analysis | Association between frequency of SMBG and HbA1c | |
| WOO 2011 [749] ABSTRACT | Cross-sectional study. No intervention. | n=325 type 1 diabetes n=293 type 2 diabetes | Cross-sectional study | Association between frequency of home glucose monitoring and HbA1c | |
| ZIEGLER 2012 [769] ABSTRACT | Cross-sectional data from an RCT | n=202 type 1 diabetes n=17 type 2 diabetes | Post-hoc analysis | Association between clinical outcomes and SMBG frequency. | |
| ZIEGLER1989 [767] | Prospective case-series. | n=14 | 21 days | Association between frequency of SMBG and HbA1c | |

**Table 58:   Studies included in review for the optimal time of day to measure blood glucose levels**

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| HILLMAN 2004 [309] | Retrospective case-series. Measured glucose levels at pre and post meal times. | n=146 type 1 diabetes | 8 weeks | Predictors of HbA1c | |
| SERVICE 2007 [643] | Post-hoc analysis (prospective case-series data) of RCT SMBG: Intensive therapy Conventional therapy | n=565 volunteers. n=296 assigned to conventional therapy; n=269 assigned to intensive therapy | 6.5 years | HbA1c | |

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| SHIMIZU 2008 [650] | Cross-sectional study. SMBG: 6 times a day pre and post each meal | n=15 type 1 diabetes | 1 week | HbA1c | |
| WILLEY 1993 [745] | Prospective case-series. SMBG: Four times daily (4/day) HBGM. Once-daily HBGM at a variable time each day (Var1/day), | n=12 IDDM participants treated three to four times daily were asked by their clinicians to perform Home Blood Glucose Monitoring (HBGM) | 4 weeks | Mean blood glucose | |

**Table 59:   Summary of studies included in the review for glucose targets**

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| COX 1994 [137] | SMBG: 50 SMBG readings over a 2 to 3 week period with a hand held computer. Prospective case-series. | n=78 Insulin Dependent Diabetic Mellitus (IDDM) | Data collected during a 6 month baseline period | HbA1c Blood glucose | |
| KOVATCHEV 2000 [395] | SMBG: all participants were instructed to use blood glucose (BG) memory meters for 4-6 months and to measure their BG two to four times a day. During the same period of time 5 to 8 HbA1c assays were performed for each subject. Prospective case-series. | n=700 participants with IDDM Data for n=608 participants were completed with SMBG and HbA1c records. | 6 months | HbA1c Blood glucose | |
| MUHLAUSER1998 [495] | Self-administered questionnaire used to assess patients' treatment goals. | n=669 with type 1 diabetes: 18 years or older | 19 months | Severe hypoglycaemia | The questionnaire consisted of 10 items which were rated on a |

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| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | Questions possibly relevant for the prediction of severe hypoglycaemia (SH) were used.<br>Prospective case-series. | Initiation of insulin therapy before 31 years of age | | | 6-point Likert scale (1 = very important; 6 = totally unimportant). |
| SERVICE 2001 [642] | SMBG:<br>Intensive therapy<br>Conventional therapy<br>Prospective case-series. | n=565 volunteers.<br>n=296 assigned to conventional therapy;<br>n=269 assigned to intensive therapy | | HbA1c<br>Blood glucose | |
| VERVOORT 1996 [721] | SMBG:<br>All treated with short-acting insulin at least three times a day and intermediate-acting insulin at night.<br>Prospective case-series. | n=31 type 1 diabetes randomly selected from the population of a diabetes outpatient clinic. | Overnight observation | Hypoglycaemia | |
| WEI 2014 [733] | SMBG values and HbA1c values.<br>Prospective case-series. | n=387<br>(237 type 1 diabetes – subgroup analysis has been done) | 12 weeks | Blood glucose values at different HbA1c measurements | |
| WHITE1982 [739] | SMBG:<br>Conventional therapy (CT)<br>Intensive therapy (IT)<br>Prospective cohort study. | n=36 participants with IDDM. 5.5% (2) of the population <18 years of age.<br>n=25 assigned to CT; n=11 non-obese assigned to IT | 4-6 months | HbA1c<br>Retinopathy | |

**Outcomes**

**Table 60:  Results of studies investigating relationship between frequency of self-monitoring of blood glucose and glucose control.**

| Study | Study design | Insulin regimen | Number of patients | Frequency of SMBG | Outcome |
|---|---|---|---|---|---|
| SMBG versus none | | | | | |
| ABDELGADIR2006 [12] | Cross-sectional | No detail | n=50 | SMBG versus not | Lower HbA1c 5.6±1.5% (SMBG) versus 9.4±2.1% (none) |
| SMBG 0 to ≥ 3 times per day | | | | | |
| BOTT 1994 [82] | Prospective case-series. | to inject NPH-insulin in the morning and at bedtime and regular insulin before meals | n=697 | 0 to ≥2 times a day | An increased frequency was associated with a lower HbA1c |
| HARTEMANN2001 [282] | Cross-sectional. Good glycaemic control. HbA <7.5% versus Poor >8.5% | Daily injections 3.1± 0.9 | n=122 | Mean 2.7 to 3.6 times a day | Well controlled group carried out more home blood glucose tests and fewer complications (physical complaints, psychological distress, leisure restrictions, conscious experience and management of hypoglycaemia, diet, difficulties at work) |
| KLEIN 1992 [381] | Prospective case-series 4 years. | 64% ≥2 insulin injections times a day; 68% combination of intermediate short-acting | n=1210 | 0 to ≥3 times a day | HbA1c decreased more from baseline with increased frequency of SMBG |
| KARTER 2001 [366] | Prospective case-series, registry cohort | Insulin injections <1 to 3 times a day | n=1159 | 0 to ≥3 times a day | An increased frequency was associated with a lower HbA1c |
| TILDESELEV | Prospective case- | The majority used 2 injections/day, with | n=934 | <1 to 1.5 times a day | An increased frequency was associated with a lower HbA1c |

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| Study | Study design | Insulin regimen | Number of patients | Frequency of SMBG | Outcome |
|---|---|---|---|---|---|
| 2004 [694] | series. 10 years | a treatment goal of ACI <8% (normal 4-6%) | | | |
| ZIEGLER 2012 [769] | Post-hoc analysis (cross-sectional data) from an RCT | NA | n=202 | ≥3 times a day | An increased frequency was associated with a lower HbA1c |
| ZIEGLER1989 [767] | Prospective case-series. 21 days | NA | n=14 | >3 times a day | An increased frequency was associated with a lower HbA1c (r=-0.85, p<0.001). |
| SMBG up to ≥4 times per day | | | | | |
| ANON 1993[687] | RCT 6.5 years | Insulin injections Intensive ≤3 times a day Conventional 1-2 times a day | n=1441 | 4 versus 1 times a day | NS difference in mortality Hypoglycaemic episodes per 100 patient-years Intensive 62 versus conventional 19 Diabetic ketoacidosis per 100 patient-years Intensive 2 versus 1.8 conventional Quality of life no difference |
| SCHIFFRIN [626] | Cross-over trial 21 months | Multiple sc. Injections or continuous sc. injections | n=21 | 4 versus 2 times a day | An increased frequency was associated with a lower HbA1c |
| ARASZKIEWICZ 2008 [42] | Prospective case-series 7.1 years | Multiple daily injections with adapting short-acting insulin for before meals | n=86 | 3.6 to 4.1 times a day | Subjects who developed retinopathy had higher HbA1c. Risk of retinopathy was associated with infrequent monitoring of blood glucose RR=5.5 (2-15.11) Risk of low-level (micro) albuminuria was associated with bad self-monitoring of glucose (RR=2.86 (1.1-7.24) |
| EVANS 1999 [201] | Retrospective case-series, registry database | No detail | n=258 | 1 to 4 times a day | HbA1c decreased 0.7% for every additional SMBG per day |
| GONDER1988 [258] | Prospective case-series 2 weeks | Fast and intermediate-acting insulin, except one | n=30 | 0.21 to 4.43 times a day | An increased frequency was associated with a lower HbA1c |

| Study | Study design | Insulin regimen | Number of patients | Frequency of SMBG | Outcome |
|---|---|---|---|---|---|
| | | who used multiple injections of regular insulin | | | |
| MINDER 2013 [484] | Cross-sectional study | Flexible intensified insulin therapy (details not given) | n=150 | 1->4 times a day | Mean HbA1c declined with increasing number of SMBGs per day<br><br>Decline continued up to at least 4 SMBGs/day before flattening<br><br>No. of SMBGs/day per 1 mmt increase and difference in HbA1c (95% CI):<br><br>• ≤4 SMBGs = -0.19% (-0.42 to 0.05)<br>• >4 SMBGs = -0.02 (-0.10 to 0.06)<br>• HbA1c graphs show there is decline until approximately 10 times a day and then HbA1c slowly increases again. |
| NATHAN 1996 [499] | Prospective case-series data from cohort study | 70% injecting insulin 2 times a day | n=231 | 1 to 4 times a day | An increased frequency was associated with a lower HbA1c |
| SCHUTT 2006 [634] | Prospective case-series >6 months | Conventional (≥4 injections/ day) or continuous or 1-3 injections/day | n=24,500 | Mean 3.1 to 4.9 times a day | One additional daily BG measurement improved HbA1c by 0.26% |
| WEITGASSER 1994 [735] | Prospective case-series 5 years | All except one received intermediate or intermediate and long-acting insulin 2 times a day and shorting acting before meal times. One was on pump | n=57 | Subgroup analysis of <4 to >4 times a day | Decrease in HbA1c from 7.2±1.6 to 6.2±1.4% |
| ZIEGLER 1993 | Cross-sectional | Target blood sugar | n=80 | 4 times a day | Greater compliance to 4 times a day was associated with |

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| Study | Study design | Insulin regimen | Number of patients | Frequency of SMBG | Outcome |
|---|---|---|---|---|---|
| [768] | | 3.6 – 7.3 mmol/litre fasting or before each meal and 5.6-7.3 mmol/litre at bedtime. 3 times a day for regular insulin; 2 times a day for intermediate-acting insulin | | | lower HbA1c |
| **SMBG up to ≥10 times per day** | | | | | |
| MILLER2013[483] | Cross-sectional registry data | NA | n=8914 | 0 to ≥10 times a day | A higher number of SMBG measurements per day was strongly associated with a lower HbA1c in all groups. |
| COX 2007 [138] | Prospective case-series | 0.48±0.26 units/kg/day | n=90 | 3 to 5 times a day  Mean 5.4±2.3 times a day | 5 times a day better predicted severe hypoglycaemia than 3 times a day |
| **SMBG: studies where measurements as times/day was not reported** | | | | | |
| SKEIE 20009 [658] | RCT 9 months | Focused regimen aimed at enhancing focus on BG self-management versus usual daily  25% on insulin pump | n=134 | Intensive (details not given) versus 1 times a day | Comparing the 2 groups, A1C was approximately 0.6% lower in the intervention group  No increase in major or minor hypoglycaemia in both groups during the study period |
| VAN TILBURG 2001 [715] | Cross-sectional | 53% ≥3 injections/day  30% insulin pump  17% 1-2 injections/day | n=30 | 25.5 ± 9.9 times a week | An increased frequency was associated with a lower HbA1c |
| SJOBERG 1988 [657] | Cross-sectional | n=34 insulin 2 times a day, n=8 3 times a | n=44 | 0 to 120 months | An increased frequency was associated with a lower HbA1c |

| Study | Study design | Insulin regimen | Number of patients | Frequency of SMBG | Outcome |
|---|---|---|---|---|---|
| | | day, n=1 4 times a day.  82% intermediate or long-acting insulin and soluble insulin. . | | | |
| NAYAK 2011[515] | Cross-sectional | NA | n=127 | NA | Blood glucose variability explained 39% of variance of HbA1c. |
| LLOYD 1993 [442] | Cross-sectional | NA | n=592 | SMBG (no detail) | An increased frequency was associated with a lower HbA1c Number of tests performed daily r=-0.12 p=0.0146 |
| CHAN [109], | Prospective case-series. 5 year, this includes a 2-week cross-sectional and a 9-month longitudinal survey. | No details | n=1898 | Regular (no detail) | SMBG versus not was associated with two to three fold increased odds of reaching the A1C goal of <7%. |
| BRINCHMANN-HANSEN 1992 [89] | Prospective case-series 7 years | Unclear | n=45 | Regular (no detail) | Intensified insulin treatment and home blood glucose monitoring improved concentrations of HbA1c from 11.2% to 9.5% |
| Studies showing no relationship between SMBG and glucose control | | | | | |
| GORDON [259] | Cross-over study 3 times for 12 weeks | Average 3.3 (0.03 to 11.8) dose changes per week | n=25 | 4 versus 1 times a day | No relationship between frequency of altering insulin dosage and HbA1c |
| MCCLEAN 2005[470] | Cross-sectional | NA | n=290 | Daily SMBG (no detail) versus no daily testing | SMBG was not associated with risk of developing retinopathy/neuropathy |
| BRUTTOMESSO 1992 [95] | Retrospective case-series, mean 23.6 months (3-83 months) | Unclear | n=17 | 0.5 to 5 times a day | A weak correlation was found between number of blood glucose readings/day and daily blood glucose level, r=0.44, and serum HbA1c r=0.45, both p<0.05 |

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| Study | Study design | Insulin regimen | Number of patients | Frequency of SMBG | Outcome |
|---|---|---|---|---|---|
| MERIMEE1994 [480] | Prospective case-series 6 months | Minimum of 2 times a day injections of insulin with supplementary insulin given on the basis of monitoring blood glucose 4 times a day | n=15 | 4 times 7 days a week then 2 days a week | HbA1c decreased despite lower frequency of SMBG |
| WOO 2011 [749] Abstract | Cross-sectional | NA | n=618 | <2 to >3 times a day | No relationship between frequency and HbA1c |
| BELL 1994 [63] | Prospective case-series. Questionnaire | History of SH 2.72 injections/ day. No history of SH 3.06 injections/ day | n=211 | 2.3 to 2.5 times a day | Patients with severe hypoglycaemia more likely to perform SMBG at home more frequently |
| BELL 1984 [65] | Prospective case-series, 3-4 months | Insulin 1-2 times a day | n=36 | <1 to 4 times a day | Frequent testing was not more prevalent in those whose haemoglobin A1 improved. |
| TILDESELEV 2004 [694] | Prospective case-series. 10 years | The majority used 2 injections/day, with a treatment goal of ACI <8% (normal 4-6%) | n=934 | <1 to 1 times a day | No relationship between frequency and HbA1c |
| BRAGD 2003 [84] | Prospective case-series. 2 different time points | Multiple injection therapy | n=178 | Multiple | SMBG not a predictor of severe hypoglycaemia |

**Table 61: Frequency of self-monitoring of blood glucose and HbA1c**

| Study | 0 | 0-1 | 0-2 | 1 | 1-2 | 2-3 | 2 | >2 | 3 | 3-4 | ≥3 | <4 | >4 | 4 | 5-6 | 5 | 6 | 7 | 7-9 | 8 | ≥10 | SBMG Non-specific |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ABDELGADIR2006 [12] Cross-sectional | 9.4± 2.1 | | | | | | | | | | | | | | | | | | | | | 5.6±1.5 |
| Bott 1994 [82] Case-series | 10.4 ±2.2 | 9.5± 1.8 | | | 9.3±1.6 | | | 8.9± 1.5 | | | | | | | | | | | | | | |
| Gordon 1991[259] Cross-over 3x12 weeks | | | | | | | 9.7± 1.8 9.7± 2.0 | | | | | | | 9.5± 2.0 9.6± 2.0 9.4± 1.9 9.6± 2.1 | | | | | | | | |
| Karter2001[366] Case-series, registry database | 9.1 | 8.9 | | 8.5 | | | | | | | 7.7 | | | | | | | | | | | |
| Klein 1992[381] Case-series, 4 years | -0.6 | -0.6 | | | -1.0 | | | -1.3 | | | -1.1 | | | | | | | | | | | |
| MILLLER 2013 [483] Cross-sectional | | | 9.6 8.6 8.4 | | | | | | | 8.6 8.0 8.0 7.6 | | | | | 8.0 7.6 7.7 7.5 | | | | 7.7 7.4 7.3 7.2 | | 7.5 7.1 7.2 6.9 | |
| Schiffrin1982 [626] Cross-over trial | | | | | | | 10.3 ±0.5 10.2 ±0.5 | | | | | | | 7.9± 0.4 8.0± 0.1 | | | | | | | | |

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| Study | 0 | 0-1 | 0-2 | 1 | 1-2 | 2-3 | 2 | >2 | 3 | 3-4 | ≥3 | <4 | >4 | 4 | 5-6 | 5 | 6 | 7 | 7-9 | 8 | ≥10 | SBMG Non-specific |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 10.0 ±0.9 10 | | | | | | | 8.2± 0.4 8.1± 0.2 8.1± 0.4 8.0± 0.6 8.6 8.7 | | | | | | | | |
| SCHUTT 2006[634] Case-series ≥4 times a day insulin | 10.5 | | | 9.9 | | | 10.1 | | 9.6 | | | | | 8.8 | | 8.2 | 7.9 | 8.1 | | 8.1 | | |
| 1-3day insulin | 9 | | | 8.7 | | | 8.3 | | 8.5 | | | | | 8.1 | | 7.8 | 7.9 | 7.7 | | | | |
| Weitgasser 1994[735] Case-series | | | | | | | | | | | | 7.2± 1.6 | 6.2± 1.4 | | | | | | | | | |
| WOO 2011[749] Cross-sectional | | | 8.65 | | 8.58 | | | | | | 8.22 | | | | | | | | | | | |
| ZIEGLER 1993[768] Cross-sectional | | | | | | | | | | | | | | 6.7± 1.1 | | | | | | | | |

**Update 2015**

**Table 62:   Results of studies reporting on the timing of measuring blood glucose levels and effect on HbA1c**

| Paper | Number of patients | SBMG regime | Result |
|---|---|---|---|
| HILLMAN2004 [309] | n=146 | 6 times a day<br><br>Before and after breakfast, lunch and dinner | Best predictors of HbA1c were post-breakfast glycaemia, pre-breakfast glycaemia and pre-dinner glycaemia |
| SERVICE2007 [643] | n=565 | 7 times a day<br><br>before and after each meal and before bedtime | The strongest correlation between HbA1c and blood glucose measurements was detected from the mean of 7 measurements over a 24 hour period.<br>The next best correlation was with mean of after breakfast+ before and after lunch+ before and after supper<br>Subsequently, it was best correlated with mean postprandial. |
| SHIMIZU 2008[650] | n=15 type 1 diabetes | 6 times a day<br><br>Fasting glucose before breakfast, lunch and dinner. Post-prandial glucose. | No significant correlation between HbA1c and fasting glucose levels<br>A correlation was found between HbA1c and all post-prandial levels. |
| WILLEY 1993 [745] | n=12 | 1 times a day versus 4 times a day<br><br>Once-daily home blood monitoring at a variable time of day versus four times daily: pre-breakfast; pre-lunch, pre-dinner; pre-bed. | Measuring blood glucose four times a day (pre-breakfast, pre-lunch, pre-dinner and pre-bed) was no better than at a variable time of the day for mean blood glucose levels. |

**Table 63:   Results of studies reporting on target of blood glucose levels and clinical outcomes**

| Author | Number of patients | SMBG regime | Result |
|---|---|---|---|
| COX 1994 [137]1994 | n=78 | 50 SMBG over 2-3 weeks at baseline and 6 months | Blood glucose index<br>• <2.75 BG index = 5.2 hypoglycaemic episodes<br>• ≥2.75 BG index = 13.6 hypoglycaemic episodes<br>• <4.6 SMBG SD = 6.5<br>• ≥4.6 SBBG SD = 12.3<br>• <9.85 HbA1c = 9.3<br>• ≥9.85 HbA1c = 6.3 |
| MUHLHAUSER 1998 [495] | n=669 | <2 times a day 15%<br>≥2 times a day 85% | Trend to show the higher the number of BG values under 3.3 the higher the number of episodes of severe hypoglycaemia.<br>Blood glucose levels at which first symptoms are felt<br>• ≥2.8 mmol/litre 66%; 2.2-2.7 mmol/litre 20%; <2.2 mmol/litre 13% never feeling symptoms 1% |
| KOVATCHEV 2000 [395]2000 | n=608 | SBMB 2-4 times a day | A lower blood glucose value was associated with a lower HbA1c level.<br>• <8.6 mM = 8.29 HbA1c<br>• 8.6- 9.8 mM = 8.7 HbA1c<br>• 9.7-10.6 mM = 9.14 HbA1c<br>• 10.6-12 mM = 9.5 HbA1c<br>• >12 mM = 10.52 HbA1c |
| SERVICE 2001 [642]2001 | n=565 | SMBG same for all patients<br>7 times a day (90 minutes post breakfast, lunch and supper values, and pre meal values and bedtime) | Association between MBG and retinopathy:<br>• <8.3 mmol/litre = NS relationship<br>• >8.3 mmol/litre = increased risk<br>• Up to 16.6 mmol/litre versus 8.3 mmol/litre 15 times increased risk |
| VERVOORT 1996 [721] | n=31 | Continuous, measuring in hospital via catheter. | Fasting blood glucose of:<br>•  ≥5.5mmol/litre was never preceded by 'early morning' hypoglycaemia.<br>• <5.5 mmol/litre at 07.30 h was associated with 'early morning' hypoglycaemia in 6 of 12 patient-nights; |

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| Author | Number of patients | SMBG regime | Result |
|---|---|---|---|
| WEI 2014 [733] | n=237 | 12 weeks:<br>• 8-point SMBG (average SMBG of 11 days per person over the 12 weeks)<br>• Monthly HbA1c | **Fasting blood glucose values for:**<br>• HbA1c of 5.5-6.49 = 122 mg/dL (113-132)<br>• HbA1c of 6.5-6.99 = 144 mg/dL (134-154)<br>• HbA1c of 7.0-7.49 = 155 mg/dL (143-168)<br>• HbA1c of 7.5-7.99 = 170 mg/dL (159-181)<br>• HbA1c of 8.0-8.49 = 178 mg/dL (161-194)<br><br>**Preprandial blood glucose values for:**<br>• HbA1c of 5.5-6.49 = 119 mg/dL (115-124)<br>• HbA1c of 6.5-6.99 = 140 mg/dL (134-147)<br>• HbA1c of 7.0-7.49 = 156 mg/dL (150-163)<br>• HbA1c of 7.5-7.99 = 159 mg/dL (151-166)<br>• HbA1c of 8.0-8.49 = 175 mg/dL (162-188)<br><br>**Postprandial blood glucose values for:**<br>• HbA1c of 5.5-6.49 = 139 mg/dL (133-145)<br>• HbA1c of 6.5-6.99 = 161 mg/dL (155-168<br>• HbA1c of 7.0-7.49 = 175 mg/dL (167-183)<br>• HbA1c of 7.5-7.99 = 190 mg/dL (180-199)<br>• HbA1c of 8.0-8.49 = 197 mg/dL (188-205)<br><br>**Bedtime blood glucose values for:**<br>• HbA1c of 5.5-6.49 = 140 mg/dL (132-148)<br>• HbA1c of 6.5-6.99 = 154 mg/dL (144-164)<br>• HbA1c of 7.0-7.49 = 180 mg/dL (164-195)<br>• HbA1c of 7.5-7.99 = 179 mg/dL (166-193)<br>• HbA1c of 8.0-8.49 = 214 mg/dL (189-240) |

| Author | Number of patients | SMBG regime | Result |
|---|---|---|---|
| WHITE 1982 [739] | n=36 | Intensive treatment group: home blood glucose<br>Conventional therapy: unclear frequency of SMBG | • All participants in the intensively treated group achieved excellent glycaemic control with preprandial blood glucose values mostly under 200 mg/dl and complete absence of glycosuria. |

**Table 64:  Summary table showing association between blood glucose levels and diabetic control**

| Fasting <5.5 mmol/litre | Fasting ≥5.5 mmol/litre | <8.3 mmol/litre | >8.3 mmol/litre | <200 mg/dl |
|---|---|---|---|---|
| Associated with early morning hypoglycaemia in 6/12 patients | Never associated with early morning hypoglycaemia | Not associated with retinopathy | Increased risk of retinopathy | "Excellent" glycaemic control with pre-prandial BG <200 mg/d |
| <.2.2 mmol/litre | 2.2-2.7 mmol/litre | ≥2.8 mmol/litre | <2.75 low BG index | ≥2.75 low BG index |
| 13% felt onset of symptoms of hypoglycaemia | 20% felt onset of symptoms of hypoglycaemia | 66% felt onset of symptoms of hypoglycaemia | 5.2 hypoglycaemic episodes | 13.6 hypoglycaemic episodes |
| <8.6 mM | 8.6 - 9.7 mM | 9.7 – 10.6 mM | 10.6 – 12 mM | >12 mM |
| 8.29% HbA1c | 8.7% HbA$_{1C}$ | 9.14% HbA1c | 9.50% HbA1c | 10.52% HbA1c |

### 8.2.5 Economic evidence

**SMBG timing and frequency**

**Published literature**

No relevant economic evaluations were identified.

**New cost-effectiveness analysis**

Original cost-effectiveness modelling was undertaken for this question. A summary is included here while the full analysis can be found in Appendix P.

The analysis was undertaken using a validated, internet-based model (IMS CORE Diabetes Model (CDM). IMS CDM is an interactive computer model developed to determine the long-term health outcomes and economic consequences of interventions for type 1 or type 2 diabetes mellitus. Separate transition probabilities and management strategies are used for each type where data exist, facilitating running diabetes type-specific analysis. IMS CDM has been widely used and validated against real-life clinical and epidemiological data.

Strategies compared in the model included different frequencies of SMBG and also included continuous glucose monitoring (CGM, see section 8.4.6), specifically:

- SMBG twice a day
- SMBG 4 times a day
- SMBG 6 times a day
- SMBG 8 times a day
- SMBG 10 times a day
- CGM

A cohort of type 1 diabetes patients with defined demographic and racial characteristics reflecting the adult type 1 diabetes population in the UK was used in the base case analysis. Lifetime horizon was used in the analysis. Health outcomes and costs are discounted at an annual rate of 3.5%. These are used to calculate the net monetary benefit (NMB) associated with the different monitoring strategies. The analysis was undertaken from the perspective of the UK NHS and PSS. A willingness to pay threshold of £20,000 per QALY gained was adopted.

The main clinical outcome used in the model is the change in HbA1c level which then influences the downstream events as defined in the CORE model. Strategy-specific HbA1c reductions were obtained from the clinical literature (see 8.2.4): the study by Miller et al.[483] was used for the SMBG frequencies as this cross-sectional study was the only one to report frequencies that were selected for comparison in the model; for the effectiveness of CGM at reducing HbA1c the meta-analysis conducted for our clinical review and reported in section 8.4.5, using the real-time CGM data only. One of the study included in the meta-analysis[439] was retrieved in the updated search at the end of the guideline and could not be included in the modelling, but the difference in HbA1c in the meta-analysis with or without the latest study was considered to be negligible (-0.34% without versus -0.30% with the study). The frequency of SMBG against which CGM was compared in the clinical studies was uncertain and therefore an assumption had been made that this was 4 times per day; this was varied in a sensitivity analysis where the reduction in HbA1c was assumed to be estimated versus a higher frequency of 10 per day (best case scenario for CGM).

The overall effectiveness estimates are reported in the table below together with the annual cost of the interventions.

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**Table 65: Effectiveness and cost data associated with the strategies in the model**

| Intervention | Average HbA1c | Average HbA1c change from baseline[a] | Average HbA1c change versus SMBG | Annual cost(b) |
|---|---|---|---|---|
| SMBG 2 | 9.11 | -0.19 | | £212 |
| SMBG 4 | 8.24 | -1.06 | | £423 |
| SMBG 6 | 7.74 | -1.56 | | £635 |
| SMBG 8 | 7.43 | -1.87 | | £847 |
| SMBG 10 | 7.21 | -2.09 | | £1,059 |
| CGM | NR | | -0.34 | £3,511 |

(a) HbA1c baseline was obtained by the National Diabetes Audit and was 8.8%
(b) Based on the average cost of lancets and strips obtained from the Drug Tariff, November 2014[518]

Hypoglycaemic event rates were not obtained from our clinical data as they showed counter-intuitive results (the higher the frequency of SMBG testing, the higher the hypoglycaemic events); this was explained by the bias inherent in cross-sectional studies where patients who are more at risk of hypoglycaemic events are more likely to test more frequently (there is an inverse relationship between cause and effect). It is also possible that more frequent testing leads to overcorrection of high glucose readings. We have kept the event rates constant for every strategy but we have changed this in a sensitivity analysis.

**Results**

The average cost and QALYs gained with each strategy is reported in Table 66. In this table interventions are ranked according to their mean net monetary benefit, which depends on the costs, QALYs and willingness to pay (set at £20,000/QALY in our analysis).

**Table 66: Base case probabilistic results in the model**

| Strategy | Mean discounted cost per patient | Mean discounted QALYs per patient | Net monetary benefit (at £20,000/QALY threshold) | Rank by NMB |
|---|---|---|---|---|
| SMBG 2 | 42,862 | 10.83 | 177659 | 5 |
| SMBG 4 | 43,027 | 11.43 | 192134 | 4 |
| SMBG 6 | 44,862 | 11.75 | 198272 | 3 |
| SMBG 8 | 47,478 | 11.93 | 200047 | 1 |
| SMBG 10 | 50,331 | 12.06 | 200091 | 2 |
| CGM | 95,241 | 11.65 | 144492 | 6 |

Overall, SMBG 8 times was ranked the most cost effective strategy in the base case analysis, however the ICER of SMBG 10 times compared with SMBG 8 times was just above the £20,000 per QALY gained threshold (£23,008/QALY). CGM is less effective and more costly than SMBG 8 and SMBG 10 when its effectiveness in terms of HbA1c reduction was assumed to be estimated via the common comparator of SMBG 4 times. The deterministic base case analysis (Table 67) showed that overall QALYs are higher than in the probabilistic sensitivity analysis and the more effective strategies are also more cost effective in the deterministic than in the probabilistic analysis. This explains why SMBG 10 times daily is the first ranking in terms of NMB in the deterministic analysis (the ICER is £15,184 per QALY, below the cost effectiveness threshold).

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**Table 67: Deterministic results (mean per patient)**

| Strategy | Costs[a] | QALYs[b] | NMB[c] | Rank[d] |
|---|---|---|---|---|
| SMBG 2 | 45,572 | 12.172 | 197,868 | 5 |
| SMBG 4 | 43,573 | 12.847 | 213,367 | 4 |
| SMBG 6 | 44,340 | 13.186 | 219,380 | 3 |
| SMBG 8 | 46,627 | 13.439 | 222,153 | 2 |
| SMBG 10 | 49,026 | 13.597 | 222,914 | 1 |
| CGM | 101,095 | 13.091 | 160,725 | 6 |

(a) *Discounted life-time costs per patient*
(b) *Discounted life-time quality-adjusted life years (QALYs) per patient*
(c) *Net monetary benefit calculated at a threshold of £20,000 per QALY gained*
(d) *Ranked in descending order according to NMB*

One way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters. The following changes were tested:

- decrease in HbA1c achieved with CGM in the meta-analysis assumed to be estimated compared with SMBG 10 times (best case scenario for CGM)
- utility approach used in the CORE model (from a minimum value approach to a multiplicative one)
- no progression of HbA1c throuhgout the years
- alternative discounting factor (1.5%) for both costs and outcomes
- cohort of patients with a more recent diagnosis of type 1 diabetes

Throughout these sensitivity analyses, either SMBG 10 or 8 times remained always the most cost effective strategies, while CGM was always more effective but more costly and the ICER was always above the £20,000 per QALY threshold.

Another analysis was conducted in a hypothetical cohort of patients with hypoglycaemia unawareness problems to test if CGM could be cost effective in this group; in this analysis the number of hypoglycaemic events was increased six-fold (from 110 events per 100 patient-years to 660 events per 100 patient-years) in the comparator (SMBG 10 and 8) while it was kept 0 in the intervention (CGM). In addition the cost of CGM was assumed to be 70% of the figure used in the base case analysis and its HbA1c reduction was assumed to be estimated compared with SMBG 10 times. In this scenario, CGM was still not cost effective and the ICER was £30,203 per QALY. However when it was compared with SMBG 4 times daily (which is considered the current practice), the ICER was £16,229 per QALY in the scenario where CGM decreased hypo events to 0.

This analysis was limited for a number of reasons: the clinical effectiveness data on different frequencies of SMBG was obtained from a cross-sectional study; a higher frequency of testing could lead to a decrease in hypoglycaemic events but these data could not be obtained from the available study. Also the population in this analysis may not be representative of people with type 1 diabetes who have problems at controlling their HbA1c level with SMBG and self-injection only. The cost effectiveness of CGM in combination with insulin pumps was not assessed and it may be that this combination is cost effective in people with glycaemic control issues.

**SMBG targets**

**Published literature**

No relevant economic evaluations were identified.

**8.2.6     Evidence statements**

**Clinical**

**Frequency of self-monitoring of blood glucose**

Low quality evidence from 35 studies (two RCTs, two cross-over studies, and 31 observational studies) showed the following:

- Evidence mostly from large studies showed that self-monitoring of blood glucose was associated with lower HbA1c levels than those who do not self-monitor blood glucose.

- Evidence mostly from large studies showed that more frequent self-monitoring of blood glucose levels up to 3 or 4 times a day is associated with lower HbA1c levels and with fewer complications such as hypoglycaemia, DKA, retinopathy, low-level (micro) albuminuria, physical complaints, psychological distress, leisure restrictions, conscious experience and management of hypoglycaemia, diet, and difficulties at work. Evidence from large studies also showed it was associated with lower mortality rates.

- Evidence mostly from large studies showed that self-monitoring of blood glucose at least 4 times a day and up to ten times a day is associated with lower HbA1c levels.

- Evidence mostly from small studies showed generally that increased frequency of self-monitoring of blood glucose is not associated with lower HbA1c levels, incidence of severe hypoglycaemia or other adverse events.

**Timing of measuring blood glucose**

Low quality evidence from 4 observational studies showed the following:

- In terms of HbA1c, evidence from large studies showed that the strongest correlation with HbA1c is the mean blood glucose reading taken after breakfast, before and after lunch and before and after dinner. And the best predictor of HbA1c level is blood glucose measured before and after breakfast, and before dinner. However, evidence from a single small showed that HbA1c did not correlate with post-prandial levels

- In terms of taking measurements at variable times of day, evidence from a single small study showed that measuring blood glucose four times a day was no better than at a variable time.

**Optimal target of blood glucose**

Low quality evidence from 7 observational studies showed the following:

- In terms of HbA1c, evidence from two large studies showed that higher blood glucose readings are associated with higher HbA1c values, and every 1% rise in HbA1c results in an increase in night-time as well as pre-and post-prandial blood glucose levels. At an HbA1c between 6.5 and 6.99, mean blood glucose values were 144 mg/dl (fasting), 140 mg/dl (preprandial), 161 mg/dl (postprandial) and 154 mg/dl (bedtime). At an HbA1c between 5.5 and 6.49, mean blood glucose values were: 122 mg/dl (fasting), 119 mg/dl (preprandial), 139 mg/dl (postprandial) and 140 mg/dl (bedtime). Evidence from a small study showed that intensively measured blood glucose levels at home achieved 'excellent' glycaemic control with preprandial blood glucose values mostly under 200 mg/dl and complete absence of glycosuria.

- In terms of hypoglycaemia, evidence from a small study showed that fewer hypoglycaemic events were associated with blood glucose readings of less than 2.75 mmol/litre. However, evidence from a large study showed that more severe hypoglycaemic events were associated with blood glucose readings of less than 3.3 mmol/litre, and hypoglycaemia symptoms were first felt by most people at more than or equal to 2.8 mmol/litre. Evidence from a small study also showed that fasting blood glucose of more than or equal to 5.5 mmol/litre is never preceded by early morning

hypoglycaemia. However, less than 5.5 mmol/litre are associated with early morning hypoglycaemia in 6/12 patient-nights.

- In terms of retinopathy, evidence from a large study showed an increased risk of retinopathy with blood glucose readings of more than 8.3mmol/litre.

**Economic**

One original cost–utility analysis found that either SMBG 10 times a day or SMBG 8 times a day was cost effective compared with other lower frequencies of SMBG and CGM. This analysis was assessed as directly applicable with potentially serious limitations.

### 8.2.7 Recommendations and link to evidence

| Recommendations | 44. Advise routine self-monitoring of blood glucose levels for all adults with type 1 diabetes, and recommend testing at least 4 times a day, including before each meal and before bed. [new 2015]

45. Support adults with type 1 diabetes to test at least 4 times a day, and up to 10 times a day if any of the following apply:
- the target for blood glucose control, measured by HbA1c level (see recommendation 39), is not achieved
- the frequency of hypoglycaemic episodes increases
- there is a legal requirement to do so (such as before driving, in line with DVLA requirements)[j]
- during periods of illness
- before and after sport
- when planning pregnancy, during pregnancy and while breastfeeding (see the NICE guideline on diabetes in pregnancy[k])
- if there is a need to know blood glucose levels more than 4 times a day for other reasons (for example, impaired awareness of hypoglycaemia, high-risk activities). [new 2015]

46. Enable additional blood glucose testing (more than 10 times a day) for adults with type 1 diabetes if this is necessary because of the person's lifestyle (for example, driving for a long period of time[l], undertaking high-risk activity or occupation, travel) or if the person has impaired awareness of hypoglycaemia. [new 2015]

47. Advise adults with type 1 diabetes to aim for:
- a fasting plasma glucose level of 5-7 mmol/litre on waking and
- a plasma glucose level of 4-7 mmol/litre before meals at other times of the day. [new 2015]

48. Advise adults with type 1 diabetes who choose to test after meals to aim for a plasma glucose level of 5-9 mmol/litre. [new 2015] |
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j    For further details about driving, see the DVLA guidance for people with type 1 diabetes
k    This guideline is currently being updated (publication expected February 2015)
l    For further details about driving, see the DVLA guidance for people with type 1 diabetes

| | **49.Support adults with type 1 diabetes to make the best use of data from self-monitoring of blood glucose through structured education (see recommendations 12 and 14). [new 2015]** |
|---|---|
| Relative values of different outcomes | To determine whether self-monitoring of blood glucose levels (SMBG) was beneficial to individuals with type 1 diabetes, the GDG reviewed whether the following parameters of SMBG had any influence on clinical outcomes: <br><br> • The frequency of SMBG <br><br> • Blood glucose targets when using SMBG <br><br> • The timing of SMBG (fasting, pre- versus post-prandial) <br><br> The impact of these parameters of SMBG was assessed for the following clinical outcomes: <br><br> • Improvement in glycaemic control, assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications. <br><br> • Reduction in hypoglycaemia and severe hypoglycaemia (requiring help from 3rd party for correction). Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes. Hypoglycaemia occurrence can limit individuals achieving improvements in glycaemic control, and any adjunct therapy that achieves an improvement in glycaemic control without producing hypoglycaemia would be considered beneficial to patients with diabetes. |
| Trade off between clinical benefits and harms | The GDG reviewed the available evidence for SMBG from randomised controlled trials (RCTs). Much of the available evidence from RCTs focused on the impact of SMBG parameters on glycaemic control, with little RCT evidence available to assess its impact on the frequency of hypoglycaemia. <br><br> **Frequency of SMBG and impact on glycaemic control** <br><br> RCT evidence showed that patients who monitored blood glucose had improved glycaemic control compared with those who did not monitor blood glucose levels at all.[12] <br><br> Clinical outcomes from a large cross-sectional study and a large case-series showed that increased blood glucose monitoring up to four times a day was associated with substantial improvements in blood glucose control.[483,634] Testing five times a day was associated with improved glycaemic control in comparison to testing three times a day.[138] In a small cross-over clinical trial, testing four times a day was associated with improved blood glucose control outcomes when compared with testing twice a day.[626] <br><br> Increased frequency of blood glucose monitoring more than four times a day was associated with further improvements in blood glucose control in two studies, with testing up to ten times day associated with an improvement in HbA1c.[483,484] .However, the increments in the clinical benefits gained were smaller with higher frequencies of blood glucose testing. From the evidence for routine testing, the GDG did not consider a test frequency of more than 8 times a day to be associated with clinically significant further improvement in glucose control. The indications for patients wanting to test at greater frequency should be discussed with the patient, and supported where the extra tests are needed to accommodate lifestyle issues. <br><br> Other large trials suggested a plateau effect with testing more than four times a day. [634] . The available evidence suggested that patients on insulin pump therapy might |

have a greater improvement in glycaemic control with increased frequency of testing than patients on multiple daily insulin regimens.[634] Davidson et al., 2007).

In contrast, the DCCT showed no evidence that an increased frequency of monitoring (more than four times a day versus one to two times a day) had any impact on quality of life. Frequency of hypoglycaemia was higher in individuals testing more frequently (62 versus 19 hypoglycaemia episodes per 100 patient years) but the glycaemic control achieved in the intensively treated group was 7.2% compared with 8.9% in the non-intensively treated group. The GDG noted that the insulin regimens in the two groups differed substantially, and that frequency of SMBG monitoring was not the only variable likely to influence clinical outcome. An observational study[282], showed that people with HbA1c <7.5% versus those with HbA1c >8.5% were doing more frequent blood tests and had less frequent hypoglycaemia associated with this increased blood glucose testing while another study[138] showed the converse, in that 5 tests per day better predicted hypoglycaemia than 3.

There was other observational study evidence[63,65,84,95,259,470,480,694] indicating that increased frequency of blood glucose testing might not improve glycaemic control, but the majority of these studies were small and less recent in comparison to those showing benefit.

Overall, no adverse outcomes were reported from an increased frequency of blood glucose monitoring.

**Optimal blood glucose targets**

Evidence was available from six RCTS regarding the impact of blood glucose targets on clinical outcomes.

**Pre-prandial targets:** One study reported that nocturnal hypoglycaemia was unlikely to occur if individuals with type 1 diabetes achieved a blood glucose level above 5.5 mmol/litre on waking. [721]A second study reported that the risk of overnight hypoglycaemia was reduced if individuals achieved a waking blood glucose above 5 mmol/litre.[115]

The GDG recognised that these recommendations were in line with recommendations from intensive education courses for type 1 diabetes. Targets for morning blood glucose levels on waking should be higher than other fasting values through the day in order to reduce the risk of nocturnal hypoglycaemia. The GDG therefore considered that fasting blood glucose targets should be 5 to 7 mmol/litre on waking in the morning and 4 to 7 mmol/litre at other times of day).

**Post-prandial glucose testing:** One study reported that the risk of complications from retinopathy were greatly reduced if a blood glucose level of less than 8.1 mmol/litre could be achieved post-prandially (The Diabetes Control and Complications Trial). The GDG therefore considered that individuals with type 1 diabetes should aim for a blood glucose level that was not above 9 mmol/litre post-prandially, whilst also avoiding hypoglycaemia, best avoided by keeping blood glucose targets always above 4.5 mmol/litre).

**Timing of SMBG testing:** Much of the available evidence looked at the relationship between timing of blood glucose testing and its ability to predict glycaemic control measures (as measured by HbA1c). Although the available RCT evidence did show that increased frequency of testing was associated with improved glycaemic control, it did not suggest an advantage in testing at specified times of day.

The GDG noted that current clinical practice is to test blood glucose levels on waking, pre-prandially and before bed. There was concern that post-prandial blood glucose testing might lead to over-correction of blood glucose levels if they were found to be high, although there was no clinical evidence from an RCT to support this concern.

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|---|---|
| | The GDG concluded that further research was required to ascertain the importance of post-prandial testing in comparison to pre-prandial testing. |
| | The GDG recommended that for four times a day testing, patients should check blood glucose levels before meals and before bed. Post-prandial blood glucose testing was considered to be useful for educational purposes (for example, when learning to carbohydrate count), and may help patients to ensure they were taking adequate amounts of insulin at mealtimes. |
| | It was emphasised by the GDG that structured education in interpreting blood glucose values (for example, in relation to food, illness, recent exercise) was essential to allow patients to make informed decisions about insulin dose adjustment for improved blood glucose control. |
| Economic considerations | One original economic model was developed which compared different frequencies of SMBG and CGM. The change in HbA1c from baseline was the main clinical outcome used in the model, which determined other events such as complications and death over a lifetime horizon. |
| | Based on the effectiveness data used in the model, glycaemic control was better with higher frequencies of monitoring and therefore the maximum overall QALY gain was achieved with a strategy of SMBG 10 times a day. The cost of undertaking one additional SMBG test in one individual each day was calculated to be £106 per year, based on the cost of one lancet and one test strip per blood glucose check. Other costs accrued over the lifetime horizon were determined by the complications and their management and therefore decreased with more effective strategies. |
| | The model showed that testing 8 times a day was the optimal strategy in the probabilistic analysis as it improved outcomes (reducing HbA1c level) at an acceptable cost compared with testing less frequently. Testing 10 times a day was the most cost effective strategy in the deterministic analysis, while in the probabilistic analysis the ICER of this strategy compared with SMBG 8 times a day was £23,003 per QALY, just above the cost effectiveness threshold. For these reasons the GDG decided that supporting people who want to test more than 4 times a day would be cost effective, although they did not believe the recommendation had to be prescriptive on a specific frequency as either 8 times or 6 times daily could be cost effective. |
| | This analysis had some important limitations in terms of uncertainty in key parameters (quality of life associated with hypo events) and missing links between model outcomes (achieved HbA1c level and hypo events).  Also the clinical effectiveness data on different frequencies of SMBG was obtained from a cross-sectional study; a higher frequency of testing could lead to a decrease in hypoglycaemic events but these data could not be obtained from the available study. The population in this analysis may not be representative of people with type 1 diabetes who have problems at controlling their HbA1c level with SMBG and self-injection only. |
| Quality of evidence | Only randomised controlled trials were included for assessment of SMBG on clinical outcomes. |
| | The GDG recognised that no trial evidence focusing solely on the impact of SMBG frequency/timing/targets was available for review. Most of the reviewed evidence was taken from RCTs that included the use of SMBG as part of the assessment, but there were none with identical insulin treatment regimens in which SMBG variations were the only variable tested. |
| | The economic evidence was assessed as directly applicable with potentially serious limitations. |
| Other considerations | Outside routine testing frequency recommendations, the GDG also recognised that individuals with type 1 diabetes were required to test blood glucose levels as a necessity for driving recommendations by the DVLA. It was recognised that there would be times where individuals with type 1 diabetes might want to test blood glucose levels more frequently (for example, before exercise, during periods of |

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illness, when considering pregnancy, breastfeeding) and that during such periods, patients should be encouraged to increase their frequency of monitoring to avoid adverse outcomes.

There is some RCT evidence to suggest that post-prandial blood glucose monitoring may be predictive of glycaemic control, and that availability of these test results might allow individuals to achieve further improvements in glycaemic control. However, analysis of the DCCT data base found only weak correlation between post-prandial glucose tests predicted HbA1c and there is anecdotal evidence [501]that post-prandial testing encourages excessive insulin administration and hypoglycaemia. Findings are not universal and the GDG recommends that research is undertaken to assess the importance of post-prandial blood glucose testing on glycaemic control and clinical outcomes.

The GDG considered whether a nocturnal blood glucose target for test results undertaken before going to bed should be provided by the NICE Guidance. However, it was recognised that a pre-bedtime glucose value would be very dependent on when an individual with type 1 diabetes went to bed and at what time they ate their evening meal before testing. The GDG therefore decided not to provide additional guidance regarding pre-bedtime blood glucose targets. pre-bedtime fasting, pre-meal and post-prandial targets as appropriate to the time of last eating before bedtime If an adult with diabetes experienced overnight hypoglycaemia whilst trying to achieve these targets, this suggests that their basal and/or prandial insulin doses should be reviewed rather than adjustment of target blood glucose levels.

50. Teach self-monitoring skills at the time of diagnosis and initiation of insulin therapy. [2004, amended 2015]

51. Carry out a structured assessment annually of self-monitoring skills, the quality and use made of the results obtained and the equipment used. Review self-monitoring skills as part of annual review, or more frequently according to need, and reinforce them where appropriate. [2004, amended 2015]

52. Teach self-monitoring of blood glucose levels to adults with type 1 diabetes as part of an integrated package that includes appropriate insulin regimens and education to help choice and achievement of optimal diabetes control. [2004, amended 2015]

53. Carry out a structured assessment of self-monitoring skills, the quality and use made of the results and the equipment used. Review self-monitoring skills as part of annual review, or more frequently according to need, and reinforce them where appropriate. [2004, amended 2015]

54. Monitoring blood glucose using sites other than the fingertips cannot be recommended as a routine alternative to conventional self-monitoring of blood glucose. [2004, amended 2015]

### 8.2.8 Research recommendations

10. In adults with type 1 diabetes, what is the clinical and cost effectiveness of post-prandial blood glucose monitoring?

## 8.3 Technologies for self-monitoring of blood glucose

### 8.3.1 Introduction

In recent years blood glucose monitoring systems have been enhanced by software which can have a number of functions. In its simplest form this software allows blood glucose data to be downloaded and displayed in a variety of formats, such as daily profiles and average days, and provides simple statistical information such as mean glucose and measures of glucose variability. Apps are available to allow information to be transferred directly or indirectly onto a Smart phone platform so that graphical and statistical analysis of blood glucose data can be viewed in a mobile setting. All these developments still rely on the user to interpret and respond to the blood glucose data.

Building on the bolus advisor software integrated into some insulin pumps, blood glucose meters are now available which will suggest a bolus insulin dose to the user on the basis of their blood glucose measurement if they input their intended carbohydrate intake. This bolus advice is based on pre-programmed information about the individual's insulin sensitivity (correction factor) and mealtime bolus ratio (units of insulin per 10 g carbohydrate).

**The GDG considered this question:**

- In adults with type 1 diabetes, what are the benefits of technologies (bolus calculators and downloads) for self-monitoring of blood glucose?

### 8.3.2 Review question: In adults with type 1 diabetes, what are the benefits of technologies (bolus calculators and downloads) for self-monitoring of blood glucose?

For full details see review protocol in Appendix C.

**Table 68: PICO characteristics of review question**

| Population | Adults ≥18 years with type 1 diabetes |
|---|---|
| Intervention/s | - SMBG (finger pricks) - bolus calculators<br>- SMBG (finger pricks) - downloads |
| Comparison/s | - SMBG (finger pricks) – standard SMBG methods |
| Outcomes | - Hypoglycaemia<br>- Severe hypoglycaemia<br>- Nocturnal hypoglycaemia<br>- HbA1c<br>- Quality of life<br>- Adverse events<br>- Adherence |
| Study design | RCTs |

### 8.3.3 Clinical evidence

Two studies have been included in this review.[266,627] Evidence from these are summarised in the clinical evidence summary below (Table 69Table 69:     Summary of studies included in the review). See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

We searched for randomised trials assessing the benefits of the following technologies for self-monitoring of blood glucose:

- Bolus calculators

- Downloads

One parallel RCT [627,770] and one cross-over trial [266] were identified. Both studies looked at bolus calculators compared with standard care (that is, no technology for SMBG). We did not look for technologies versus carbohydrate counting; these have been included as part of the carbohydrate counting review. However, the 3-arm Schmidt RCT did include a carbohydrate counting arm; the results of this arm/comparison are not included here but have been reported as part of the carbohydrate counting review.

Studies included participants that were assessed in both inpatient and outpatient hospital settings.

Outcomes reported include:

- Adverse events
- HbA1c
- Hypoglycaemia
- Hypoglycaemia Fear Survey (HFS)
- Problem Areas in Diabetes (PAID)
- Quality of life (QoL)

Included studies did not report on the following outcomes:

- Adherence
- Nocturnal hypoglycaemia
- Severe hypoglycaemia

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**Table 69:   Summary of studies included in the review**

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| GROSS 2003 | Bolus calculator software implemented on a PDA platform versus standard bolus period | n=49 Type 1 diabetes Continuous Subcutaneous Insulin Infusion (CSII) | 7 days | Hypoglycaemic events/week Adverse events | Cross-over RCT (7 days each arm) |
| SCHMIDT 2012 | 3 arm trial. Used 2 relevant arms: CarbCount Automated Bolus Calculator (CarbCountABC) versus non-carb count control (no calculator) | Type 1 diabetes n= 51 (n=8, control; n=22, CarbCount Automated Bolus Calculator) | 16 weeks | HbA1c Hypoglycaemia Fear Survey (HFS) Problem Areas In Diabetes (PAID) Audit of Diabetes-Dependent Quality of Life (ADDQoL) | - |

**Table 70:   Evidence summary tables: bolus calculator versus no technology (less than 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute Difference<br>Bolus | Control event rate (per 1000 patients)<br>No technology |
|---|---|---|---|---|---|
| HbA1c (%) | 1 study (n=30) | Serious | MODERATE | MD 0.60 lower (1.40 lower to 0.20 higher | -0.1 final value in control group |
| HFS: (0-100 scale) - higher scores indicate more fear | 1 study (n=30) | Very serious | LOW | MD 1.48 lower (9.07 lower to 6.11 higher) | -1.92 final value in control group |
| PAID: (0-100 scale) - higher scores indicate more problems | 1 study (n=30) | Serious | MODERATE | MD 3.6 lower (19.54 lower to 12.34 higher) | -3.3 final value in control group |
| ADDQoL: Total (-9 to 9) - higher scores indicate positive impact | 1 study (n=30) | Serious | MODERATE | MD 0.20 lower (1.39 lower to 0.99 higher) | 0.6 final value in control group |
| Severe hypoglycaemia | 1 study (n=30) | Very serious | LOW | 34 fewer per 1000 (from 115 fewer to 746 more) | 10 |
| Hypoglycaemic event/week | 1 study (n=49) | No serious impression | MODERATE | MD 0.30 lower (1.49 lower to 0.89 higher) | 3.4 final value in control group |
| Adverse events | 1 study (n=49) | No serious imprecision | MODERATE | 0 events in each arm | |

### 8.3.4 Economic evidence

**Published literature**

No relevant economic evaluations were identified.

### 8.3.5 Evidence statements

**Clinical**

**Bolus calculator versus no technology for SMBG**

Moderate and Low quality evidence from single studies showed that there was a clinically significant benefit of SMBG with bolus calculators versus no technology at less than or equal to 6 months for HbA1c and the number of people experiencing episodes of severe hypoglycaemia.

Moderate and Low quality evidence from single studies showed that there was no clinically significant difference between SMBG with bolus calculators versus. no technology at less than or equal to 6 months for the QoL scores of HFS, PAID, and ADDQOL; and for both the number of hypoglycaemic events/week and number of adverse events.

**Economic**

No relevant economic evaluations were found.

### 8.3.6 Recommendations and link to the evidence

| Recommendations | 55.Educate adults with type 1 diabetes about how to measure their blood glucose level, interpret the results and know what action to take. [new 2015] |
|---|---|
| Relative values of different outcomes | The key issue for this question is whether the use of simple technological aids is clinically useful in allowing people with type 1 diabetes to better interpret and react to their blood glucose measurements. This should be manifest as better (lower) HbA1c levels indicating better overall control of diabetes.<br><br>As discussed previously, there is a risk that lower HbA1c levels may be achieved at the expense of an increase in episodes of hypoglycaemia, and this was also regarded as an important outcome measure. The balance between HbA1c and hypoglycaemia might also be reflected in Quality of Life data, and the GDG also included this among the important outcomes. |
| Trade-off between clinical benefits and harms | There was evidence in a single study of a benefit of bolus calculators on both HbA1c and severe hypoglycaemia in the short term (<6 months). There was no statistically significant difference in the relatively small study, but the effect size, if genuine, would be of clear clinical benefit.<br><br>There was no clinical benefit for any of the QOL outcomes that were reported in the studies.<br><br>The GDG did not regard the use of bolus calculators as having the potential to do any harm, providing people are educated in their use and interpretation of the output. |

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| Recommendations | **55. Educate adults with type 1 diabetes about how to measure their blood glucose level, interpret the results and know what action to take. [new 2015]** |
|---|---|
| Economic considerations | No economic evidence was found on this question.<br><br>Bolus calculators can be standalone devices, come with blood glucose monitoring devices, online or on smartphone apps. The cost is likely to be small – free to £15. Patients are likely to require training to use and understand bolus calculators. This may be provided as an additional part of structured education programmes but the additional cost of GP/nurse/clinic time should be considered.<br><br>There may be a cost element if people wish to switch from a simple glucometer to one which allows SMBG downloads. Again patients will require training, which may be available through structured education programmes, and there is an additional cost to the GP/nurse/clinics if they need to download the information, read and understand the data.<br><br>Smartphone apps come in all shapes and sizes (and correspondingly costs). They range from glucometer add-ons (iBGstar - £24) to bolus calculators and blood glucose diaries (no cost). Again patients will require training, which may be available through structured education programmes, and this does have a cost impact in terms of healthcare professionals' time and resource. |
| Quality of evidence | The evidence of improvement in HbA1c and severe hypoglycaemia was from a single study which had a very small sample size (n=30). [627] |
| Other considerations | The GDG noted the absence of studies examining the impact of apps and bolus calculators on diabetes outcomes. The GDG members discussed their experience: some people with type 1 diabetes find apps that record their SMBG helpful, and bolus calculators or apps that calculate meal insulin doses based on carbohydrate counting may reduce the need for mental arithmetic skills, although GDG members also discussed concerns that automated downloads if SMBG data may dis-empower users from self-reflection. There is anecdotal evidence that use of bolus calculators that incorporate an estimate of insulin action from recent insulin administration may be helpful in reducing over-bolusing. |

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### 8.3.7  Research recommendations

**11. In adults with type 1 diabetes who have chronically poor control of blood glucose levels, what is the clinical and cost effectiveness of continuous glucose monitoring technologies?**

## 8.4  Continuous glucose monitoring (CGM) compared with self-monitoring of blood glucose

### 8.4.1  Introduction

Self-monitoring of blood glucose (SMBG) is the cornerstone of diabetes self-management. There is evidence that increased frequency of blood glucose monitoring improves overall blood glucose control, as assessed by glycosylated haemoglobin (HbA1c) (see Section 10). However, the utility of

blood glucose monitoring is limited by the fact that the measurement represents a single point in time, and cannot inform the user as to the trend in blood glucose levels. Continuous glucose monitoring addresses these limitations, but is significantly more expensive and has its own limitations.

Several different technologies have been developed to provide CGM, and a number of these have been commercialised, with varying success. Currently all the available CGM technologies are based on wire-based enzyme-tipped electrode technology. The wire is inserted subcutaneously, usually into the abdomen. Interstitial fluid glucose is involved in an enzyme catalysed reaction which generates an electrical signal transmitted wirelessly from the sensor to a remote, portable monitor. This signal is transformed into an interstitial fluid glucose measurement. Then, using information obtained from calibrating the interstitial fluid glucose values against conventionally measured capillary glucose values (obtained by SMBG), the interstitial fluid glucose value is converted into an estimate of blood glucose, which is displayed on the monitor. This usually consists of a numerical display of the last glucose reading along with a graphical display of the glucose trend.

The glucose reading displayed is not as accurate as a capillary glucose measurement obtained by SMBG, as it is a close approximation generated by the CGM system, but the main limitation of the technology is the lag time between the interstitial fluid glucose measurement and blood glucose. There are two components to this: a physiological lag due to the time it takes for blood and interstitial glucose to equilibrate, which is most marked at times of rapid blood glucose change; and an analytical lag due to the time it takes the system to process the interstitial fluid data and transform this into the generated blood glucose value.

CGM systems can be classed as either real-time or retrospective. A real-time system displays the glucose data, usually both numerically and graphically, such that the user can respond to changes in glucose readings in real-time, but can also download the glucose data to analyse and make retrospective changes to insulin delivery. A retrospective system does not display any data, but stores it so that it can only be used for later download and analysis. The sensors have a recommended life of 5, 6 or 7 days depending on the brand. CGM can be used continuously or intermittently.

- In adults with type 1 diabetes, is retrospective continuous glucose monitoring more effective than care without continuous glucose monitoring (with SMBG) for improving diabetic control?

- In adults with type 1 diabetes, is real-time continuous glucose monitoring more effective than SMBG continuous glucose monitoring for optimum diabetic control?

- In adults with type 1 diabetes, is continuous real-time monitoring more effective than intermittent real-time monitoring for optimum diabetic control?

### 8.4.2 Review question: In adults with type 1 diabetes, is retrospective continuous glucose monitoring more effective than care without continuous glucose monitoring (with SMBG) for improving diabetic control?

For full details see review protocol in Appendix C.

**Table 71: PICO characteristics of review question**

| Population | • ≥50% Adults with type 1 diabetes.  <br>• ≥70% type 1 diabetes |
|---|---|
| Intervention/s | Retrospective CGM |
| Comparison/s | Care without CGM (with SMBG) – comparison group must be on similar insulin regimen as the treatment group |
| Outcomes | • HbA1c (continuous)  <br>• Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or |

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| | |
|---|---|
| | continuous outcome, depending how it is reported) |
| | • Quality of life – (continuous) or patient satisfaction |
| | • Adverse events – (dichotomous) |
| | • Adherence (dichotomous) |
| **Study design** | RCT |

### 8.4.3 Review question: In adults with type 1 diabetes, is real-time continuous glucose monitoring more effective than SMBG continuous glucose monitoring for optimum diabetic control?

For full details see review protocol in Appendix C.

**Table 72:  PICO characteristics of review question**

| | |
|---|---|
| **Population** | • ≥50% Adults with type 1 diabetes<br>• ≥70% type 1 diabetes |
| **Intervention/s** | Real-time CGM |
| **Comparison/s** | Care without CGM (with SMBG) |
| **Outcomes** | • HbA1c (continuous)<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported)<br>• Quality of life – (continuous) or patient satisfaction<br>• Adverse events – (dichotomous)<br>• Adherence (dichotomous) |
| **Study design** | RCT |

### 8.4.4 Review question: In adults with type 1 diabetes, is continuous real-time monitoring more effective than intermittent real-time monitoring for optimum diabetic control?

For full details see review protocol in Appendix C.

**Table 73:  PICO characteristics of review question**

| | |
|---|---|
| **Population** | • ≥50% Adults with type 1 diabetes.<br>• ≥70% type 1 diabetes |
| **Intervention/s** | Intermittent real-time CGM |
| **Comparison/s** | Continuous real-time CGM – comparison group must be on similar insulin regimen as the treatment group |
| **Outcomes** | • HbA1c (continuous)<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported)<br>• Quality of life – (continuous) or patient satisfaction<br>• Adverse events – (dichotomous)<br>• Adherence (dichotomous) |
| **Study design** | RCT |

### 8.4.5 Clinical evidence

Fourteen studies have been included in this review.[58 60 114 164 241 310 516 530 573 574 679 439,641,681] Evidence from these are summarised in the clinical evidence summaries below (Table 74 and Table 75). See

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also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix I and exclusion list in Appendix K.

This review has updated the relevant parts of a recent Cochrane review [410] on CGM.

We searched for randomised trials assessing effectiveness of the following for improving diabetic control:

- Retrospective CGM care compared with care without CGM (with SMBG) (Table 76).
- Real-time CGM care compared with care without CGM (with SMBG) (Table 77).
- Continuous real-time CGM compared with intermittent real-time CGM for improving diabetic control.

Eleven parallel randomised trials [60 114 164 241 310 516 530 573 679 439,681] and three cross-over trials [58 574,641] were identified.

- Retrospective CGM versus SMBG (three studies were found –Table 74). [114 516 681]
- Real-time CGM versus SMBG (eleven studies were found –Table 75). [58 60 164 241 310 516 530 573 574 439,641,679]

- Continuous real-time CGM versus intermittent real-time CGM – no studies were found that met the inclusion criteria for this review.

Four trials included both children and adults [58 60 310 679] and three [241 114 516] included both Type 1 and Type 2 diabetes. Data for these populations and types of diabetes were reported separately in all but two of these trials [58, 241]. For the trials that reported these groups separately, only the data for adults with type 1 diabetes has been included for this review.

Studies included participants that were assessed in both inpatient and outpatient hospital settings.

Outcomes reported include:
- Adverse events
- HbA1c
- Hypoglycaemia
- Quality of life (QoL)
- Severe hypoglycaemia

Included studies did not report on the following outcomes:
- Adherence
- Patient satisfaction

For the purpose of this review, the follow-up periods for the outcomes reported have been grouped into less than or equal to 6 months and more than 6 months.

There was significant heterogeneity between the RT-CGM studies for the outcome of HbA1c. Pre-specified subgroup analyses were:

3. different types of CGM device (MiniMed only, other devices, and Guardian RT-device)
4. different populations (adults versus mixed adults and younger people).

Neither of the subgroup analyses explained the heterogeneity.

**Update 2015**

**Table 74:   Summary of studies included in the review – retrospective CGM versus SMBG**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| CHICO 2003[114a] | CGM (Disetronic, MiniMed) versus SMBG (frequent capillary glucose measurement) | n=105 diabetic participants (75 (71%) with type 1 diabetes, 30 (29%) with type 2 diabetes) were included. For the type 1 diabetes population: n=40, CGM; n=35, SMBG. | 3 months | HbA1c | CGM group monitored three days using the CGM and were instructed to enter glucose meter values (at least four a day). SMBG: At least 8 measurements per day for 3 days: before each meal, 2h after meals, at bedtime, and at 4:00 am |
| NEWMAN 2009[516a] | CGM (MiniMed) + nurse feedback at 6, 12 and 18 months versus SMBG | n=106 adults with type 1 diabetes n=53, CGM; n=52, SMBG | 18 months | HbA1c | CGM: Participants were requested to wear it for 72 hours. SMBG: At patient's normal frequency |
| TANENBERG 2004[681b] | CGM (Medtronic MiniMed) versus SMBG | n=128 adult participants with insulin treated diabetes (97 (76%) having type 1 diabetes). n=62, CGM ; n=66, SMBG | 3 months | HbA1c Severe hypoglycaemia | CGM: 2 periods of 3 days (week 1 and week 3). SMBG: At least 4 times each day and in response to symptoms of hypoglycaemia for the duration of the study. |

(a) *Population consisted of both type 1 diabetes and type 2 diabetes adults. However, data for each of these populations was reported separately, and so only the data for the type 1 diabetes subgroup has been included in this review.*

(b) *The population consisted of both type 1 diabetes and type 2 diabetes adults. No type 1 diabetes subgroup analysis was reported and so the data for this study are based on mixed population of type 1 diabetes and type 2 diabetes. However, most of the population was type 1 diabetes (>70%).*

**Update 2015**

**Table 75: Summary of studies included in the review – real-time CGM versus SMBG**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| BATTELINO 2012[58] Cross-over RCT | CGM (Minimed Medtronic) unmasked results versus CGM masked results and SMBG | n=153; 53% adults and 47% children. n=77 CGM sensor on first; n=76 SMBG sensor off first | 6 months | HbA1c Severe hypoglycaemia | Both intervention and control groups fitted with MiniMed Medtronic insulin pump systems with CGM facility. Each treatment period was 6 months long, with a 4 month washout phase between two periods. |
| BECK 2010 (JDRF QoL)[60b] (JDRF Study) | CGM versus SMBG | Type 1 diabetes adult population. n=122, CGM; n=106; SMBG. | 26 weeks | Quality of Life (QoL). Hypoglycaemia fear survey (HFS) Problem areas in diabetes (PAID) | CGM: Participants were instructed to use the CGM daily if possible. SMBG: Perform BGM ≥4 times per day. |
| DEISS 2006[164] | CGM (Guardian RT) versus SMBG | n=162 adults and children (adults = 50%) with type 1 diabetes | 3 months | HbA1c | CGM: Guardian RT continuously (arm 1) or biweekly for 3 day periods every 2 weeks (arm 2). |
| HIRSCH 2008[310b] | CGM (Medtronic) versus SMBG + insulin pump | n=146 participants between 12 and 72 years with type 1 diabetes. Type 1 diabetes population. Adult (18-80 years) = 98 (67%) n=49, CGM; n=49, SMBG | 26 weeks | HbA1c | CGM: Continuous Subcutaneous Insulin Infusion (CSII) therapy, augmented with real-time CGM. Unclear frequency SMBG: Insulin pump plus standard glucose monitoring. Unclear frequency |
| GARG 2006[241c] | CGM (DexCom STS) | n=91 adults (type 1 diabetes = | 10 days | Severe hypoglycaemia | Both intervention and |

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| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | unmasked results + check accuracy with home glucose meter versus CGM masked results and SMBG | 75 [82%]; type 2 diabetes = 16 p18%]). n=47 CGM n=44 SMBG | | | control groups fitted with Dexcom STS systems for three 72 hour periods and asked for regular SMBG readings (~8/day). All blinded to results in first study period. Intervention groups unblinded for study period 2 and 3. |
| LITTLE 2014[439] | CGM (medtronic device) versus SMBG | n=96 adults type 1 diabetes n=48 each group | 24 weeks | HbA1c Severe hypoglycaemia Adverse events | |
| O'CONNELL 2009[530] | CGM (Paradigm Metronic Minimed) versus SMBG | n=62 adults and children with type 1 diabetes. n=31, CGM; n=31, SMBG. | 3 months | HbA1c | |
| RACCAH 2009 [573] | CGM (Paradigm Metronic Minimed) versus SMBG + insulin pump | n=132 adults and children with type 1 diabetes. Adults = 61%. n=55, CGM; n=60, SMBG. | 6 months | HbA1c Hypoglycaemia | All patients continued to perform finger prick measurements for glucose self-monitoring as they did before the study. |
| RADERMECKER 2010[574] Cross-over RCT | CGM (Guardian Medtronic) + SMBG versus SMBG | n=13 adults with type 1 diabetes n=7 started with CGM plus SMBG ; n=6 started with SMBG only. | 24 weeks | HbA1c Diabetic Quality of Life (DQOL total score) Hypoglycaemic episodes. | CGM: Permanent use of a CGM device which displays estimated blood glucose levels at 5-minute intervals plus SMBG. SMBG: Usual frequency used by patients. |
| SEQUEIRA 2013[641] cross-over RCT | CGM versus SMBG | n=39 adults type 1 diabetes | Up to 28 weeks | HbA1c | Unclear if RT or retrospective CGM. Appears |

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | | | | | to be RT, |
| TAMBORLANE 2008[679]** | CGM + check accuracy with home glucose meter versus SMBG | n=322 adults and children (stratified into three groups according to age: ≥25 years, 15 to 24 years, and 8 to 14 years) with type 1 diabetes. Adult population = 65%. ≥25 years: n=52, CGM ; n=46, SMBG 15 to 24 years: n=57, CGM; n=53, SMBG | 26 weeks | HbA1c Severe hypoglycaemia. | CGM: Patients were instructed to use the device on a daily basis. CGM devices: Dexcom Seven, Paradigm Real-Time Insulin Pump CGMS (Medtronic) FreeStyle Navigator (Abbot Diabetes Care) SMBG: At least 4 times a day |

(a)  The population consisted of both type 1 diabetes and type 2 diabetes adults. However, data for each of these populations was reported separately, and so only the data for the type 1 diabetes subgroup has been included in this review.

(b)  The population consisted of both adults and children. However, data for each of these populations was reported separately, and so only the data for the adult population has been included in this review.

(c)  The population consisted of both type 1 diabetes and type 2 diabetes adults. No type 1 diabetes subgroup analysis was reported and so the data for this study are based on mixed population of type 1 diabetes and type 2 diabetes. However, most of the population was type 1 diabetes (≥70%).

**Continuous real time CGM versus intermittent real time CGM**

No studies were included in this review.

**Table 76:   Clinical evidence summary table: Retrospective CGM versus SMBG (less than or equal to 6 months follow-up)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000 patients) |
|---|---|---|---|---|---|
| HbA1c (%) | 2 studies (n=180) | No serious imprecision | MODERATE | MD 0.09 lower (0.44 lower to 0.26 higher) | -0.62 |
| % change in HbA1c | 1 study (n=105) | No serious imprecision | HIGH | MD 1.9 lower (5.58 lower to 1.78 higher) | -3.1 |
| Severe hypoglycaemia | 1 study (n=109) | Very serious | LOW | 2 more per 1000 (from 16 fewer to 288 more) | 17 |

**Table 77:   Clinical evidence summary table: Real-time CGM care versus care without CGM (with SMBG) (less than or equal to 6 months follow-up and more than 6 months follow-up)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000 patients) |
|---|---|---|---|---|---|
| HbA1c (%) (≤6 months) | 9 studies (n=739) | Serious | VERY LOW | MD 0.30 lower (0.46 to 0.14 lower) | -0.25 |
| HbA1c % (SD data not given) | 1 study (n=39) | Serious imprecision | SERIOUS IMPRECISION | Both groups final HbA1c was 8.3% | |
| Hypoglycaemia (episodes/day) (≤6 months) | 2 studies (n=118) | Serious imprecision | VERY LOW | MD 0.15 higher (0.10 lower to 0.40 higher) | 0.075 |
| Severe hypoglycaemia (per 100 patient years) | 1 study (n=153) | Very serious imprecision | LOW | MD 2.87 higher (3.79 lower to 9.53 higher) | 2.87 |
| Severe hypoglycaemia – no. of patients (≤6 months) | 3 studies (n=251) | Very serious imprecision | VERY LOW | 12 fewer per 1000 (from 37 fewer to 63 more) | 50 |
| Severe hypoglycaemia (annualised rate:patient-year) | 1 study (n=96) | Very serious imprecision | VERY LOW | MD 0.10 lower (0.88 lower to 0.68 higher) | 8.1 |
| Quality of Life (scale 0-100): | 1 study (n=226) | No serious | MODERATE | MD 1.4 higher (0.18 | 54.1 |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000 patients) |
|---|---|---|---|---|---|
| physical health | | imprecision | | lower to 2.98 higher) | |
| Quality of Life (scale 0-100): mental health | 1 study (n=226) | No serious imprecision | MODERATE | MD 0.30 lower (2.87 lower to 2.27 higher) | 48.7 |
| Quality of Life (scale 0-100): hypoglycaemia fear survey | 1 study (n=226) | No serious imprecision | MODERATE | MD 2.27 lower (6.01 lower to 0.61 higher) | 36 |
| Quality of Life (scale 0-100): problem areas in diabetes | 1 study (n=226) | No serious imprecision | MODERATE | MD 0.10 lower (3.85 lower to 3.65 higher) | 18.2 |
| Quality of life total score (scale 0-100) | 1 study (n=9) | Serious imprecision | LOW | MD 3 lower (7.38 lower to 1.38 higher) | 0.7 |
| Adverse events | 2 studies (n=211) | Very serious imprecision | VERY LOW | 59 fewer per 1000 (from 82 fewer to 14 more) | 93 |

### 8.4.6 Economic evidence

**Published literature**

No studies were identified in CG15 for this review questions.

Two studies were included in the guideline update that compared real-time CGM with SMBG.[335,478] These are summarised in the economic evidence profile below (Table 78). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

In addition, one original economic analysis was conducted in the guideline update. For more details please see Section 8.2.5 and Appendix P.

No relevant economic evaluations comparing either retrospective CGM and SMBG or intermittent real-time and continuous real-time CGM were identified.

One study that met the inclusion criteria was selectively excluded due to more applicable evidence being available[516]. This is summarised in Appendix L, with reasons for exclusion given.

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**Update 2015**

**Table 78:   Economic evidence profile: Real-time continuous glucose monitoring versus self-monitoring of blood glucose**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects (QALYs) | Cost effectiveness (£ per QALY gained) | Uncertainty |
|---|---|---|---|---|---|---|---|
| McQueen 2011[478] [US] | Partially applicable[a] | Potentially serious limitations[b] | Probabilistic decision analytic model with a 33 year time horizon performed from a societal perspective, with effectiveness data from a single randomised trial. | £15,193 | 0.523 | **£29,029** | At a £30K threshold, CGM has a 48% probability of being cost effective. The societal ICER was most sensitive to changes in the utility of diabetes with no complications, the annual cost of CHD and, the probability of transition from diabetes with no complications to the CHD state. |
| Huang 2010[333] [US] | Partially applicable[c] | Potentially serious limitations[d] | Simulation model with a lifetime time horizon performed from a societal perspective, with effectiveness data from a single randomised trial. | £38,297 | 0.60 | **£63,828** | Limited sensitivity analysis was undertaken from a societal perspective. There was a considerable amount of uncertainty around the ICER with the confidence interval spanning from CGM being dominant to being dominated. However, if only two test strips were used per day for calibration, then CGM would be cost saving. |
| NCGC model (see Appendix P) | Directly applicable | Potentially serious limitations[e] | CGM compared with the most cost-effective frequency of SMBG (SMBG 8 times daily) | £47,763[f] | -0.287[f] | **CGM is dominated[f]** | CGM was never cost effective at the £20,000 per QALY threshold even when:<br>• the decrease in HbA1c with CGM was assumed to be estimated versus SMBG 10 times |

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| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects (QALYs) | Cost effectiveness (£ per QALY gained) | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | | | | | • the cost of CGM was decreased by 30%<br>• the two conditions above were kept and hypoglycaemic events were assumed to be 0 with CMG and 660 per 100-patient years with SMBG 10 times<br>• annual HbA1c progression was 0<br>• discounting factor was 1.5% for both costs and outcomes |

(a) *Study performed from a US societal perspective.*

(b) *Study does not model the effects of hypoglycaemia, reductions in hypoglycaemic events or reductions in the fear of hypoglycaemia; includes all SMBG costs in CGM arm; assumes there is a constant probability of diabetes complication over time; a single trial provides the effectiveness data; discount rates used are not in line with the NICE reference case; non-UK utility weights are used.*

(c) *Study was performed from a US societal perspective. However, the NCGC calculated the ICER from a healthcare payer perspective which is presented here.*

(d) *Study does not model the effects of hypoglycaemia, reductions in hypoglycaemic events or reductions in the fear of hypoglycaemia; a single trial provides the effectiveness data; discount rates and utilities used are not in line with the NICE reference case; limited sensitivity analysis*

(e) *Uncertainty in key parameters (quality of life associated with hypo events) and missing links between model outcomes (achieved HbA1c level and hypo events).The population in this analysis may not be representative of people with type 1 diabetes who have problems at controlling their HbA1c level with SMBG and self-injection only. The cost effectiveness of CGM in combination with insulin pumps was not assessed and it may be that this combination is cost effective in people with glycaemic control issues.*

(f) *Results are reported in this table for the comparison of CGM versus the most cost effective frequency of SMBG in the probabilistic analysis (8 times per day), assuming the decrease in HbA1c had been estimated versus SMBG 4 times.*

**Unit costs**

**Table 79:   SMBG cost**

| Tests per day | Cost Per day | Cost per week | Cost per year |
|---|---|---|---|
| 1 | £0.29 | £2.03 | £106 |
| 2 | £0.58 | £4.06 | £212 |
| 3 | £0.87 | £6.09 | £318 |
| 4 | £1.16 | £8.12 | £423 |
| 5 | £1.45 | £10.15 | £529 |
| 6 | £1.74 | £12.18 | £635 |
| 7 | £2.03 | £14.21 | £741 |
| 8 | £2.32 | £16.24 | £847 |
| 9 | £2.61 | £18.27 | £953 |
| 10 | £2.90 | £20.30 | £1,059 |

*Assumes no cost of glucose monitor*
*Assumes single use lancets and single use blood glucose strips at 3.84p and 26.01p each respectively*

**Table 80:   Cost of CGM strategy**

| Intervention | Item | Unit cost | Units per year | Annual cost |
|---|---|---|---|---|
| Dexcom G4 | Receiver | £1750 | 1/5 | £374[a] |
|  | Sensors | £250/4 | 52 | £3,250 |
|  | Transmitters | £275 | 2 | £550 |
|  | Calibration | £0.29 | 2*365[b] | £212 |
|  | **Total** |  |  | **£4,392** |
| Abbott Freestyle | Receiver | £950 | 1/5 | £203[a] |
|  | Sensors | £288/6 | 60 | £2,880 |
|  | Transmitters | Na [c] | 0 | 0 |
|  | Calibration | £0.29 | 1*365 [d] | £106 |
|  | **Total** |  |  | **£3,189** |
| Medtronic RT Guardian | Receiver | £1,059[e] | 1/5 | £227[a] |
|  | Sensors | £420/10 | 60 | £2,520 |
|  | Transmitters | £490[f] | 1[f] | £490 |
|  | Calibration | £0.29 | 2*365[b] | £212 |
|  | **Total** |  |  | **£2,965** |
|  |  | **Total average cost (first year)** |  | **£3,511** |
|  |  | **Total average cost (second year and after)** |  | **£3,674** |

(a) *Annual cost estimated assuming a five year life span and a discount (dis) of 3.5% using the formula: purchase cost/(1-1/(1+dis)^(life span -1))/dis)*
(b) *Assuming SMBG for calibration is performed twice a day*
(c) *Rechargeable*
(d) *On average calibration is performed once per day*
(e) *Total initial cost of £1,599 included also the cost of sensors, which has been subtracted by the initial cost.*
(f) *Except for the first year*

**New economic analysis**

New economic analysis was prioritised for this question. A summary is reported in section 8.2.5. The full analysis can be found in Appendix P.

### 8.4.7 Evidence statements

**Clinical**

**Retrospective CGM care versus care without CGM (SMBG)**

High, Moderate, and Low quality evidence, mainly from single studies, showed no clinical difference at less than or equal to 6 months between retrospective CGM and SMBG for HbA1c, and number of people experiencing episodes of severe hypoglycaemia.

**Real-time CGM care versus care without CGM (SMBG)**

Moderate, Low and Very low quality evidence at less than or equal to 6 months, mainly from single studies (except for HbA1c and hypoglycaemia) showed: no clinical difference between retrospective CGM and SMBG for hypoglycaemia (episodes/day), severe hypoglycaemia (per 100 patient years), severe hypoglycaemia (annualised rate), adverse events, nor for the QoL measures of physical health, mental health, HFS, PAID and total score. However there was a clinically important benefit of CGM for reduction in HbA1c, and the number of people experiencing episodes of severe hypoglycaemia.

**Economics**

- Two cost–utility analyses found that CGM was not cost effective compared with SMBG in people with type 1 diabetes (ICERs: £29,029 per QALY gained and £63,828 per QALY gained respectively). These analyses were assessed as partially applicable with potentially serious limitations.
- One original cost-utility analysis found that in people with type 1 diabetes SMBG (8 times a day) was dominant (less costly and more effective) compared with CGM. This analysis was assessed as directly applicable with potentially serious limitations.

### 8.4.8 Recommendations and link to the evidence

| Recommendations | |
|---|---|
| | 56. Do not offer real-time continuous glucose monitoring routinely to adults with type 1 diabetes. [new 2015]<br><br>57. Consider real-time continuous glucose monitoring for adults with type 1 diabetes who are willing to commit to using it at least 70% of the time and to calibrate it as needed, and who have any of the following that persist despite optimised use of insulin therapy and conventional blood glucose monitoring:<br>  • more than 1 episode a year of severe hypoglycaemia with no obviously preventable precipitating cause<br>  • complete loss of awareness of hypoglycaemia<br>  • frequent (more than 2 episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities<br>  • extreme fear of hypoglycaemia. [new 2015]<br><br>58. For people who are having continuous glucose monitoring, use the principles of flexible insulin therapy with either a multiple daily injection insulin regimen or continuous subcutaneous insulin infusion (CSII or insulin pump) therapy. [new 2015]<br><br>59. Continuous glucose monitoring should be provided by a centre with expertise in its use, as part of strategies to optimise a person's HbA1c levels and reduce the frequency of hypoglycaemic episodes. [new 2015] |

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| Relative values of different outcomes | Three linked questions were posed in order to evaluate the potential benefits of continuous glucose monitoring. The first two compared "standard" SMBG with CGM using either retrospective or real-time CGM values. The third question concerned continuous versus intermittent real-time CGM. |
|---|---|
| | For each of these questions the main outcomes of interest were glucose control as assessed by HbA1c levels, which must be balanced against episodes of hypoglycaemia. The GDG were also interested in any Quality of Life data. |
| Trade off between clinical benefits and harms | Three studies[114 516,681] compared retrospective CGM with SMBG, although two of these[114 516] did not report hypoglycaemia. There was very little difference between study arms in either HbA1c or in episodes of hypoglycaemia (in the single study[681] which reported this latter outcome there was only one episode of defined severe hypoglycaemia in each group). Neither study reported quality of life. |
| | There were eleven studies[58 60 164 241 310 516 530 573 574 439,641,679] of real-time CGM compared with SMBG, and these showed a decrease in HbA1c levels of 0.30% which the GDG regarded as just clinically significant. Again the majority of studies did not report hypoglycaemia, although the limited data available did not show any increase in this parameter to offset the reduction in HbA1c. Quality of life was considered in 2 studies,[60,574] although the measurement tool was not the same across studies so that data could not be synthesised. Differences in quality of life were generally small but the physical health and the hypoglycaemia fear survey components tended to favour CGM while the quality of life total score tended to favour SMBG. However the differences were not considered to be clinically important. |
| | No studies were found comparing continuous with intermittent CGM but it was noted that benefit in all studies was achieved only with high levels of CGM use. |
| Economic considerations | Two cost-utility analyses from the USA were considered by the GDG.[333,478] A Technology Appraisal from the UK was also found but excluded from consideration, primarily because of a short (18 month) time horizon and because it combined data from type 1 and type 2 diabetes. The two included studies concluded that CGM is more effective than SMBG, but this is not cost effective due to its high cost when the £20,000 per QALY threshold is applied. Neither study included hypoglycaemia among the outcome measures despite reduction in hypoglycaemia being one of the theoretical benefits of CGM. The studies also used data on macro-vascular complications from a population comprising mainly people with type 2 diabetes. The cost-effectiveness estimates in both studies were well above £20,000 |
| | An original economic analysis compared SMBG with different frequencies to CGM; this analysis showed that CGM is more effective (increases QALYs) compared with SMBG up to 4 times but it is not more effective than SMBG 8 or 10 times a day; CGM is also more costly than any selected frequencies of SMBG (up to 10 times daily). SMBG 8 times daily was the most cost-effective strategy in the probabilistic analysis while SMBG 10 times daily was the most cost effective strategy in the deterministic analysis; in both analyses CGM was more costly and less effective than these strategies. In the base case analysis, the decrease in HbA1c level obtained with CGM in the meta-analysis of studies comparing CGM with SMBG was assumed to have been estimated compared with SMBG 4 times daily. In order to test whether CGM could be cost effective in some circumstances, a series of sensitivity analyses were conducted where the effectiveness of CGM at reducing HbA1c level was assumed to be estimated compared with SMBG 10. In these analyses CGM was not dominated anymore but |

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its high cost was not offset by its increase in effectiveness. A subgroup analysis on people with hypo unawareness who have a risk of hypoglycaemic events 6 times higher than in the other type 1 diabetes population was conducted; in this analysis, the baseline risk of hypo events was increased and the effectiveness of CGM at reducing hypo events was 100% (no events occurred in the CGM arm of the model) and the cost of CGM was decreased by 30%. The results showed that the ICER of CGM versus SMBG 10 times daily was £30,203 per QALY, which is still above the NICE threshold. This analysis had some important limitations in terms of uncertainty in key parameters (quality of life associated with hypo events) and missing links between model outcomes (achieved HbA1c level and hypo events).

Also the clinical effectiveness data on different frequencies of SMBG was obtained from a cross-sectional study; a higher frequency of testing could lead to a decrease in hypoglycaemic events but these data could not be obtained from the available study. The population in this analysis may not be representative of people with type 1 diabetes who have problems at controlling their HbA1c level with SMBG and self-injection only. The cost effectiveness of CGM in combination with insulin pumps was not assessed and it may be that this combination is cost effective in people with glycaemic control issues, , also because the prices of CGM equipment is lower when used in conjuction with insulin pumps.

Intermittent real-time CGM will inherently be less costly than continuous real-time CGM as it is used for short periods. However, it is unclear what the quality-of-life impact of this intervention will be as patients switch between this and SMBG.

Retrospective CGM will again be less costly and its use as a diagnostic tool may be cost-effective if it enables patients with diabetes with poor control to understand how to better manage their condition, leading to a superior control, reducing complications and increasing quality-of-life.

| | |
|---|---|
| Quality of evidence | The GDG were disappointed that there were few data on retrospective CGM, particularly on hypoglycaemia. Moreover, two studies were of only 3 months duration, which is only just enough time to produce a change in HbA1c, and not long enough to see if this benefit is sustained. The GDG also noted that in the study by Chico et al., the frequency of glucose measurement in the SMBG arm was 8 times daily which could be difficult to adhere to in everyday practice. Several problems were noted with the studies of real-time CMG: <br> • Most of the studies were of less than 6 months duration, and in some it was not clear over what period monitoring was actually performed. <br> • The people recruited had low baseline rates of hypoglycaemia. This reduces the ability to detect a difference in hypoglycaemic episodes, one of the main potential benefits of a superior monitoring method. <br> • The frequency of blood glucose measurement in the SMBG arm varied between studies, and in some was higher than would be manageable for many patients <br> • Although the HbA1c improvement with CMG was clinically and statistically significant, there was unexplained heterogeneity. <br> The published economic evidence was assessed as partially applicable with potentially serious limitations. <br> The original economic analysis conducted for this guideline was assessed as directly applicable with potentially serious limitations. |
| Other considerations | Although the studies of retrospective CGM showed no bio-medical benefit, the GDG discussed the possible educational benefits. Retrospective CGM potentially allows pattern recognition of episodes of poor control. However, not all GDG members were convinced of this, since it relies on accurate recollection of activities on the part of the diabetic person. The GDG concluded that this aspect required further research, but was not robust enough to influence their recommendations at the present time. |

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It was clear to the GDG that current data do not support the routine use of CGM. There is some evidence of clinical benefit but this is not compelling, and it is not currently a cost-effective intervention. However, there are some clinical situations in which routine management fails to control episodes of hypoglycaemia despite efforts to optimise both monitoring and treatment. The GDG did not want their recommendations to remove the possibility of using CGM in such cases, and therefore agreed by consensus a recommendation which set out the situations in which a trial of CGM might be warranted.

The 2004 GDG recommended that fructosamine should not be used as a routine substitute for HbA1c estimation. This recommendation has been stood down because changes in clinical practice have rendered it redundant. Now HbA1c is used universally, whereas both methods were used at the time of the 2004 guideline.

**Update 2015**

# 9 Insulin therapy

The 2015 GDG updated the evidence and recommendations from the original guideline (CG15) for insulin regimens. New insulin formulations that have become available since 2004 (including insulin degludec, insulin degludec-aspart combinations and insulin detemir) have been considered as part of the evidence review.

Insulin therapy content from CG15 that has been superseded by the update can be found in Appendix S.

## 9.1 Introduction

Type 1 diabetes mellitus is treated by the administration of exogenous insulin. Currently, insulin can only be given effectively by injection and it needs to reach its effector sites via the circulation. Insulin can be administered intravenously, when its onset of action is fast, and its duration of action short, but for routine use, insulin is administered by the person with diabetes via the subcutaneous route.

The healthy pancreas secretes insulin directly into the liver via the hepatic portal vein in response to a variety of signals, keeping plasma glucose concentrations in a narrow range. A low dose of insulin is required at all times to control endogenous glucose production, primarily by the liver. When food is consumed, and absorbed into the circulation a much higher amount of insulin is required for a relatively short time, both to suppress endogenous glucose production and to dispose of glucose entering the circulation from the meal, storing excess glucose in muscle, fat and liver against future need. It is the aim of therapeutic insulin regimens to replicate, as far as possible, this physiological circulating insulin profile of continuous provision of basal insulin, with rapid-acting insulin provided at times of need.

Insulins for subcutaneous injection are manufactured to have different rates of absorption into the circulation. Absorption of active insulin needs to be fast and complete (rapid-acting) for use before eating and for treating high plasma glucose concentrations; the absorption is retarded and prolonged in intermediate and long-acting insulins intended to provide basal insulin replacement.

Insulin preparations have evolved since crystalline insulin was introduced in the early 1920s. Originally extracted and increasingly purified directly from animal pancreas, modern insulins are more commonly synthesized using genetic engineering. The insulin gene, either replicating the human insulin gene, or with the gene modified to confer some perceived benefit in terms of timing and site of insulin action, is used to generate large quantities of insulin by microorganisms. Current targets of insulin manufacture include the making of a faster onset, shorter acting insulin for meal use; and a longer, smoother acting insulin for basal replacement. It is hoped that combinations of such insulins will improve plasma glucose control with reduced risk of hypoglycaemia. It is also desirable that the action profile of each insulin will be reproducible, so that the insulin has a predictable effect day after day.

**The updated review questions in this chapter are:**

**For insulin regimens:**

- In adults with type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus NPH) for optimal diabetic control?

- In adults with type 1 diabetes, is once-daily basal insulin more effective than twice-daily basal insulin for optimal diabetic control?

- In adults with type 1 diabetes, which are the most effective rapid-acting insulins for meal times: analogues versus human (intermediate NPH), for optimal diabetic control?

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- In adults with type 1 diabetes, what are the most effective mixed insulins (degludec-aspart versus glargine versus NPH) for optimal diabetic control?
- In adults with type 1 diabetes, are metformin (with or without insulin), or GLP1-agonists (with or without insulin) as effective as insulin alone for optimal diabetic control?

**For insulin delivery:**

- In adults with type 1 diabetes, what is the optimum needle length for insulin delivery?
- In adults with type 1 diabetes, what is the optimum injection site and rotation for insulin delivery?

## 9.2 Insulin regimens

### 9.2.1 Long-acting insulin

An insulin that has a long and flat duration of action is expected to be optimal for basal replacement, with minimal numbers of injections required to provide basal cover that reliably lasts at least 24 hours. Basal insulin replacement needs to provide glucose control between meals and overnight, with minimal risk of hypoglycaemia between meals and at night. Reducing the number of injections needed to provide basal cover is desirable, but issues around flexibility, to address situations such as the delayed risk of hypoglycaemia after increased physical exertion or increased alcohol consumption, and the normal diurnal variation in basal insulin requirement, need to be accommodated. Current insulins for basal replacement in common use in the UK include the human intermediate acting insulins, such as the isophane or Neutral Protamine Hagedorn (NPH) insulins (human, porcine or bovine); the insulin analogues detemir and glargine, which have flatter 'peakless' insulin action profiles[428,565]and more recently the very long-acting insulin degludec[288]Each new basal insulin analogue has data to suggest less day to day variability than earlier insulins and more prolonged duration of action,[289,589] with the newest and most expensive basal insulin replacement at the time of scoping the work of the GDG (insulin degludec) showing particularly low variation and long duration of action.[288] Increased cost of the newer insulins, especially degludec, need to be balanced against better glycaemic control with less risk of hypoglycaemia.

There is evidence that, at least in some people, neither NPH nor detemir nor glargine provide 24 hour glucose control with a once-daily injection,[48,418] and because of stress laid on flexibility of basal dosing in structured education programmes such as DAFNE.[31,9]

### 9.2.1.1 Review question: In adults with type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus NPH) for optimal diabetic control?

For full details see review protocol in Appendix C.

**Table 81: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
|---|---|
| Intervention/s | Long-acting insulins:<br>• detemir<br>• degludec<br>• glargine<br>• NPH/other intermediate<br>Note: only UK licensed interventions and doses will be considered |
| Comparison/s | Each other (all of the above)<br>Note: only UK licensed interventions and doses will be considered |
| Outcomes | Outcomes |

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| | |
|---|---|
| | • HbA1c (continuous)<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported)<br>• Quality of life – measured by DQoL or any measure used in the studies retrieved (continuous)<br>• Adverse events – Cancer (dichotomous)<br>• Injection site issues<br>• Weight gain/loss<br>• DKA |
| **Study design** | RCTs |

### 9.2.1.2 Clinical evidence

We searched for randomised trials comparing the effectiveness of any of the long-acting insulins versus each other in adults with type 1 diabetes.

Twenty-eight studies in 30 papers[56,72,76,78,111,231,255,290,291,303,303,318,324,325,342,386,423,462,558,559,569,582,584,589,602,603,607,667,707,762] were included in the review (two studies were published each as 2 papers[72,72,76,290,324]); see Table 82. Evidence from the included studies are summarised in the clinical GRADE evidence profile below Table 83). Some study data was not in a suitable format for including in the meta-analyses, and so has been included separately in GRADE. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

Because we were updating the NICE TA on insulin glargine (TA53) we included in our review the 4 studies[559,582,584,602] from the TA that were conducted in people with type 1 diabetes. The TA assessment report referred to six other publications, but these were all abstracts and not full papers. We also included the one long-acting insulin RCT[303] found in the original 2004 guideline (CG15).[506] A Cochrane review[716] was also found which compared intermediate versus long-acting insulins in type 1 diabetes. However this was used as a source of references, rather than directly incorporated into this review since it was published in 2008 and new studies have been published since then.

There were several recent conference abstracts found and one study design protocol. Authors of conference abstracts were contacted in an attempt to obtain further data for the long-acting insulin comparisons for which we found very little published RCT evidence. These comparisons were:

- Degludec versus NPH– no conference abstracts were found which met our inclusion criteria
- Degludec versus detemir – no conference abstracts were found which met our inclusion criteria
- Detemir versus glargine – no conference abstracts were found which met our inclusion criteria
- Degludec versus glargine – one conference abstract[133] was found which met our inclusion criteria. The authors did not respond and so no additional data were obtained.

#### Outcomes

There were no data reported in any of the studies for the following outcomes:

- Cancer
- DKA

#### Subgroup analyses for heterogeneity

Where there was heterogeneity between studies in the meta-analyses for the critical outcomes (HbA1c and major/severe hypoglycaemia), it was agreed that this would be explored using pre-specified subgroups in the protocol. These were:

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- Baseline HbA1c (differences between studies in baseline HbA1c levels)
- Different doses/regimens (clinically relevant regimens)
- Elderly/older people/frailty (if there were significant differences between studies in subject ages)
- Baseline weight (if possible, bearing in mind that some studies give BMI and some give weight in kg)
- Baseline hypoglycaemia (if this is known and there are significant differences).

We were unable to explore heterogeneity based on baseline HbA1c, because the percentage was similar between most of the studies (between 7.5% and 8.5%), and baseline hypoglycaemia could not be considered because it was not reported in most of the studies. Studies did not consistently report the weight of patients in the same units, or units that could be standardised (they reported either BMI or kg), and so it was not possible to do a subgroup analysis based on baseline weight. It was also inappropriate to do a subgroup analysis based on mean age at baseline, because the baseline age was very similar between studies (most were between 35 -45 years of age) and there were no studies in much older people. Nearly all studies used a 'titration' regimen and so it was not possible to explore dosage as a reason for heterogeneity.

The only possible pre-specified subgroup analysis was clinically relevant regimen: giving the long-acting insulins either once or twice/day as per current clinical practice. Current practice for basal insulin regimens is as follows:

- Glargine - once/day
- Degludec - once/day
- Detemir – once or twice/day
- NPH – twice/day (this is still sometimes used once daily, but the GDG believe this is less common and less appropriate that twice/day and so was not considered in our sub-group analysis)

 Clinically relevant regimen for our critical outcomes (HbA1c, and severe hypoglycaemia) showed the following:

- for degludec versus glargine: all studies included in the meta-analysis used the clinically relevant regimen
- for detemir versus glargine: none of the studies included in the meta-analysis used the clinically relevant regimen
- for detemir versus NPH: for the outcome of HbA1c, clinically relevant regimen explained the significant heterogeneity between the trials. For the outcome of major hypoglycaemia, clinically relevant regimen increased the heterogeneity between the trials.
- For glargine versus NPH: for the outcome of severe hypoglycaemia, clinically relevant regimen explained the significant heterogeneity between the trials. There was no heterogeneity between the trials for the outcome of HbA1c.

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**Table 82:   Summary of included studies**

| Study | Intervention | Comparison | Short-acting insulin used during study | Population size | Follow-up | Comments |
|---|---|---|---|---|---|---|
| **Degludec versus Glargine** | | | | | | |
| BIRKELAND 2011 and HOME 2012[72,324] | Degludec – dose 1 Degludec – dose 2<br><br>Once/day | Glargine<br><br><br>Once/day | Aspart | n=178 | 16 weeks | Regimen true to current clinical practice (once/day versus once/day) |
| HELLER 2012/BODE 2013 – BEGIN trialb[290 76] | Degludec<br><br>Once/day | Glargine<br><br>Once/day | Aspart | n=629 (main RCT)/ n=469 (extension) | 52 weeks and 104 weeks (extension trial of additional 52 weeks) | Regimen true to current clinical practice (once/day versus once/day) |
| MATHIEU 2013 [462] | Degludec<br><br>Once/day | Glargine<br><br>Once/day | Aspart | n=329 (using only the 2 relevant arms) | 26 weeks (the main RCT) | Regimen true to current clinical practice (once/day versus once/day) |
| **Detemir versus Glargine** | | | | | | |
| HELLER 2009[291] | Detemir<br><br>Once/day or twice/day (66% ended on twice/day) | Glargine<br><br>Once/day | Aspart | n=443 | 52 weeks | Data given separately for detemir once/day and detemir twice/day. |
| RENARD 2011[589] | Detemir<br><br>Once/day | Glargine<br><br>Once/day | Glulisine | n=88 | 16 weeks | |
| **Detemir versus NPH** | | | | | | |
| BARTLEY 2008[56] | Detemir<br><br>Twice/day (started | NPH<br><br>Twice/day | Aspart | n=497 | 24 months | Regimen in most patients was true to current clinical practice (twice/day versus twice/day) |

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| Study | Intervention | Comparison | Short-acting insulin used during study | Population size | Follow-up | Comments |
|---|---|---|---|---|---|---|
| | off as once/day but only 37% of patients remained on once/day) | (started off as once/day but only 45% of patients remained on once/day) | | | | |
| GOLEN 2013[255] | Detemir<br><br>Once/day | NPH<br><br>Once/day | Aspart | n=28 (cross-over RCT) | 12 weeks | |
| HERMANSEN 2001[303] | Detemir<br><br>Once/day (but 63% had twice/day) | NPH<br><br>Once/day | Human Insulin | n=59 | 6 weeks | |
| HERMANSEN 2004[302] | Detemir<br><br>Twice/day | NPH<br><br>Twice/day | Aspart | n=595 | 18 weeks | |
| HOME 2004[318] | Detemir<br><br>Twice/day | NPH<br><br>Twice/day | Aspart | n=408 | 16 weeks | Regimen true to current clinical practice (twice/day versus twice/day)<br>Slightly higher HbA1c levels (8.7% and 8.5% respectively) |
| KOLENDORF 2006[386] | Detemir<br><br>Twice/day | NPH<br><br>Twice/day | Aspart | n=130 | 16 weeks | Regimen true to current clinical practice (twice/day versus twice/day) |
| DELEEUW 2005[423] | Detemir<br><br>Twice/day | NPH<br><br>Twice/day | Aspart | n=428 | 6 months main treatment plus 6 months extension | Regimen true to current clinical practice (twice/day versus twice/day) |
| PIEBER 2005[558] | Detemir | NPH | Aspart | n=400 | 16 weeks | Regimen true to current clinical |

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| Study | Intervention | Comparison | Short-acting insulin used during study | Population size | Follow-up | Comments |
|---|---|---|---|---|---|---|
| | Twice/day | Twice/day | | | | practice (twice/day versus twice/day) |
| RUSSELL-JONES 2004[607] | Detemir<br><br>Once/day | NPH<br><br>Once/day | Human Insulin | n=747 | 6 months | |
| STANDL 2004[667] | Detemir<br><br>Twice/day | NPH<br><br>Twice/day | Human Insulin | n=461 | 6 months main treatment plus 6 months extension | Regimen true to current clinical practice (twice/day versus twice/day) |
| VAGUE 2003[707] | Detemir<br><br>Twice/day | NPH<br><br>Twice/day | Aspart | n=448 | 6 months | Regimen true to current clinical practice (twice/day versus twice/day) |
| ZACHARIAH 2011[762] | Detemir<br><br>Once or twice/day (only 22% on twice/day) | NPH<br><br>Once or twice/day | Aspart | n=23 | 16 weeks | |
| **Degludec versus Detemir** | | | | | | |
| IWAMOTO 2013[342] | Degludec<br><br>Once/day | Detemir<br><br>Once/day | Aspart | n=65 | 6 weeks | |
| **Glargine versus NPH** | | | | | | |
| BOLLI 2009[78] | Glargine<br><br>Once/day | NPH<br><br>Twice or more/day (84% twice/day) | Lispro | n=175 | 24 weeks | Regimen in most patients was true to current clinical practice (twice/day versus twice/day) |
| CHATTERJEE 2007[111] | Glargine | NPH | Aspart | n=58 | 16 weeks | Regimen true to current clinical practice (once/day versus |

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| Study | Intervention | Comparison | Short-acting insulin used during study | Population size | Follow-up | Comments |
|---|---|---|---|---|---|---|
| | Once/day | Twice/day | | | | twice/day) |
| FULCHER 2005[231] | Glargine<br><br>Once/day | NPH<br><br>Once/day | Lispro | n=125 | 30 weeks | Higher baseline HbA1c levels (9.2% and 9.7% respectively). |
| HOME 2005[325] | Glargine<br><br>Once/day | NPH<br><br>Once or twice /day (% not given) | Human insulin | n=602 | 28 weeks | |
| PIEBER 2000[559] | Glargine<br><br>Once/day | NPH<br><br>Once or twice /day (47.3% on twice/day – thus counted as once/day as most started on once/day) | Human insulin | n=333 | 4 weeks | |
| PORCELLATTI 2004[569] | Glargine<br><br>Once/day | NPH<br><br>Four/day | Lispro | n=121 | 1 year | Regimen of NPH (4 times/day) is unusual and does not reflect current clinical practice<br>Lower baseline HbA1c levels: 7.1% in both groups |
| RASKIN 2000[582] | Glargine<br><br>Once/day | NPH<br><br>Once or twice /day (% not given) | Lispro | n=619 | 16 weeks | |
| RATNER 2000[584] | Glargine | NPH | Regular insulin | n=534 | 28 weeks | |

| Study | Intervention | Comparison | Short-acting insulin used during study | Population size | Follow-up | Comments |
|---|---|---|---|---|---|---|
| | Once/day | Once or twice /day (% not given) | | | | |
| ROSENSTOCK 2000[602] | Glargine | NPH | Regular insulin | n=256 | 4 weeks | Regimen in most patients was true to current clinical practice (twice/day versus twice/day) |
| | Once/day | Once or twice /day (70% twice/day) | | | | |
| ROSSETTI 2003[603] | Glargine | NPH | Lispro | n=51 | 3 months | Regimen of NPH (4 times/day) is unusual and does not reflect current clinical practice |
| | Once/day | Four/day | | | | |

**Table 83:  Evidence summary table: Degludec versus glargine**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br>Degludec | Control value: event rate (per 1000 patients) or median value<br>Glargine |
|---|---|---|---|---|---|
| HbA1c decrease (≤6 months ) | 2 studies (n=566) | None | MODERATE | MD 0.13 lower (0.25 to 0.01 lower) | 0.60 |
| HbA1c decrease (>6 months) | 1 study (n=629) | None | MODERATE | MD 0.01 lower (0.14 lower to 0.16 higher) | 0.39 |
| Body weight change, kg (≤6 months) | 2 studies (n=566) | None | VERY LOW | MD 0.39 lower (0.82 lower to 0.04 higher) | 1.2 |
| Body weight change, kg (>6 months) | 1 study (n=629) | None | MODERATE | MD 0.2 higher (0.51 lower to 0.91 higher) | 1.6 |
| Severe hypoglycaemia, no. of people (≤6 months) | 1 study (n=326) | Very serious | VERY LOW | 3 more per 1000 (from 5 fewer to 12 more) | 99 |
| Severe hypoglycaemia, no. of people (> 6 months) | 1 study (n=629) | Serious | LOW | 21 more per 1000 (from 30 | 102 |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Degludec | Control value: event rate (per 1000 patients) or median value<br><br>Glargine |
|---|---|---|---|---|---|
| | | | | fewer to 105 more) | |
| SF36 Physical component score (≤6 months) | 1 study (n=118) | None | MODERATE | MD 0.67 higher (2.31 lower to 3.65 higher) | -0.41 |
| SF36 Mental component score (≤6 months) | 1 study (n=118) | None | MODERATE | MD 3.01 higher (0.31 to 5.71 higher) | -1.13 |
| Serious adverse events, no. of people (≤6 months) | 1 study (n=326) | Very serious | VERY LOW | 2 fewer per 1000 (from 21 fewer to 30 more) | 50 |
| Serious adverse events, no. of people (>6 months) | 1 study (n=629) | Very serious | VERY LOW | 4 fewer per 1000 (from 41 fewer to 66 more) | 108 |
| Injection site reactions, no. of people (≤6 months) | 1 study (n=326) | Very serious | VERY LOW | 1 fewer per 1000 (from 11 fewer to 15 more) | 25 |

**Table 84: Evidence summary table: Detemir versus glargine**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Detemir | Control value: event rate (per 1000 patients) or median value<br><br>Glargine |
|---|---|---|---|---|---|
| HbA1c decrease (≤6 months) | 2 studies (n=495) | None | MODERATE | MD 0.00 higher (0.12 lower to 0.13 higher) | 0.37 |
| HbA1c final (>6 months) | 1 study (n=156) | None | MODERATE | Data provided: MD 0.01%, 95% CI -0.13 to +0.16 | |
| Severe symptomatic hypoglycaemia (number of patients) - ≤6 months | 1 study (n=176) | Serious | LOW | 68 fewer per 1000 (from 99 fewer to 26 more) | 114 |
| Major hypoglycaemic episodes/patient-year- >6 months | 1 study (n=447) | Serious | LOW | Data provided: RR 0.94, 95% CI 0.74 to 1.18 | |
| Body weight change, kg- ≤6 months | 1 study (n=78) | Very serious | VERY LOW | Data provided: -0.2kg versus 0kg | |
| Body weight change, kg- >6 months | 1 study (n=447) | Very serious | VERY LOW | Data provided: MD -0.06, 95% CI -0.84 to +0.73 | |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Detemir | Control value: event rate (per 1000 patients) or median value<br>Glargine |
|---|---|---|---|---|---|
| Injection site reactions (number of patients) - >6 months | 1 study (n=447) | None | MODERATE | 66 more per 1000 (from 6 more to 320 more) | 14 |

**Table 85: Evidence summary table: Detemir versus NPH**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Detemir | Control value: event rate (per 1000 patients) or median value<br><br>NPH |
|---|---|---|---|---|---|
| HbA1c (≤6 months) | 8 studies (n=2646) | None | LOW | MD 0.09 lower (0.16 to 0.02 lower) | 7.5 |
| HbA1c, change from baseline (≤6 months) | 1 study (n=595) | Serious | VERY LOW | Data provided: -0.5% versus -0.28% | |
| HbA1c, change from baseline (≤6 months) | 1 study (n=130) | Serious | LOW | Data provided: -0.3% versus -0.3% | |
| HbA1c (>6 months) | 3 studies (n=1083) | None | VERY LOW | MD 0.08 lower (0.22 lower to 0.05 higher) | 7.6 |
| HbA1c, change from baseline (>6 months) | 1 study (n=428) | Serious | VERY LOW | Data provided: -0.64% versus -0.56% | |
| Body weight change- ≤6 months | 5 studies (n=1713) | None | VERY LOW | MD 0.84 lower (1.10 to 0.58 lower) | 0.86 |
| Body weight change- ≤6 months | 1 study (n=130) | Serious | LOW | Data provided: -0.3kg versus +1.0 kg (period 1) and -0.2 kg versus +1.3 kg (period 2) | |
| Body weight change- >6 months | 1 study (n=497) | Serious | LOW | Data provided: +1.7 kg versus +2.7 kg | |
| Body weight change- >6 months | 1 study (n=428) | Serious | VERY LOW | Data provided: -0.1 kg versus +1.2 kg | |
| Body weight change- >6 months | 1 study (n=461) | Serious | VERY LOW | Data provided: -0.3 kg versus +1.4 kg | |
| Major hypoglycaemia (no. of patients) - ≤6 months | 7 studies (n=2392) | Serious | VERY LOW | 18 fewer per 1000 (from 33 fewer to 3 more) | 80 |
| Major hypoglycaemia (episodes) - ≤6 months | 1 study (n=113) | Very serious | VERY LOW | Data provided: 4 versus 11 episodes | |
| Severe hypoglycaemia, episodes - ≤6 months | 1 study (n=52) | Serious | LOW | Data provided: 19 versus 33 episodes | |
| Major hypoglycaemia - >6 months | 3 studies (n=1099) | None | LOW | 62 fewer per 1000 (from 21 fewer to 93 fewer) | 193 |
| Injection site reactions - >6 months | 2 studies (n=604) | Very serious | VERY LOW | 5 more per 1000 (from 3 fewer to 49 more) | 4.3 |

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**Table 86: Evidence summary table: Glargine versus NPH**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br>Glargine | Control value: event rate (per 1000 patients) or median value<br>NPH |
|---|---|---|---|---|---|
| HbA1c (≤6 months) | 7 studies (n=2235) | None | LOW | MD 0.09 lower (0.15 to 0.03 lower) | 7.5 |
| HbA1c, final (≤6 months) | 1 study (n=60) | Serious | LOW | Data provided: MD -0.19, 95% CI -0.36 to +0.01 | |
| HbA1c (>6 months) | 1 study (n=121) | None | HIGH | MD 0.40 lower (0.44 to 0.36 lower) | 7.1 |
| HbA1c, change from baseline (>6 months) | 1 study (n=125) | Serious | VERY LOW | Data provided: -0.89 versus -0.67 | |
| Severe hypoglycaemia (≤6 months) | 7 studies (n=2194) | None | VERY LOW | 55 fewer per 1000 (from 35 fewer to 69 fewer) | 114 |
| Serious hypoglycaemia, episodes/patient/month - ≤6 months | 1 study (n=175) | Serious | VERY LOW | Data provided: 1.01 versus 0.88 | |
| Severe hypoglycaemia (>6 months) | 1 study (n=121) | None | HIGH | Zero events in both arms | |
| Severe hypoglycaemia – events/100 patient days (>6 months) | 1 study (n=125) | Serious | VERY LOW | Data provided: 0.87 versus 0.99 | |
| Body weight change (≤6 months) | 1 study (n=619) | Serious | VERY LOW | Data provided: +0.12 kg versus +0.54 kg | |
| Body weight change (>6 months) | 1 study (n=125) | Serious | VERY LOW | Data provided: +1.97 kg versus +2.34 kg | |
| Body weight change (>6 months) | 1 study (n=121) | Serious | MODERATE | No weight change with either treatment | |
| QoL, WED: impact, satisfaction, general worries and diabetes-related worries (≤6 months) | 1 study (n=175) | Serious | VERY LOW | NS difference between the groups except diabetes-related worries was SS better in the glargine group | |
| QoL, DTSQ (≤6 months) | 1 study (n=60) | Serious | LOW | NS difference between groups for hyper or hypo glycaemia.<br>Greater satisfaction with glargine (4 points). | |
| ADDQoL (≤6 months) | 1 study (n=60) | Serious | LOW | NS difference between the groups, p=0.08 | |
| Injection site reactions (≤6 months) | 3 studies (n=1339) | Serious | VERY LOW | 15 more per 1000 (from 9 fewer to 50 more) | 55 |

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| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Glargine | Control value: event rate (per 1000 patients) or median value<br><br>NPH |
|---|---|---|---|---|---|
| Injection site reactions (≤6 months) | 1 study (n=128) | Very serious | VERY LOW | 34 fewer per 1000 (from 86 fewer to 119 more) | 111 |
| Injection site pain (≤6 months) | 2 studies (n=1153) | None | VERY LOW | 44 more per 1000 (from 11 more to 137 more) | 6.9 |

**Table 87:   Evidence summary table: Degludec versus detemir**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Degludec | Control value: event rate (per 1000 patients) or median value<br><br>Detemir |
|---|---|---|---|---|---|
| Severe hypoglycaemia, no. of patients - ≤6 months | 1 study (n=65) | None | MODERATE | Zero events in both arms | |
| Adverse events - ≤6 months | 1 study (n=65) | None | MODERATE | Zero events in both arms | |
| Serious adverse events - ≤6 months | 1 study (n=65) | None | MODERATE | Zero events in both arms | |

### 9.2.1.3 Network meta-analysis

We also conducted a network meta-analysis (NMA) as part of this review, because the review was concerned with comparing the effectiveness of several different long-acting insulins with both direct and indirect comparisons.

The studies included within the review formed two networks of evidence for the critical outcomes identified by the GDG, that is, a separate network is developed for each of the two outcomes: HbA1c, and severe/major hypoglycaemia. The analyses were based on 28 studies, of four different long-acting insulins, in seven main different regimens in the HbA1c network. The seven regimens are:

- insulin NPH (once daily),
- insulin NPH (twice daily),
- insulin NPH (four times daily),
- insulin glargine (once daily)
- insulin detemir (once daily),
- insulin detemir (twice daily),
- insulin degludec (once daily).

In addition to the above regimens, we also included trials of insulin NPH and insulin detemir which used more than one regimen in the same arm (i.e. once or twice). Hence, two more regimens were also included in the network: insulin NPH (once or twice daily) and insulin detemir (once or twice daily). Thus, in total nine regimens were included in this network.

In the severe/major hypoglycaemia network, 16 studies were included. These related to the same four long-acting insulins but in eight different regimens only as insulin NPH four times was not included in this network. An RCT comparing insulin detemir (once daily) versus insulin degludec (once daily) has not been included in the NMA as it has not reported HbA1c data and reported zero severe/major hypoglycaemia events in both trial arms[342]. The diagrams of the evidence networks for both outcomes are illustrated in Figure 3 and Figure 4, respectively.

Study data for the first outcome, change in HbA1c, were combined regardless of follow-up time; but short-term results of less than four weeks were excluded, as the GDG considered that HbA1c and the occurrence of severe/major hypoglycaemia would not be changed in this time. Follow-up time was taken into account in the model used for the analysis of severe/major hypoglycaemia outcome data.

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**Figure 3:    Network for first outcome: HbA1c level**
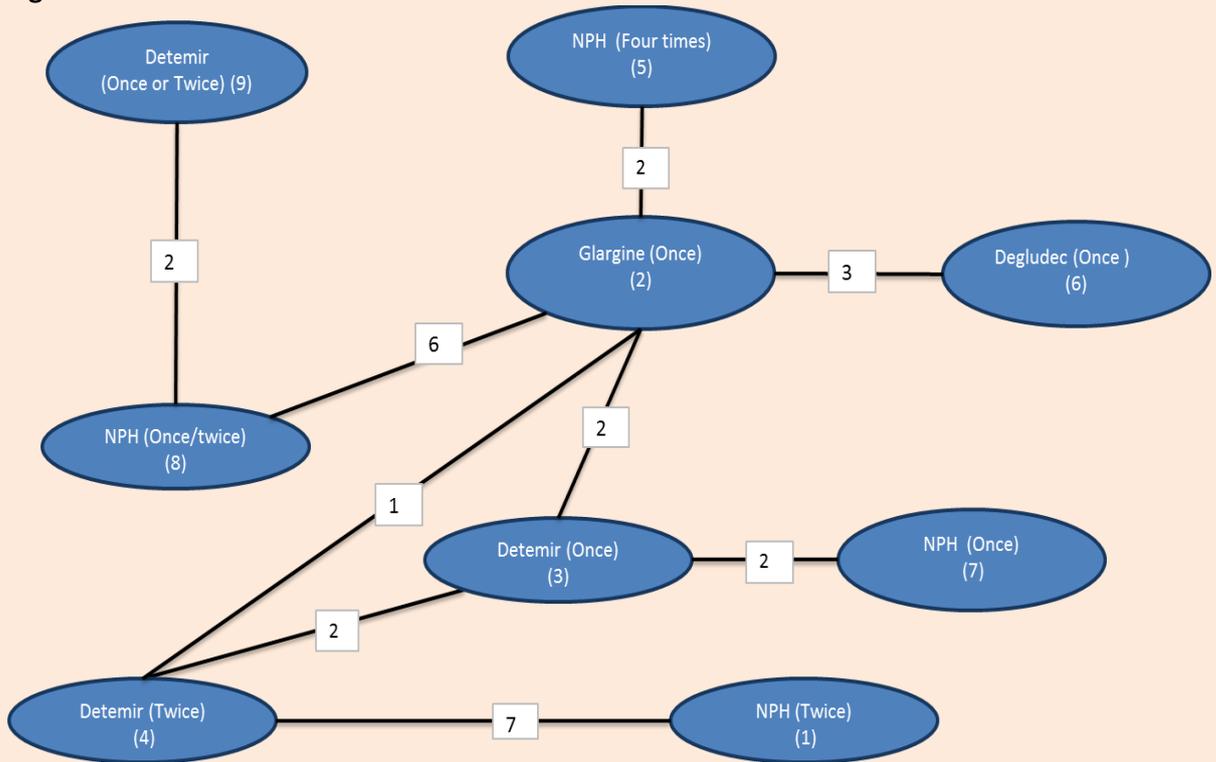


**Figure 4:    Network for severe/major hypoglycaemia**
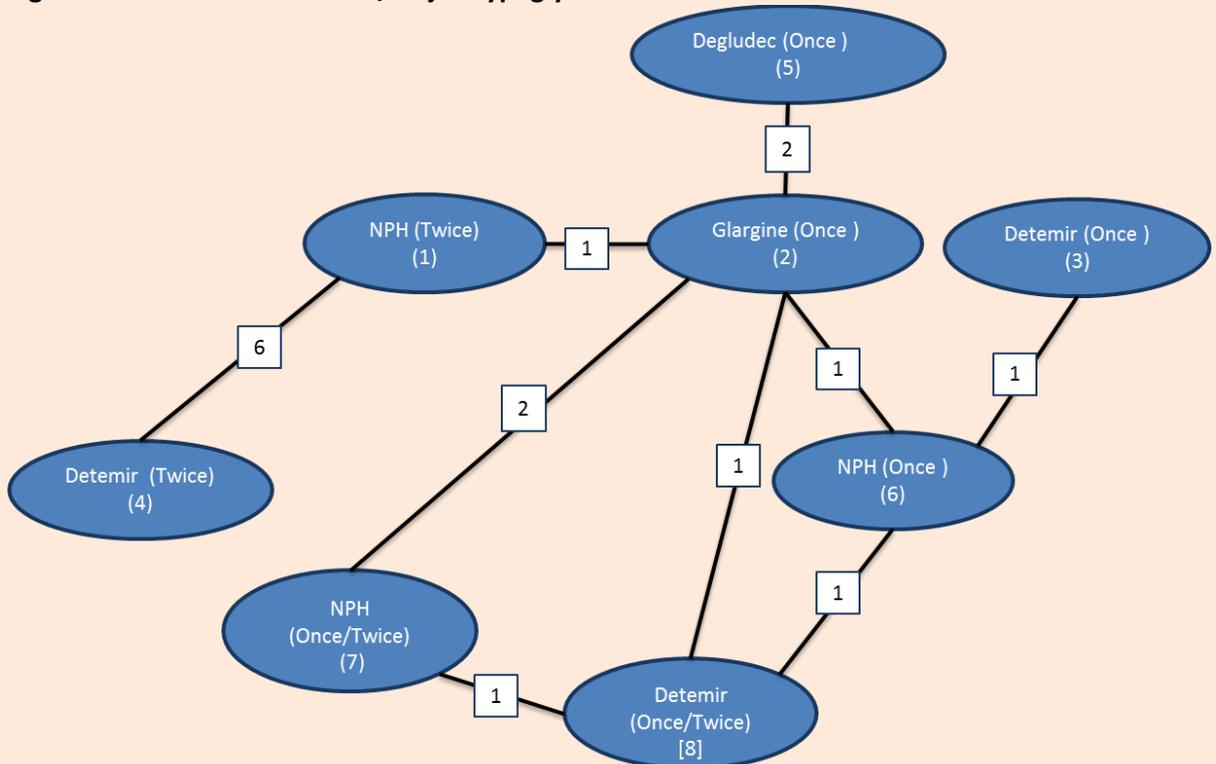


In the first network that examined the change in HbA1c, only insulin detemir (twice daily) is significantly more effective than NPH (twice daily) in reducing HbA1c. All other treatment

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comparisons versus insulin NPH (twice daily) in this network cross the line of no difference and statistical significance is not achieved. No network inconsistency was identified between the direct meta-analysis and the NMA results for any comparison. The results of this network are presented in Table 88 .

**Table 88:   Mean change in HbA1c from baseline**

| Insulin | Mean change[a] | Difference compared with NPH (twice daily)[a] | Lower 95% CrI | Upper 95% CrI |
|---|---|---|---|---|
| NPH (twice daily) | -0.320 | | | |
| Glargine (once daily) | -0.423 | -0.104 | -0.335 | 0.138 |
| Detemir (once daily) | -0.395 | -0.076 | -0.274 | 0.130 |
| Detemir (twice daily) | -0.483 | -0.164 | -0.273 | -0.048 |
| NPH (four times daily | -0.008 | 0.310 | 0.022 | 0.622 |
| Degludec (once daily) | -0.351 | -0.032 | -0.308 | 0.255 |
| NPH (once daily) | -0.281 | 0. 039 | -0.248 | 0.332 |
| NPH (once or twice daily) | -0.377 | -0.057 | -0.312 | 0.205 |
| Detemir (once or twice daily) | -0.532 | -0.212 | -0.565 | 0.170 |

(a)  Median of the posterior distribution for the mean change.

In the ranking of insulin regimens, insulin detemir (once or twice daily) was ranked first, followed by insulin detemir (twice daily), insulin glargine (once daily), insulin detemir (once daily), insulin NPH (once or twice daily), insulin degludec (once daily), insulin NPH (twice daily), insulin NPH (once daily) and insulin NPH (four times daily). The credible interval around the ranks were wide for all treatments, spanning at least six ranks, except for NPH (four times daily) which could only be ranked either eighth or ninth. (see Figure 5).

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**Figure 5: Rank order for insulin regimens – reduction in HbA1c**



In the second network, none of the comparisons had a treatment effect that reached statistical significance. No network inconsistency was identified between the direct meta-analysis and the NMA results for any comparison. Results are presented in Table 89.

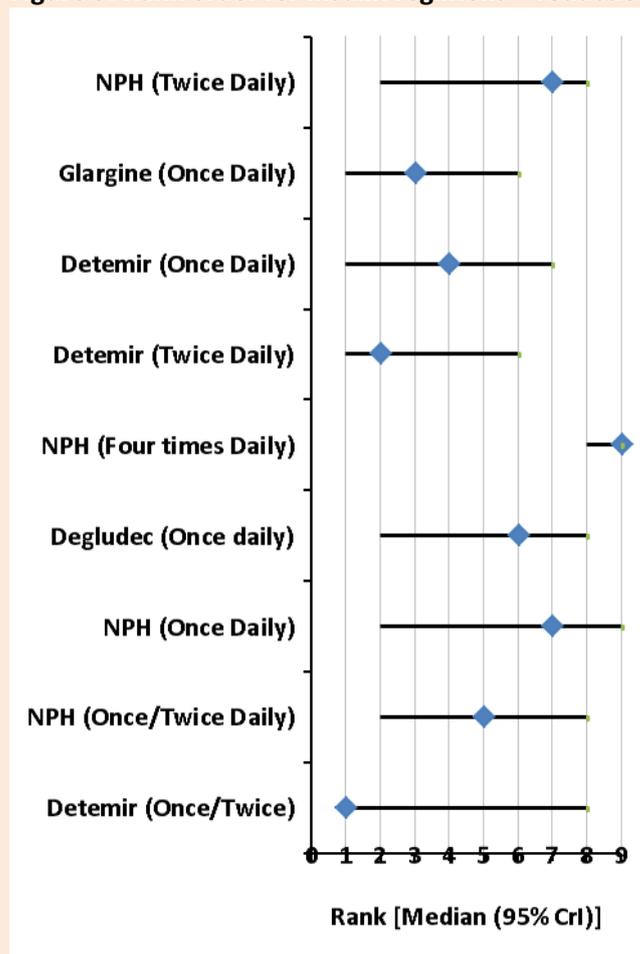**Table 89:   Rate of severe/major hypoglycaemic events**

| Insulin | Rate (events per person year) | Rate ratio compared with NPH (twice daily) | Rate ratio lower 95% CrI | Rate ratio upper 95% CrI |
|---|---|---|---|---|
| NPH (twice daily) | 0.46 | | | |
| Glargine (once daily) | 0.47 | 1.33 | 0.02 | 101.20 |
| Detemir (once daily) | 0.61 | 0.96 | 0.54 | 1.74 |
| Detemir (twice daily) | 0.44 | 1.08 | 0.02 | 62.97 |
| Degludec (once daily) | 0.50 | 1.18 | 0.02 | 73.12 |
| NPH (once daily) | 0.54 | 1.63 | 0.03 | 94.43 |
| NPH (once or twice daily) | 0.75 | 0.63 | 0.01 | 36.24 |
| Detemir (once or twice daily) | 0.29 | 1.04 | 0.02 | 54.47 |

*(a)  Median of the posterior distribution for the mean change.*

All interventions had very wide credible intervals around their median rank, which made it difficult to fully characterise the order of efficacy. On the basis of the median rank, none of the insulin regimens is ranked first. Insulin detemir (once or twice daily) intervention is ranked second. Insulin detemir (twice daily), insulin glargine (once daily), insulin NPH (twice daily) and insulin degludec (once daily) have median rank of four followed by insulin NPH (once daily) and insulin detemir (once daily) both in rank five, then insulin NPH (once/twice) (see Figure 6).

**Figure 6: Rank order for insulin regimens – severe/major hypoglycaemia**
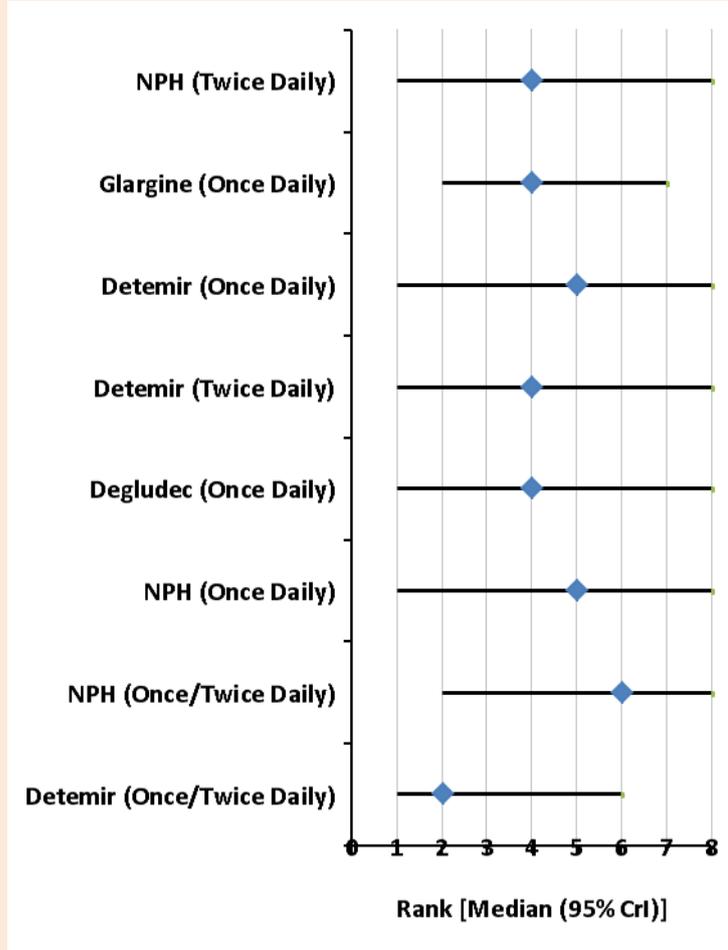


For detailed explanation on methodology and results of NMA refer to Appendix M.

#### 9.2.1.4 Economic evidence

**Published literature**

Ten studies were included with the relevant comparison from the update search.[103,265,474,542,544,556,704,708,710,729]

In addition, one original economic analysis was conducted in the guideline update. For more details please see below and Appendix N.

CG15 included one study relevant to this review; NICE TA53[504] which recommends insulin glargine as a treatment option for people with type 1 diabetes.

Three studies that met the inclusion criteria were selectively excluded due to more applicable evidence being available[198,271,709].

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Seven studies identified in CG15 have been selectively excluded due to the availability of more applicable evidence or they do not answer this particular evidence review question.
154,180,299,543,668,688,752

The included papers are summarised in the economic evidence profile below. See also the study selection flow chart in Appendix E and study evidence tables in Appendix H. Those studies selectively excluded are summarised in Appendix L, with reasons for exclusion given.

**Update 2015**

**Table 90:   Economic evidence profile: Insulin detemir versus neutral protamine Hagedorn**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Palmer2004[542] [UK] | Directly applicable[a] | Potentially serious limitations[b] | Analysis performed using the IMS-CDM. | £1,707 | 0.09 QALYs | £19,285 | Probabilistic sensitivity analysis demonstrated a 58% probability that detemir will be cost effective over NPH at a £30K threshold. Deterministic sensitivity analysis maintained the ICER around the £20K threshold and was only significantly higher when a shorter time horizon was considered. |
| Palmer 2007[544] [UK] | Directly applicable[a] | Potentially serious limitations[c] | Analysis performed using the IMS-CDM. | £1,654 | 0.66 QALYs | £2,500 | Probabilistic sensitivity analysis demonstrated a 95% probability that insulin detemir will be cost effective over NPH at a £25K threshold. The ICER was most sensitive to the efficacy of HbA1c. When only HbA1c is taken into account, the ICER increases to £12,598 per QALY gained. All other deterministic sensitivity analyses resulted in ICERs below £4,000 per QALY gained. |
| Cameron 2009[103] [CANADA] | Partially applicable[d] | Minor limitations[e] | Analysis performed using the IMS-CDM. This is an abridged version of a report by CADTH[104] | £2,313 | 0.011 QALYs | £206,488 | Probabilistic sensitivity analysis demonstrated a 10.8% probability that insulin detemir will be cost effective over NPH at a £26K threshold. Deterministic sensitivity analysis maintained that insulin detemir was unlikely to be cost-effective in all analyses except when QALY gains are incorporated for fear of hypoglycaemia, where |

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| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | | | | | the ICER decreases to £13,669. |
| Valentine 2006[710] [USA] | Partially applicable[f] | Potentially serious limitations[g] | Analysis performed using the IMS-CDM. | £6,649 | 0.698 QALYs | £9,526 | Probabilistic sensitivity analysis demonstrated a 100% probability that insulin detemir will be cost effective over NPH at a £30K threshold. Deterministic sensitivity analysis maintained insulin detemir as cost-effective over NPH at the £20K per QALY gained threshold. |
| Tunis 2009[704] [CANADA] | Partially applicable[h] | Potentially serious limitations[i] | Analysis performed using the IMS-CDM. | £6,181 | 0.475 QALYs | £12,989 | Probabilistic sensitivity analysis demonstrated a 56.1% probability that insulin detemir will be cost effective over NPH at a £24K threshold. Deterministic sensitivity showed the model was most sensitive to changes in utilities for hypoglycaemic events. When utilities are reduced, the ICER increases up to £107,526 per QALY gained. |
| Valentine 2011[708] [SWEDEN] | Partially applicable[j] | Potentially serious limitations[k] | Analysis performed using the IMS-CDM. | £1,804 | 0.53 QALYs | £3,443 | Probabilistic sensitivity analysis demonstrated a 99.9% probability that insulin detemir will be cost effective over NPH at a £20K threshold. The ICER was most sensitive to changes in HbA1c and hypoglycaemia event rates yet did not change the decision on cost-effectiveness. |

(a)  Study performed from a UK NHS perspective
(b)  Although the sources of clinical data that have been included are appropriate, no systematic review has been conducted and the sources may have been selectively included; the meta-analysis used for the clinical data has not been published, meaning we are unable to appraise the quality; the trials included within the meta-analysis lead to a high proportion of male

patients, which may bias the results due to differing complication risks between genders; due to the progression of type 1 diabetes, the starting age of this cohort appears high. However, this may have been chosen as the risk equations within the complication modules are applicable for a higher age group; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial data was for between 16 week and 6 months; uncertainty around particular key clinical inputs including effectiveness of treatments in reducing HbA1c and reductions in hypoglycaemic events were not explored in a sensitivity analysis; insulin doses used within the analysis were not reported; there was no QALY gain given to a reduction in hypoglycaemic events. This may have reduced the overall benefits of insulin detemir; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

(c) The baseline event and clinical effectiveness data was derived from a single trial19, which demonstrated a larger reduction in HbA1c and hypoglycaemic events for insulin detemir than what either previous trials or the NCGCs meta-analysis demonstrated; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trial was for 18 weeks; due to the progression of type 1 diabetes, the starting age of this cohort appears high. However, this may have been chosen as the risk equations within the complication modules are applicable for a higher age group; particular complication costs were taken from previous economic evaluations and not calculated from UK sources; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

(d) Study performed from a Canadian healthcare payer perspective

(e) There are discrepancies between the effectiveness data in the clinical review and economic review. However the authors explained this is due to the meta-analysis being updated over time; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trials included had short follow-up times; the report is not completely incremental as it provides the results of four pairwise simulations; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

(f) Study performed from a US healthcare payer perspective.

(g) Although the sources of clinical data that have been included are appropriate, no systematic review has been conducted and the sources may have been selectively included; insulin doses used within the analysis were not reported; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial data was for between 18 weeks. However, this was shortened to 5 years in a sensitivity analysis; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources that did not comply with the NICE reference case; a 3% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

(h) Study performed from the perspective of the Canadian provincial government

(i) Although the sources of clinical data that have been included are appropriate, no systematic review has been conducted and the sources may have been selectively included; baseline characteristics come from the DCCT42, which may not be completely representative due to the studies age; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial follow-up was only for 24 months; uncertainty around particular key clinical inputs including effectiveness of treatments in reducing HbA1c and cost of insulin treatments were not explored in a sensitivity analysis; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

(j) Study performed from a Swedish healthcare payer perspective

(k) Although the sources of clinical data that have been included are appropriate, no systematic review has been conducted and the sources may have been selectively included; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial follow-up was only for 24 months; Utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources, which did not comply to the NICE reference case; particular complication costs were based on either mixed populations or type 2 diabetes specific patients; a 3% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

**Table 91: Economic evidence profile: Insulin glargine versus neutral protamine Hagedorn**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| TA53[504]/Warren 2004[729] [UK] | Directly applicable[a] | Very serious limitations[b] | Model that uses insulin therapies to estimate the incidence of hypoglycaemia and the resultant cost and QALYs, dependant on method of administration. Long-term complications were only taken into consideration in the sensitivity analysis. | £573 - £816 | NR | £3, 496-£4,978 | The model was highly sensitive to the utility gained from reducing fear of hypoglycaemia. If the model assumes no utility gained, the ICER increases to between £389,356 and £554,411. Other variables are also subject to sensitivity analysis such as introducing a reduction in HbA1c, using different fear assumptions and changing the rate of discounting. Overall, the ICER for ranges from £954 - £554,411 highlighting considerable uncertainty. |
| McEwan2007[474] [UK] | Directly applicable[a] | Very serious limitations[c] | This analysis is performed on a de novo patient level simulation model that includes seven key complications of type 1 diabetes. Five varying scenarios were analysed. | Scenario 1: £1,097 Scenario 2: £1,080 Scenario 3: £1,043 Scenario 4: £1,371 Scenario 5: £1,096 | Scenario 1: 0.12 QALYs Scenario 2: 0.12 QALYs Scenario 3: 0.14 QALYs Scenario 4: 0.14 QALYs Scenario 5: 0.34 QALYs | Scenario 1: £8,807 Scenario 2: £8,668 Scenario 3: £7,391 Scenario 4: £9,767 Scenario 5: £3,189 | No probabilistic sensitivity analysis was undertaken. The deterministic sensitivity analysis held the majority of mean ICER values remained under the £20K threshold. If insulin glargine is assumed to only have a 2-year treatment effect, using the best assumptions in the most favourable scenario, the ICER increases to £47,445 per QALY gained. |
| Cameron 2009[103] [CANADA] | Partially applicable[d] | Minor limitations[e] | Used IMS-CDM. This is an abridged version of a report by CADTH[104] | £1,823 | 0.039 QALYs | £46,829 | Probabilistic sensitivity analysis demonstrated a 25.1% probability that insulin detemir will be cost effective compared with NPH at a |

**Update 2015**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | | | | | £26K threshold. Deterministic sensitivity analysis maintained that insulin glargine was unlikely to be cost-effective in all analyses except when QALY gains are incorporated for fear of hypoglycaemia, where the ICER decreases to £9,173. |
| Grima2007[265] [CANADA] | Partially applicable[f] | Very serious limitations[g] | This analysis is performed on a Markov model that models a number of micro and macrovascular complications alongside mortality dependant on the level of HbA1c maintained | £733 | 0.067 QALYs | £10,903 | Deterministic sensitivity analysis was undertaken. The ICER was most sensitive to the efficacy of insulin glargine varying between £4,904 and £89,170 dependant on its ability to reduce HbA1c. |
| Pfohl 2012[556] [Germany] | Partially applicable[h] | Potentially serious limitations[i] | This analysis is performed on discrete event simulation model that includes 5 long-term complications and 2 acute complications of type 1 diabetes. Results are determined by the combination of HbA1c and hypoglycaemic events. | Saves £4,552[j] | 0.39 QALY | Glargine is dominant | Probability Glargine dominant: 80.4% Glargine was still dominant in these scenarios: its effectiveness in HbA1c level or hypoglycaemia events was reduced, time horizon was decreased up to 5 years, and discount rate was 0%, 5% or 10%. Glargine was dominant in all the variation of + or – 10% of the following parameters: acquisition costs, all risk factors, cost offset,- event-related treatment costs, all demographic parameters, risk of events, all disutilities. It was not dominant anymore when its effectiveness was varied but with no cost offsets. |

*(a)   Study performed from a UK NHS perspective*

(b)  The main assumption that insulin glargine has no advantage over NPH for improved HbA1c level is not borne out in our clinical review; cohort characteristics are not detailed in the study but can be calculated from the DCCT42; the source of baseline event data has been excluded in the NCGC clinical review; quality-of-life weights are taken from a cost of illness study in children and adolescents and long term weights are taken from the industry submission which is confidential; costs included in the model are limited and costs for long-term complications are taken from the industry submission; the sensitivity analysis appears very limited with no sensitivity analysis undertaken on the variables used in long term complication analysis; all health effects are only taken into account in the sensitivity analysis of the model; discount rates used for costs and QALYs not reported; time horizon is too short to account for all costs and outcomes.

(c)  One meta-analysis used for the clinical data has not been published, meaning we are unable to appraise the quality; ; the effectiveness data has come from non-inferiority trials and as such has not been powered to detect a difference between the regimens; Framingham data to estimate cardiovascular events is likely to underestimate the rate at which they occur and may lead to an underestimate of costs; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources; the model does not include subsequent cardiovascular events and the likes of angina and heart failure are not included due to the lack of adequate risk equations, leading to conservative endpoints and estimates as certain costs will be excluded as not all health effects are included within the model.

(d)  Study performed from a Canadian healthcare payer perspective

(e)  There are discrepancies between the effectiveness data in the clinical review and economic review. However the authors explained this is due to the meta-analysis being updated over time; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trials included had short follow-up times; the report is not completely incremental as it provides the results of four pairwise simulations; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

(f)  Study performed from a Canadian public payer perspective

(g)  Although a systematic review was undertaken, one study was chosen from these as being an average representation; there is very limited detail provided on the cohorts' characteristics; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources; insulin use is provided but no other resources are; particular complication costs were taken from previous economic evaluations; the cost for insulin glargine was provided by the manufacturer and many not be representative of the true cost; uncertainty around particular key clinical inputs were not explored in a sensitivity analysis; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%.

(h)  Study performed from a German third party payer perspective

(i)  The source of effectiveness data was a meta-regression analysis that included studies that were excluded from our clinical review. UKPDS risk engine which focused exclusively on type 2 diabetes was used for long-term complications. Discounting was performed at a different rate to that required by the NICE reference case. Sensitivity analysis was limited as parameters of the same type were varied together by plus or minus 10%. Distributions for Monte Carlo simulations were not reported.

(j)  2010 Euros converted into GBP using the purchasing power parities.[535] Cost components were: insulin costs including acquisition costs, discount of pharmacy to the third party payer, deduction of co-payments, cost of delivery devices, test strips, needles and glucose monitoring devices (less frequent monitoring and administration with glargine); cost of complications (acute and long-term).

**Table 92: Economic evidence profile: Insulin detemir versus insulin glargine**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Cameron 2009[103] [CANADA] | Partially applicable[a] | Minor limitations[b] | This analysis was calculated by the NCGC using the data provided | £1,045 | -0.091 QALYs | Insulin detemir dominated by insulin glargine | NA |
| Valentine2006[710] [USA] | Partially applicable[c] | Potentially serious limitations[d] | This analysis is performed using the IMS-CDM. | -£1,318 | 0.063 QALYs | Insulin detemir is dominant over insulin glargine | Probabilistic sensitivity analysis demonstrated an 80% probability that insulin detemir will be cost effective compare to insulin glargine at a £30K threshold. In addition, a number of parameters were varied in a deterministic sensitivity analysis. Insulin detemir remained dominant over insulin glargine in all but one analysis, where the cost of insulin detemir is increased by 15%, yet is still cost-effective. |

(a) *Study performed from a Canadian healthcare payer perspective*

(b) *There are discrepancies between the effectiveness data in the clinical review and economic review. However the authors explained this is due to the meta-analysis being updated over time; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trials included had short follow-up times; the report is not completely incremental as it provides the results of four pairwise simulations; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.*

(c) *Study performed from a US healthcare payer perspective.*

(d) *Although the sources of clinical data that have been included are appropriate, no systematic review has been conducted and the sources may have been selectively included; insulin doses used within the analysis were not reported; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although trial data was for between 18 weeks. However, this was shortened to 5 years in a sensitivity analysis; utilities are derived from the UKPDS trial, which focused exclusively on type 2 diabetes, and other non-UK sources that did not comply with the NICE reference case; a 3% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations*

**Update 2015**

**New cost-effectiveness analysis**

Original cost-effectiveness modelling was undertaken for this question. A summary is included here. Evidence statements summarising the results of the analysis can be found below. The full analysis can be found in Appendix N.

**Model structure**

The analysis was undertaken using a validated, internet-based model (IMS CORE Diabetes Model (CDM). IMS CDM is an interactive computer model developed to determine the long-term health outcomes and economic consequences of interventions for type 1 or type 2 diabetes mellitus. Separate transition probabilities and management strategies are used for each type where data exist, facilitating running diabetes type-specific analysis. IMS CDM has been widely used and validated against real-life clinical and epidemiological data.

It simulates diabetes progression using a series of 17 interlinked, inter-dependent sub-models which simulate the following diabetes complications: angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer, amputation and non-specific mortality. Each of these sub-models is a Markov model which uses time-, state- and diabetes type-dependent probabilities that have been derived from published sources. Interaction between the individual complication sub-models is mediated through the use of Monte Carlo simulation using tracker variables, allowing future events to be determined by patient history; thus overcoming the "memoryless" nature of Markov models., [537]

**Model comparators**

The following long-acting insulin regimens were compared against each other:

- Insulin detemir (once daily)

- Insulin detemir (twice daily)

- Insulin glargine (once daily)

- Insulin degludec (once daily)

- Insulin NPH (once daily)

- Insulin NPH (twice daily)

- Insulin NPH (four times daily).

The daily dose was assumed to be the same for all comparators (24 units). This dose would be given in divided doses for comparators with higher dosing frequency (twice or four times daily). This was examined in a sensitivity analysis, where the daily dose was set to 20 units.

**Analysis**

A cohort of type 1 diabetes patients with defined demographic and racial characteristics reflecting the young adult type 1 diabetes population in the UK was used in the base case analysis. Lifetime horizon was used in the analysis. Health outcomes and costs are discounted at an annual rate of 3.5%. These are used to calculate the net monetary benefit (NMB) associated with the different long-acting insulin regimens. The analysis was undertaken from the perspective of the UK NHS and Personal Social Services (PSS).

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Two outcomes were used to characterise treatment effectiveness: reduction in HbA1c and number of sever/major hypoglycaemic events. Relative treatment effects were based on the NMA of the clinical evidence identified in the systematic review undertaken for the guideline. For details of the NMA methods and results, see section 9.2.1.3 and Appendix M.

The mean change in HbA1c achieved using each long-acting insulin regimen was applied to the baseline HbA1c level obtained from the NDA data (8.6%). The number of severe/major hypoglycaemic events associated with the use of each long-acting insulin regimen was calculated from the NMA. These can be found in Table 89, Section 9.2.1.3.

The IMS CDM default inputs for costs, utilities and transition probabilities were validated with the GDG members and, if more relevant/better quality evidence was identified, updated. A list of model parameters is reported in the economic appendix N. Treatment-specific costs that were likely to differ among the comparator insulin regimens included the costs of the long-acting insulin and the needles. The cost of monitoring, nurse time and other consumables are likely to be either the same or their differences are negligible regardless of the long-acting insulin or insulin regimen used. Hence, these costs were not included in the analysis.

**Summary of results**

The base case probabilistic analysis results show that insulin detemir (twice daily) is the most clinically effective, with the highest mean QALYs gained over life-time horizon (see Table 93). It was the also the optimal choice in terms of cost-effectiveness, offering the highest NMB compared with all other long-acting insulin regimens. Insulin glargine (once daily) ranked second.

**Table 93: Base case probabilistic analysis results**

| Insulin | Costs (mean per patient)[a] | QALYs (mean per patient)[b] | NMB[c] | Rank[d] |
|---|---|---|---|---|
| Degludec (once daily) | £44,276 | 10.997 | £175,664 | 6 |
| Detemir (once daily) | £41,881 | 11.02 | £178,479 | 4 |
| Detemir (twice daily) | £41,398 | 11.098 | £180,562 | 1 |
| Glargine (once daily) | £41,087 | 11.051 | £179,933 | 2 |
| NPH (four times daily) | £42,941 | 10.753 | £172,119 | 7 |
| NPH (once daily) | £40,516 | 10.941 | £178,304 | 5 |
| NPH (twice daily) | £40,573 | 10.985 | £179,127 | 3 |

(a) Discounted life-time costs per patient
(b) Discounted life-time quality-adjusted life years (QALYs) per patient
(c) Net monetary benefit calculated at a threshold of £20,000 per QALY gained
(d) Ranked in descending order according to NMB

The deterministic base case analysis results (Table 94) showed the same ranking. When the ICERs were calculated, insulin detemir (twice daily) had an ICER of £6,617 per QALY gained compared with insulin glargine (once daily).

**Table 94: Base case deterministic anlysis results**

| Insulin | Costs (mean per patient)[a] | QALYs (mean per patient)[b] | NMB[c] | Rank[d] |
|---|---|---|---|---|
| Degludec (once daily) | £46,955 | 12.358 | £200,205 | 6 |
| Detemir (once daily) | £43,976 | 12.38 | £203,604 | 4 |
| Detemir (twice daily) | £43,296 | 12.484 | £206,384 | 1 |
| Glargine (once daily) | £42,962 | 12.427 | £205,578 | 2 |
| NPH (four times daily) | £46,402 | 12.091 | £195,418 | 7 |

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| Insulin | Costs (mean per patient)[a] | QALYs (mean per patient)[b] | NMB[c] | Rank[d] |
|---|---|---|---|---|
| NPH (once daily) | £42,629 | 12.294 | £203,251 | 5 |
| NPH (twice daily) | £42,925 | 12.34 | £203,875 | 3 |

(e) Discounted life-time costs per patient
(f) Discounted life-time quality-adjusted life years (QALYs) per patient
(g) Net monetary benefit calculated at a threshold of £20,000 per QALY gained
(h) Ranked in descending order according to NMB

In relation to the frequency of administration, twice-daily regimens appeared to be more cost effective compared with once-daily regimen. Twice-daily insulin detemir had higher NMB compared with the once-daily regimen. Similarly, twice-daily regimen of insulin NPH had a higher NMB compared with the once-daily option.

The model results were tested in a wide range of sensitivity analyses which showed that the optimal choice (insulin detemir twice daily) was the most cost effective at the £20,000 per QALY gained threshold in all analyses.

This original economic analysis utilises reduction in HbA1c as one of two main clinical outcome measures. HbA1c is an intermediate outcome measure, but it is considered to be a reliable proxy measure with validated links to clinical outcomes. It has to be highlighted that this analysis models the progression of type 1 diabetes and its complications in the UK type 1 diabetes adult population, so its results cannot be extrapolated to the paediatric population or other groups not covered by the guideline scope.

### 9.2.1.5 Evidence statements

**Clinical**

**Degludec versus glargine**

Moderate and Low quality evidence, mostly from individual studies, showed no clinically important benefit of degludec over glargine for any of the outcomes assessed. These were:

- HbA1c (less than or equal to 6 months and more than 6 months)
- Body weight reduction (less than or equal to 6 months and more than 6 months)
- Number of people experiencing episodes of severe hypoglycaemia (less than or equal to 6 months and more than 6 months)
- Quality of Life: SF-36 physical and mental component (less than or equal to 6 months)
- Serious adverse events (less than or equal to 6 months and more than 6 months)
- Injection site reactions (less than or equal to 6 months)

**Detemir versus glargine**

Low quality evidence from a single study showed a clinically important benefit of detemir over glargine for the following outcomes:

- Number of people experiencing severe symptomatic hypoglycaemia (less than or equal to 6 months)

Moderate quality evidence, from one large study, showed a clinically important benefit of glargine over detemir for the following outcomes:

- Number of people with injection site reactions (more than 6 months)

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Moderate and Low quality evidence, all from individual studies, showed no clinically important benefit of detemir over glargine for the following outcomes:

- HbA1c (less than or equal to 6 months and more than 6 months)
- Major hypoglycaemic episodes/patient/year (more than 6 months)
- Body weight reduction (less than or equal to 6 months and more than 6 months)

**Detemir versus NPH**

The evidence showed a clinically important benefit of detemir over NPH for the following outcomes:

- Body weight reduction at less than or equal to 6 months (5 studies, Very low quality evidence) and at more than 6 months (1 study, Low quality evidence).
- Number of people experiencing episodes of major hypoglycaemia at less than or equal to 6 months (7 studies, Very low quality evidence) and at more than 6 months (3 studies, Low quality evidence)
- The number of episodes of major hypoglycaemia at less than or equal to 6 months (1 study, Very low quality evidence).
- Episodes of severe hypoglycaemia at less than or equal to 6 months (1 study, Low quality evidence)

Very low quality evidence from two studies showed a clinically important benefit of NPH over detemir for the following outcomes:

- Number of people with injection site reactions (more than 6 months)

Low and Very low quality evidence showed no clinically important benefit of detemir over glargine for the following outcomes:

- HbA1c at less than or equal to 6 months (8 studies and 2 individual studies that could not be included in the main meta-analysis) and at more than 6 months (3 studies and 1 additional study that could not be included in the main meta-analysis)
- Body weight reduction at less than or equal to 6 months (1 study that could not be included in the main meta-analysis) and at more than 6 months (2 individual studies)

**Detemir versus NPH - heterogeneity**

There was significant heterogeneity between trials for the outcome of HbA1c at less than or equal to 6 months and more than 6 months in the meta-analysis for detemir versus NPH. When only studies that used the current clinical practice regimen were included in the meta-analysis, the significant heterogeneity disappeared. However the effect size and 95% CI hardly changed.

There was visible heterogeneity between trials for the outcome of major hypoglycaemia at less than or equal to 6 months and more than 6 months in the meta-analysis for detemir versus NPH. When only studies that used the current clinical practice regimen were included in the meta-analysis, the data still looked heterogeneous. However the effect size and 95% CI dramatically changed from a statistically significant benefit of Detemir at 6 months, to NS difference between the groups.

**Glargine versus NPH**

The evidence showed a clinically important benefit of glargine over NPH for the following outcomes:

- HbA1c at more than 6 months (but this was compared with NPH 4 times/day which is not a clinically relevant regimen; one study, High quality evidence).
- Severe hypoglycaemia at less than or equal to 6 months (7 studies, Very low quality evidence).
- Injection site pain at less than or equal to 6 months (1 study, Very low quality evidence).

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The evidence showed no clinically important benefit of glargine over NPH for the following outcomes:

- HbA1c reduction (7 studies, Low quality evidence) and final values (1 study, Low quality evidence) at less than or equal to 6 months, and reduction at more than 6 months (1 study, Very low quality evidence).

- Serious hypoglycaemia episodes/patient/month at less than or equal to 6 months (1 study, Very low quality evidence), severe hypoglycaemia episodes (1 study, High quality evidence) and severe hypoglycaemia events/100 patient days (1 study Very low quality evidence) at more than 6 months.

- Change in body weight at less than or equal to 6 months and more than 6 months (1 study, Very low quality evidence and 1 study, Moderate quality evidence)

- QoL: WED, DTSQ, and ADDQoL at less than or equal to 6 months (single studies of low and Very low quality evidence).

- Injection site reactions at less than or equal to 6 months (3 studies, Very low quality evidence) and at more than 6 months (1 study, Very low quality evidence)

**Glargine versus NPH - heterogeneity**

There was significant heterogeneity between trials for the outcome of severe hypoglycaemia at less than or equal to 6 months in the meta-analysis for glargine versus NPH. When only studies that used the current clinical practice regimen were included in the meta-analysis, the significant heterogeneity disappeared and the results were based on 2 studies. However, the effect size and 95% CI drastically changed from a statistically significant benefit of glargine, to NS difference between the groups at less than or equal to 6 months.

**Degludec versus detemir**

Moderate quality evidence from a single small study showed that there was no clinical benefit of degludec over detemir at less than or equal to 6 months for the outcomes of:

- Number of people experiencing episodes of severe hypoglycaemia

- Number of people with adverse events (adverse events)

- Number of people with serious adverse events (serious adverse events)

9.2.1.6    **Economic**

- Five cost-utility analyses found that insulin detemir was cost effective compared with NPH (ICERs: £2,500, £3,443, £9,526, £12,989 and £19,285 per QALY gained). These analyses were assessed as directly or partially applicable with potentially serious limitations.

- Another cost-utility analysis found that insulin detemir was not cost effective compared with NPH (ICER: £206,488 per QALY gained). This analysis was assessed as partially applicable with minor limitations.

- Four cost-utility analyses found that insulin glargine was either dominant or cost effective compared with NPH (ICERs: £3,496 - £4,978, £3,189 - £9-767 and £10,903 per QALY gained). These analyses were assessed as directly or partially applicable with very serious limitations.

- Another cost-utility analysis found that insulin glargine was not cost effective compared with NPH (ICER: £46,829 per QALY gained). This analysis was assessed as partially applicable with minor limitations.

- One cost-utility analysis found that insulin detemir was dominant (less costly and more effective) over insulin glargine. This study was assessed as partially applicable with potentially serious limitations.

- One original cost utility analysis found that insulin detemir (twice daily) was cost effective compared with insulin glargine (once daily), insulin detemir (once daily), insulin degludec (once daily), insulin NPH once, twice or four times daily for people with type 1 diabetes. This analysis is directly applicable, with potentially serious limitations

**9.2.1.7 Review question: In adults with type 1 diabetes, is once-daily basal insulin more effective than twice-daily basal insulin for optimal diabetic control?**

For full details see review protocol in Appendix C.

**Table 95: PICO characteristics of review question**

| Population | Adults with type 1 diabetes. |
| --- | --- |
| | • Adult is defined as aged over 18 years |
| Intervention | Basal/long-acting insulin given once/day: detemir, degludec, degludec/aspart, glargine, NPH<br><br>Note: only UK licensed interventions and doses will be considered |
| Comparison | Basal/long-acting insulin given twice/day: detemir, degludec, degludec/aspart, glargine, NPH<br><br>Note: only UK licensed interventions and doses will be considered |
| Outcomes | • HbA1c<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported<br>• Quality of life<br>• Adverse events<br>• Adherence |
| Study design | • RCTs, observational studies (prospective cohort studies)<br>• Unit of randomisation: individual patient |

**9.2.1.8 Clinical evidence**

One study has been included in this review. [418] Evidence from this is summarised in the clinical evidence summary below (Table 97). See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix I and exclusion list in Appendix K.

We searched for randomised trials and prospective cohort studies assessing effectiveness of:

- Once-daily basal insulin care compared with twice-daily basal insulin care for optimal diabetic control in adults with type 1 diabetes (Table 96).

One parallel randomised trial [418] was identified. This trial included adults with type 1 diabetes mellitus and used injections detemir insulin, with bolus doses of insulin aspart (aspart) given three times daily at meal times. The insulin injections were given at bed time for the once-daily regimen and at breakfast and bed time for the twice-daily regimen.

Outcomes reported include:

- HbA1c

- Hypoglycaemia

Included study did not report on the following outcomes:

- Adherence

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- Adverse events
- Quality of life (QoL)

For the purpose of this review, the follow-up periods for the outcomes reported have been grouped into less than or equal to 6 months and more than 6 months.

**Table 96: Summary of studies included in the review –long-acting insulin once daily versus twice daily**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| LE FLOCH 2009[418] | Once-daily (at bedtime) versus twice-daily (before breakfast and at bed time) injections of detemir, with bolus doses of insulin aspart (aspart) given three times daily at meal times. | 512 participants with insulin treated type 1 diabetes (n=250, once-daily detemir ; n=262, twice-daily detemir) | 4 months | HbA1c Hypoglycaemia | Initial doses of detemir were to equal previous basal insulin doses, either injected at bed time (once-daily group) or half before breakfast and half at bedtime (twice-daily group). Total insulin doses were similar with once daily and twice-daily detemir (62 [SD 31] versus 64 SD 29 units/day, respectively) but detemir doses were lower with once-daily dosing (29 [SD 18] versus. 20 units/day). |

**Table 97: Evidence summary table: Once-daily basal insulin versus twice-daily basal insulin (less than or equal to 6 months follow-up)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000 patients) |
|---|---|---|---|---|---|
| HbA1c (%) | 1 study (n=520) | No serious imprecision | HIGH | MD 0.12 higher (0.01 lower to 0.25 higher) | -0.5% |
| Hypoglycaemia (events per patient per 14 days) | 1 study (n=520) | No serious imprecision | HIGH | MD 0.21 lower (0.46 lower to 0.04 higher) | 24 events |

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#### 9.2.1.9 Economic evidence

**Published literature**

No relevant economic evaluations were identified.

**New cost-effectiveness analysis**

Original cost-effectiveness modelling was undertaken for this question. A summary is reported in Section 9.2.1.3. The full analysis can be found in Appendix N.

#### 9.2.1.10 Evidence statements

**Clinical**

**Once-daily basal insulin (long-acting) versus twice-daily basal insulin**

**HbA1c (%) – less than or equal to 6 months follow-up -** High quality evidence from a single study showed no clinically important difference between once-daily basal insulin compared with twice-daily basal insulin for HbA1c at less than or equal to 6 months.

**Hypoglycaemia (events per patient per day) –** less than or equal to 6 months follow-up - High quality evidence from a single study showed no clinically important difference between once-daily basal insulin compared with twice-daily basal insulin for reduction in hypoglycaemia at less than or equal to 6 months.

**Economic**

No relevant economic evaluations were identified.

One original cost utility analysis found that twice-daily regimens were cost effective compared with once-daily regimens of the same insulin (insulin detemir and NPH) for people with type 1 diabetes. This analysis is directly applicable, with potentially serious limitations.

**9.2.1.11**   **Recommendations and link to evidence**

| | |
|---|---|
| | 60. Offer multiple daily injection basal-bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. [new 2015]<br><br>61. Do not offer non-basal-bolus insulin regimens for treating adults newly diagnosed with type 1 diabetes. [new 2015]<br><br>62. Offer twice-daily insulin detemir as basal insulin therapy for adults with type 1 diabetes. [new 2015]<br><br>63. Consider, as an alternative basal insulin therapy for adults with type 1 diabetes:<br><br>  • an existing insulin regimen being used by the person that is achieving their agreed targets<br><br>  • once-daily insulin glargine if insulin detemir is not tolerated or if twice-daily basal insulin injection is not acceptable to the person. [new 2015]<br><br>64. For guidance on the use of continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes, see **Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus** (NICE technology appraisal guidance 151). [new 2015] |
| **Recommendations** | |
| Relative values of different outcomes | When considering the use of different insulin regimens in type 1 diabetes, impact on clinical outcomes were considered in the following order of importance:<br><br>Improvement in glycaemic control - assessed by:<br>• Reduction in HbA1c . Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications.<br>• Reduction in the incidence of hypoglycaemia. Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes, and an obstacle to improved control. Any therapy that achieves an improvement in glycaemic control without producing hypoglycaemia would be beneficial to patients with diabetes, in particular:<br>  o Reduction in incidence of severe hypoglycaemia (requiring help from 3rd party for correction), which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes.<br>  o Reduction in the incidence of nocturnal hypoglycaemia.<br><br>Adverse events - the literature was reviewed for any incidence of neoplastic disease associated with the use of long-acting insulins.<br><br>Incidence of diabetic ketoacidosis (DKA) - the literature was reviewed to see if any particular choice of insulin regimen was associated with an increased incidence of DKA.<br><br>Quality of life - the benefits gained from improvements in glycaemic control with a particular insulin regimen may be outweighed by the need to adhere to an insulin |

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| | regimen requiring an increased frequency of injections.

Injection site issues - associated with choice of insulin therapy.

Impact on weight - initiation and intensification of insulin-based therapies are associated with increases in weight. The literature was reviewed to see if weight gain was associated with any particular choice of insulin therapy.

The following long-acting insulins were considered by the GDG review panel, with their impact on clinical outcomes, compared with each other:
- Detemir (once or twice daily)
- Glargine (once daily)
- Degludec (once daily)
- Neutral Protamine Hagedorn (NPH) insulin (once daily, twice daily or four times daily) |

| Trade-off between clinical benefits and harms | A network meta-analysis was conducted as part of the GDG's review to allow comparison of the effectiveness of 4 different long-acting insulins (detemir, glargine, degludec, NPH) and their different frequencies of administration. The network meta-analysis allowed comparison of outcomes from multiple pair-wise insulin studies. It was undertaken by the GDG because data available from other studies and meta-analyses did not allow sufficient comparison of clinical outcomes with the use of currently available insulins. This meta-analysis formed a network of evidence to assess the critical outcomes of glycaemic control (HbA1c outcomes) and severe/major hypoglycaemia.

In the network meta-analysis, the mean change in HbA1c from baseline was estimated for each regimen in the network. The clinical effectiveness estimate as measured by the cahnge in HbA1c for each of the basal insulin regimens compared with insulin NPH (twice daily) were as follows (results given as mean difference [lower 95% credible interval to upper 95% credible interval]):
Once- or twice-daily detemir (-0.212 [-0.565 to 0.170]) % HbA1c
Twice-daily detemir (-0.164 [-0.273to -0.048]) %
Once-daily glargine (-0.104 [-0.335 to 0.138]) %
Once-daily detemir (-0.076 [-0.274 to 0.130])%
Once- or twice-daily NPH (-0.057 [-0.312 to 0.205) %
Once-daily degludec (-0.032 [-0.308 to 0.255]) %
Once-daily NPH (0.039 [-0.248 to 0.332])%
Four times a day NPH (0.310 [0.022to 0.622])%

Baseline hypoglycaemia event rate for insulin NPH (twice daily), the network comparator, calculated as a weighted average from the included trials was 0.46 events per person year. The rate ratios of sevre/major hypoglycaemic events for the insulin regimens compared with insulin NPH (twice daily) as obtained from the NMA are (results given as rate ratio [lower 95% credible interval – upper 95% credible interval]):
- Once- or twice-daily detemir (1.04 [0.02 to 54.47]
- Twice-daily detemir (1.08 [0.02 to 62.97])
- Once-daily glargine (1.33 [0.02 to 101.20])
- Once-daily degludec (1.18 [0.02 to 73.12])
- Once-daily NPH (1.63 [0.03 to 94.43))
- Once-daily detemir (0.96 [0.54 to 1.74]) |

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- Once- or twice-daily NPH (0.63 [0.01 to 36.24])

Insulin NPH (four times daily) was not included in the network meta-analysis of severe/major hypoglycaemia events, and its event rate was thus considered to be the same as that for NPH twice daily when incorporated in the economic model.

None of the insulin regimens achieved significance for improvement in severe/major hypoglycaemia rates compared with insulin NPH (twice daily). The GDG noted that wide confidence intervals for severe/major hypoglycaemia rates were reported in individual study outcomes as well as very wide credible intervals around the mean estimates from the NMA, and therefore some uncertainty remains regarding the insulin ranking for impact on severe/major hypoglycaemia.

The conclusions from the basal insulin NMA for improvement in glycaemic control and severe hypoglycaemia outcomes is that of the specified frequency insulin regimens, twice-daily detemir was the most clinically effective basal insulin choice for improvement in HbA1c and in the rate of severe/major hypoglycaemia, though with much more uncertainty for the hypoglycaemia outcome.

Twice-daily detemir use was associated with the highest annualised rate of survival over the 80 year time horizon in the economic model.

No difference in body weight change was noted in trials comparing degludec with glargine (Birkeland 2011, Heller 2012). Body weight change was less with detemir use when compared with NPH outcomes (Hermansen 2004, Hoem 2004, Russell-Jones 2004, Zachariah 2011).

Assessment with SF-36 surveys reported no difference in physical assessments of quality of life but better mental outcomes were reported with degludec users (Home 2012).

Fewer injection site reactions were reported with glargine use in trials comparing outcomes with detemir (Heller 2009), and fewer injection site reactions were also reported with NPH in comparison to detemir (Standl 2004, Leeuw 2005), although these findings did not achieve significance. No significant differences in injection site reactions were reported in comparisons between glargine and NPH (Pieber 2000, Ratner 2000, Fulcher 2006), although more pain at the injection site was reported with glargine use compared with NPH (Raskin 2000, Ratner 2000).

No RCT data were available regarding neoplastic disease outcomes or the incidence of DKA associated with basal insulin choice.

**Once- versus twice-daily outcomes:**

It has been suggested that twice-daily basal rate insulin injection regimens might be associated with improvement in HbA1c and a reduction in the risk of nocturnal hypoglycaemia (Ashwell 2006), although one study has suggested that overall incidence of hypoglycaemia might be increased with a twice-daily basal insulin regimens (Le Floch 2009). Increased frequency of severe hypoglycaemia was noted with twice-daily NPH regimens compared with once-daily regimens.

It was recognised by the GDG that insulin regimens requiring a greater number of insulin injections might have a negative impact on quality of life. However, this was not demonstrated in the Diabetes Control and Complications Trial , nor is it found in

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| | |
|---|---|
| | studies on structured education utilising flexible insulin regimens. The GDG also recognised that the burden of an increased number of injections may be counterbalanced by an improvement in blood glucose control, increased lifestyle flexibility regarding meal timing, and increased confidence in managing insulin regimens. |
| Economic considerations | Four papers were available for review of cost-effectiveness analyses of the basal insulin regimens (Valentine 2006, Cameron 2009, Golin 2013, Iwamoto 2013). However, an original cost-effectiveness analysis of basal insulin regimens was undertaken using the IMS-CORE diabetes model.<br><br>No relevant economic analyses were identified comparing once-daily versus twice-daily basal insulin regimen costs. This question was covered by the original insulin model developed for this guideline. The GDG made the assumption that in once versus twice-daily regimens, the overall daily dose of insulin was likely to be similar. The cost of an individual insulin was therefore unlikely to be substantially different for once versus twice-daily basal regimens, and extra costs would arise from the need for extra injection needles: the cost of the needles was assumed to be £0.11 (weighted average cost of needles) for the economic model.<br><br>The IMS-CORE diabetes model uses a structure of 17 Markov sub-models that simulate the progression of complications from diabetes. The model has been extensively validated and can be used to explore the economic value of interventions over the course of the disease. Economic modelling is based on the benefits of lowering HbA1c mediated through a reduction in long-term complications, and on the short-term costs by reduction in severe hypoglycaemia.<br><br>The model considered the type 1 diabetes population in the UK utilising data from the National Diabetes Audit. The mean age of this population was 43 years old at entry into the model, with mean duration of diabetes of 16.92 years and baseline HbA1c of 8.6 %, with baseline complication rate taken to be zero, with the exception of stroke, angina for which we had data for the general UK population and neuropathy (as per baseline risk in DCCT study). The impact of varying basal insulin regimens on clinical outcomes was assessed over a lifetime horizon for calculation of costs and QALYs considered from a UK NHS perspective.<br><br>The model showed that insulin detemir (twice daily) is the most clinically effective, with the highest mean QALYs gained over life-time horizon (11.098 QALYs). It was also the optimal choice in terms of cost-effectiveness, offering the highest net monetary benefit (NMB) compared with all other long-acting insulin regimens. insulin glargine (once daily) came second in terms of ranking by NMB.<br><br>The NMB rankings for each of the basal insulin regimens were as follows, where the highest in ranking is the optimal strategy:<br><br>• Twice-daily detemir<br>• Once-daily glargine<br>• Twice-daily NPH<br>• Once-daily detemir<br>• Once-daily NPH<br>• Once-daily degludec<br>• Four times daily NPH<br><br>Importantly, the GDG recognised that twice-daily basal insulin regimens were more cost-effective in the long-term despite the need for increased outlay, due to their greater impact on clinical outcomes in adults with type 1 diabetes.<br><br>The model results were tested in a wide range of sensitivity analyses which showed |

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| | that the optimal choice (insulin detemir twice daily) was the most cost effective at the £20,000 per QALY gained threshold in almost every sensitivity analysis performed. |
|---|---|
| | Current insulin analogues (glargine and detemir) are due to come off patent in late 2014/early 2015. However, the magnitude of the change in their prices is still unknown and thus, it is difficult to assess how this would impact their relative cost effectiveness. |
| | Insulin degluded is currently priced at a much higher level than both insulin detemir and insulin glargine with no evidence of improved effectiveness, and hence, it is currently dominated by both of them. |
| Quality of evidence | Only UK licensed long-acting insulin preparations were considered in the analysis, and only clinical outcomes from randomised controlled trials in adults with type 1 diabetes were reviewed by the GDG. Some study data was not in a suitable format for inclusion in the meta-analyses, and was assessed separately in GRADE. |
| | Impact of choice of insulin on glycaemic control (measured by HbA1c) and incidence of severe hypoglycaemia were assessed by the meta-analysis, with no studies of <4 weeks duration included in the meta-analysis. Although choice of rapid-acting insulin differed in some of the studies compared for the meta-analysis, the comparator arm within each individual study used the same short-acting insulin regimens and the only variable was the choice of basal insulin. |
| | Available evidence for comparison of outcomes between degludec and glargine was of Moderate to Low quality at serious risk of bias (Birkeland 2011, Home 2012, Heller 2012, Bode 2013). |
| | Available evidence for comparison of outcomes between detemir and glargine was of Moderate to Very low quality evidence at serious risk of bias (Heller 2009, Renard 2011). |
| | Available evidence for comparison of outcomes between detemir and NPH was of Low to Very low quality evidence at serious to very serious risk of bias (Hermansen 2001, Vague 2003, Hermansen 2004, Home 2004, Russell-Jones, 2004, Standl 2004, Leeuw 2005, Kolendorf 2006, Bartley 2008, Zachariah 2011). |
| | Available evidence for comparison of outcomes between glargine and NPH was of High to Very low quality evidence, with some evidence at no serious risk of bias (Porcellatti 2004) but other studies at very serious risk of bias (Pieber 2000, Raskin 2000, Ratner 2000, Rosenstock 2000, Fulcher 2005, Home 2005, Bolli 2009, Chatterjee 2007). |
| | Little published RCT evidence that met the GDG's inclusion criteria was available for:<br>• Degludec versus NPH – No conference abstracts available<br>• Degludec versus detemir – No conference abstracts available<br>• Detemir versus glargine – No conference abstracts available<br>• Degludec versus glargine – one conference abstract available but authors did not respond to request for follow-up data |
| | Evidence for comparison of once versus twice-daily basal insulin regimens consisted of one parallel RCT and two cross-over randomised RCTs of High to Very low quality with no serious to serious risk of bias (Stades 2002, Ashwell 2006, Le Floch 2009 ). |
| | The economic evidence was assessed as directly or partially applicable with either minor, potentially serious or very serious limitations. |

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| Other considerations | The currently available evidence reviewed by the GDG had little RCT clinical outcome data for insulin regimens using twice-daily glargine in adults with type 1 diabetes. No subsequent economic analyses investigating the cost-effectiveness of twice-daily glargine could therefore be undertaken, and there is currently no available literature reporting the cost effectiveness of twice-daily glargine regimens. The GDG made its recommendation for twice-daily detemir based on RCT clinical outcome evidence and available economic analyses; however, the clinical and economic outcomes versus twice-daily glargine remain unknown and the GDG were unable to comment on whether this regimen is more effective in improving clinical outcomes than twice-daily detemir.

The GDG were unable to make a full assessment of degludec as there is currently insufficient data regarding its clinical effectiveness in comparison to other insulin regimens. |

**65. Discuss and respect cultural preferences in agreeing the insulin regimen for an adult with type 1 diabetes. [2004]**

#### 9.2.1.12 Research recommendations

12. **As background insulins with different (usually longer) action profiles are developed, research will be required to determine how they are best used in structured education programmes, particularly into the need for dose adjustment for flexible lifestyles, for example intermittent exercise or alcohol consumption; their ability to improve clinical outcomes and their long term safety data and cost effectiveness compared with currently recommended regimens.**

13. **Research is required to look at the impact of different intensities of glycaemic control soon after diagnosis (for example inpatient intravenous insulin management versus outpatient multiple daily dose insulin injection therapies) on long-term outcomes in adults with type 1 diabetes and whether selection of basal-bolus insulin regimens at diagnosis might produce long-term benefits through improved glucose control soon after diagnosis.**

### 9.2.2 Rapid-acting insulin

An insulin with a fast onset, high peak and rapid offset of action would be expected to provide better post-meal glucose control with less risk of hypoglycaemia later, especially at night, and be effective if given at the time of eating, rather than slightly before eating, as recommended for current rapid-acting insulins. Newer insulin analogues are therefore being designed to achieve faster onset, higher peak and shorter action of the insulin, as this would be expected to minimise both the rise in plasma glucose after eating and achieve the other targets.[319] The rapid-acting insulin analogues, insulins aspart, lispro and glulisine, are popular but remain more expensive than older insulins. Meanwhile, some insulin users detect subtle differences between different insulins.

#### 9.2.2.1 Review question: In adults with type 1 diabetes, which are the most effective rapid-acting insulins for meal times: analogues versus human (intermediate NPH), for optimal diabetic control?

For full details see review protocol in Appendix C.

**Table 98: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
| --- | --- |
| Intervention/s | Rapid-acting insulins |

Update 2015

| **Comparison/s** | Each other |
|---|---|
| **Outcomes** | Outcomes<br><br>• HbA1c (continuous)<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported)<br>• Quality of life – measured by DQoL or any measure used in the studies retrieved (continuous)<br>• Adverse events – Cancer (dichotomous)<br>• Injection site issues<br>• Weight gain/loss<br>• DKA |
| **Study design** | RCTs |

#### 9.2.2.2 Clinical evidence

We searched for randomised trials comparing the effectiveness of any of the short-acting insulins versus each other in adults with type 1 diabetes.

Twenty six studies in 28 papers[34,38,91,93,110,122,181,186-189,211,233,292,293,317,322,367,409,524,557,581,678,723 81,242,321,323] were included in the review (one study was published as 3 papers[81,321,323]); see Table 99. Evidence from the included studies are summarised in the clinical evidence summary below (Table 99). Some study data was not in a suitable format for including in the meta-analyses, and so has been included separately in GRADE. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

A Cochrane review[652] was also found which compared short-acting insulin analogues versus regular human insulins in both type 1 diabetes and type 2 diabetes. However this was used as a source of references rather than directly incorporated into this review since it was published in 2009 and new studies have been published since then, and the review also included studies that did not match our review protocol (because they included type 2 diabetes, or young people and children).

Data for the outcomes of HbA1c and severe hypoglycaemia were further analysed by performing subgroup analyses to see if there was an effect of using different basal regimens of NPH. Data for the SA insulin comparisons that used basal NPH (Lispro versus human, and Aspart versus human), were therefore divided into the following subgroups:

• NPH once/day
• NPH twice/day
• NPH mixed once or twice/day, more than twice/day, or regimen not stated.

**Outcomes**

There was no data reported in any of the studies for the following outcomes:

• Cancer
• DKA

**Subgroup analyses for heterogeneity**

For most of the drug comparisons, there was no heterogeneity between studies in the meta-analyses for the critical outcomes of HbA1c and major or severe hypoglycaemia. Where there was heterogeneity, it was not significant and it could be explained by differences in follow-up time (less than or equal to 6 months and more than 6 months).

*Update 2015*

**Table 99:  Summary of studies included in the review**

| Study | Interventionᵃ | Comparisonᵃ | Long-acting insulin used during study | Population size | Follow-up | Commentsᵇ |
|---|---|---|---|---|---|---|
| Lispro versus human insulin | | | | | | |
| PFUTZNER 1996[557] | Lispro<br><br>Regimen not mentioned | Regular Human<br><br>Regimen not mentioned | NPH<br><br>Regimen not mentioned | n=107<br>Cross-over RCT<br>Type 1 diabetes | 3 months treatment (each period of the cross-over) | |
| ANNUZZI 2001[38] | Lispro<br><br>Before meals | Regular human<br><br>Before meals | NPH<br><br>Once/day | n=85<br>Cross-over RCT<br>Type 1 diabetes | 3 months treatment (each period of the cross-over) | In both arms, patients were also taking an isocaloric diet |
| VIGNATI 1997[723] | Lispro<br><br>Before meals | Regular human<br><br>Before meals | NPH<br><br>Twice/day | n=379<br>Cross-over RCT<br>Mixed population: Type 1 diabetes/type 2 diabetes, but includes a type 1 diabetes subgroup analysis. | 2 months treatment (each period of the cross-over) | |
| GALE 2000[233] | Lispro<br><br>Before meals | Regular human<br><br>Before meals | NPH<br><br>Once/day | n=93<br>Cross-over RCT<br>Type 1 diabetes | 12 weeks treatment (each period of the cross-over) | |
| FERGUSON 2001[211] | Lispro<br><br>Before meals or mixed with NPH as a twice/day regimen | Regular human<br><br>Before meals or mixed with NPH as a twice/day regimen | NPH<br><br>Once/day or mixed with SA insulin as a twice/day regimen (% on each are not given) | n=40<br>Cross-over RCT<br>Type 1 diabetes | 12 weeks treatment (each period of the cross-over) | Insulin regimen was either a standard basal-bolus MDI regimen, or a twice/day mixed basal plus bolus regimen. Percentages not given of patients who were on each of these. |

Update 2010

| Study | Intervention[a] | Comparison[a] | Long-acting insulin used during study | Population size | Follow-up | Comments[b] |
|---|---|---|---|---|---|---|
| HOLLEMAN 1997[317] | Lispro<br><br>Before meals | Regular human<br><br>Before meals | NPH<br><br>Once/day | n=199<br>Cross-over RCT<br>Type 1 diabetes | 12 weeks treatment (each period of the cross-over) | |
| CHAN 2004[110] | Lispro<br><br>Before meals | Regular human<br><br>Before meals | NPH<br><br>Twice/day | n=199 (n=12, type 1 diabetes)<br>Cross-over RCT<br>Mixed population: type 1 diabetes/type 2 diabetes, but has done a type 1 diabetes subgroup analysis. | 12 weeks treatment (each period of the cross-over) | |
| HELLER 1999[292] | Lispro<br><br>Before meals | Regular human<br><br>Before meals | NPH<br><br>Once/day | n=165<br>Cross-over RCT<br>Type 1 diabetes | 12 weeks treatment (each period of the cross-over) | |
| ANDERSON 1997[34] | Lispro<br><br>Before meals | Regular human<br><br>Before meals | NPH or ultralente (% on each not given)<br><br>Once or twice/day (50% on each) | n=11,008<br>Cross-over RCT<br>Type 1 diabetes | 3 months treatment (each period of the cross-over) | NPH taken once/day by 50% of participants, and the other 50% took it twice/day. |
| LALLI 1999[409] | Lispro<br><br>Before meals | Regular human<br><br>Before meals | NPH<br><br>Three or four times/day (Lispro group); twice/day for most patients in RH group. | n=56<br>RCT<br>Type 1 diabetes | 1 year | Participants were near-normoglycaemia (HbA1c of 6.0-7.5%) |
| CIOFETTA 1999[122] | Lispro | Regular human | NPH | n=16<br>RCT | 3 months treatment | |

| Study | Intervention[a] | Comparison[a] | Long-acting insulin used during study | Population size | Follow-up | Comments[b] |
|---|---|---|---|---|---|---|
| | Before meals | Before meals | Once/day | Type 1 diabetes | | |
| LILLY 1994[186] | Lispro | Regular human | NPH | n=167 RCT | 1 year | Percentages not given of patients who were on once/day NPH or twice/day NPH. |
| | Before meals | Before meals | Once or twice/day (% on each are not given) | Type 1 diabetes | | |
| LILLY 1995A[187] | Lispro | Regular human | NPH | n=169 RCT | 1 year | |
| | Before meals | Before meals | Regimen not mentioned | Type 1 diabetes | | |
| LILLY 1995B[188] | Lispro | Regular human | NPH | n=98 RCT | 1 year | |
| | Before meals | Before meals | Once/day | Type 1 diabetes | | |
| LILLY 1995C[189] | Lispro | Regular human | NPH | n=1008 Cross-over RCT | 3 months treatment (each period of the cross-over) | Percentages not given of patients who were on once/day NPH or twice/day NPH. |
| | Before meals | Before meals | Once or twice/day (% on each are not given) | Type 1 diabetes | | |
| BRUNETTI 2010[93] | Lispro | Regular human | GLARGINE | n=395 RCT | 16 weeks treatment | |
| | Before meals | Before meals | Once/day | Type 1 diabetes | | |
| **Lispro versus glulisine** | | | | | | |
| DREYER 2005A[181] | Lispro | Glulisine | GLARGINE | n=683 Type 1 diabetes | 26 weeks treatment | |
| | Before meals | Before meals | Once/day | | | |
| KAWAMORI 2009[367] | Lispro | Glulisine | GLARGINE | n=267 Type 1 diabetes | 28 weeks treatment | In both arms, patients were also following an intensive diet and exercise regime |
| | Before meals | Before meals | Once/day | | | |

**Update 2015**

| Study | Intervention[a] | Comparison[a] | Long-acting insulin used during study | Population size | Follow-up | Comments[b] |
|---|---|---|---|---|---|---|
| Aspart versus human insulin | | | | | | |
| HOME 1998[322] | Aspart <br><br> Before meals | Regular human <br><br> Before meals | NPH <br><br> Once or twice/day (% on each are not given) | n=104 <br> Cross-over RCT <br> Type 1 diabetes | 4 weeks treatment (each period of the cross-over) | |
| TAMAS 2001[678] | Aspart <br><br> Before meals | Regular human <br><br> Before meals | NPH <br><br> Twice or three times/day (% on each are not given) | n=423 <br> RCT <br> Type 1 diabetes | 12 weeks treatment | Percentages not given of patients who were on twice/day NPH or three times/day NPH. |
| NIELSEN 1995[524] | Aspart <br><br> Before meals | Regular human <br><br> Before meals | NPH <br><br> Once/day | n=21 <br> Cross-over RCT <br> Type 1 diabetes | 8 weeks treatment (each period of the cross-over) | |
| BROCK 2011[91] | Aspart <br><br> Before meals | Regular human <br><br> Before meals | NPH <br><br> Twice/day | n=16 <br> Cross-over RCT <br> Type 1 diabetes | 8 weeks treatment (each period of the cross-over) | |
| RASKIN 2000A[581] | Aspart <br><br> Before meals | Regular human <br><br> Before meals | NPH <br><br> Once/day | n=882 <br> Type 1 diabetes | 6 months treatment | |
| HELLER 2004[293] | Aspart <br><br> Before meals | Regular human <br><br> Before meals | NPH <br><br> Once or twice/day (mostly once/day) | n=155 <br> Cross-over RCT <br> Type 1 diabetes | 16 weeks treatment (each period of the cross-over) | 23% (mean of two groups) of patients were taking NPH twice/day by end of the study. |
| HOME 2000/BOTT 2003/HOME 2006[81,321,323] | Aspart <br><br> Before meals | Regular human <br><br> Before meals | NPH <br><br> Once or twice/day | n=1070 (n=753 in extension) <br> RCT | 6 months treatment; plus 30 month extension | Percentages not given of patients who were on once/day NPH or twice/day NPH. |

| Study | Intervention[a] | Comparison[a] | Long-acting insulin used during study | Population size | Follow-up | Comments[b] |
|-------|------------|-----------|-------------------------------|----------------|-----------|----------|
| | | | (% on each are not given) | Type 1 diabetes | | |
| Glulisine versus human insulin | | | | | | |
| GARG 2005[242] | Glulisine<br>Before meals<br><br>Glulisine<br>After meals | Regular human<br><br>Before meals | GLARGINE<br><br>Once/day | n=860<br>RCT – 3 arms<br>Type 1 diabetes | 12 weeks treatment | |

(a)  In all studies (unless specified), the dose of the intervention and comparison long-acting insulins were titrated
(b)  In all studies that reported it, the mean baseline HbA1c varied between 6.2% and 9.0%

**Table 100: Evidence summary table: Lispro versus human insulin**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Lispro | Control value: event rate (per 1000 patients) or median value<br><br>Human |
|----------|------------------|-------------|--------------|-------------------|----------------------|
| HbA1c % (final value) - ≤6 months basal once a day | 5 | No serious imprecision | LOW | MD 0.03 lower (0.16 lower to 0.10 higher) | 7.4 |
| HbA1c % (final value) - ≤6 months basal twice a day | 1 | Serious | LOW | MD 0.1 lower (0.31 lower to 0.11 higher) | 7.9 |
| HbA1c % (final value) - ≤6 months basal mixed or not stated | 4 | Serious | VERY LOW | MD 0.05 lower (0.08 to 0.02 lower) | 8.2 |
| HbA1c % (final value) - ≤6 months GLULISINE basal insulin | 3 | No serious imprecision | LOW | MD 0.15 lower (0.31 lower to 0.01 higher) | 7.1 |
| HbA1c % (final value) - >6 months basal once a day | 1 | Very serious[b] | VERY LOW | MD 0.07 lower (0.98 lower to 0.84 higher) | 7.8 |
| HbA1c % (final value) - >6 months basal mixed or not stated | 3 | No serious imprecision | LOW | MD 0.33 lower (0.47 to 0.2 lower) | 8.2 |

**Update 2015**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Lispro | Control value: event rate (per 1000 patients) or median value<br><br>Human |
|---|---|---|---|---|---|
| Severe/major hypoglycaemia (no. of patients) | 6 | No serious imprecision | LOW | 2 fewer per 1000 (from 0 fewer to 3 fewer) | 6.6 |
| Severe/major hypoglycaemia (no. of patients) - ≤6 months basal once a day | 3 | Serious | VERY LOW | 86 fewer per 1000 (from 1 to 114 fewer) | 128 |
| Severe/major hypoglycaemia (no. of patients) - ≤6 months basal mixed or not stated | 2 | Serious | VERY LOW | 1 fewer per 1000 (from 2 fewer to 1 more) | 4.9 |
| Severe/major hypoglycaemia (no. of patients) - >6 months basal mixed or not stated | 1 | No serious imprecision | MODERATE | 0 | 0 |
| Severe hypoglycaemia (episodes) - ≤6 months basal once a day | 2 | No serious imprecision | LOW | MD 9.46 lower (17.81 to 1.11 lower) | 34 |
| Severe hypoglycaemia (episodes) - ≤6 months basal mixed or not stated | 1 | Serious | VERY LOW | MD 29 lower (61.73 lower to 3.73 higher) | 84 |
| Hypoglycaemia/minor hypo (no. of patients) ALL TRIALS (≤6 months and >6 months) | 4 | No serious imprecision | LOW | 27 more per 1000 (from 33 fewer to 93 more) | 668 |
| Hypoglycaemia/minor hypo (no. of patients) - ≤6 months | 1 | Serious | LOW | 46 more per 1000 (from 46 fewer to 162 more) | 508 |
| Hypoglycaemia/minor hypo (no. of patients) - >6 months | 3 | No serious imprecision | LOW | 8 more per 1000 (from 65 fewer to 82 more) | 816 |
| Hypoglycaemia (episodes) - ≤6 months | 1 | No serious imprecision | LOW | MD 381 lower (741.05 to 20.95 lower) | 1156 |
| Hypoglycaemia (episodes) - >6 months | 1 | No serious imprecision | MODERATE | MD 4.1 lower (5.75 to 2.45 lower) | 11.5 |
| Hypoglycaemia (episodes/month) - ≤6 months | 4 | No serious imprecision | VERY LOW | MD 0.62 lower (0.91 to 0.33 lower) | 5.8 |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference Lispro | Control value: event rate (per 1000 patients) or median value Human |
|---|---|---|---|---|---|
| Hypoglycaemia/mild hypo (episodes/patient/month) - ≤6 months | 3 | No serious imprecision | VERY LOW | MD 0.24 lower (0.64 lower to 0.16 higher) | 7.2 |
| Hypoglycaemia/mild hypo (episodes/patient/month) - >6 months | 3 | No serious imprecision | LOW | MD 0.19 lower (1.11 lower to 0.724 higher) | 3.7 |
| Nocturnal hypoglycaemia (episodes) - ≤6 months | 2 | No serious imprecision | LOW | MD 132.26 lower (187.13 to 77.39 lower) | 247 |
| Nocturnal hypoglycaemia (episodes/month) - ≤6 months | 1 | No serious imprecision | LOW | MD 1.1 lower (1.79 to 0.41 lower) | 1.8 |
| Weight, kg (final value) - ≤6 months | 4 | Very serious | VERY LOW | MD 0.36 lower (2.1 lower to 1.38 higher) | 3.7 |
| Weight, kg (final value) - >6 months | 3 | No serious imprecision | VERY LOW | MD 0.09 higher (2.37 lower to 2.55 higher) | 71.6 |
| QoL - WED score - ≤6 months | 1 | Serious | VERY LOW | MD 0.0 | 2.1 |

**Table 101: Evidence summary table: Lispro versus glulisine**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference Lispro | Control value: event rate (per 1000 patients) or median value Glulisine |
|---|---|---|---|---|---|
| HbA1c % (final value) - >6 months | 2 | No serious imprecision | MODERATE | MD 0.01 lower (0.15 lower to 0.13 higher) | 7.5 |
| Hypoglycaemia (episodes/patient-month) - >6 months | 1 | No serious imprecision | MODERATE | MD 0.07 higher (0.03 lower to 0.17 higher) | 3.9 |
| Hypoglycaemia (episodes/patient -months) - | 1 | Very serious | VERY LOW | MD 0.16 lower (0.83 lower to | 3.6 |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference

Lispro | Control value: event rate (per 1000 patients) or median value

Glulisine |
|---|---|---|---|---|---|
| >6 months | | | | 0.51 higher) | |
| Severe hypoglycaemia (episodes/patient - month) - >6 months | 1 | Serious | LOW | Mean difference 0.0 | 0.02 |
| Severe hypoglycaemia (episodes/patient - months) - >6 months | 1 | No serious imprecision | MODERATE | MD 0.01 lower (0.03 lower to 0.01 higher) | 0.03 |
| Nocturnal hypoglycaemia (episodes/patient -months) - >6 months | 1 | No serious imprecision | MODERATE | MD 0.02 lower (0.15 lower to 0.11 higher) | 0.55 |
| Injection site reactions (no. of patients) - >6 months | 1 | Very serious | VERY LOW | 9 more per 1000 (from 13 fewer to 57 more) | 32 |

**Table 102: Evidence summary table: Aspart versus human insulin**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute Difference

Aspart | Control value: event rate (per 1000 patients) or median value

Human |
|---|---|---|---|---|---|
| HbA1c % (final value) - ≤6 months basal once a day | 3 | No serious imprecision | LOW | MD 0.15 lower (0.26 to 0.04 lower) | 7.8 |
| HbA1c % (final value) - ≤6 months basal twice a day | 1 | Serious | VERY LOW | MD 0,0 | 7.0 |
| HbA1c % (final value) - ≤6 months basal mixed or not stated | 2 | No serious imprecision | LOW | MD 0.14 lower (0.21 to 0.07 lower) | 8.1 |
| HbA1c % (final value) - >6 months basal mixed or not stated | 1 | No serious imprecision | LOW | MD 0.16 lower (0.32 lower to 0 higher) | 8.3 |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute Difference Aspart | Control value: event rate (per 1000 patients) or median value Human |
|---|---|---|---|---|---|
| Severe/major hypoglycaemia (no. of patients) ALL STUDIES (≤6 months and >6 months) | 3 | Serious | VERY LOW | 20 fewer per 1000 (from 48 fewer to 13 more) | 185 |
| Severe/major hypoglycaemia (no. of patients) - ≤6 months basal mixed or not stated | 2 | Serious | LOW | 19 fewer per 1000 (from 47 fewer to 17 more) | 144 |
| Severe/major hypoglycaemia (no. of patients) - >6 months basal mixed or not stated | 1 | No serious imprecision | LOW | 25 fewer per 1000 (from 90 fewer to 56 more) | 312 |
| Hypoglycaemia/minor hypo (no. of patients) - ≤6 months basal mixed or not stated | 2 | No serious imprecision | VERY LOW | 19 more per 1000 (from 25 fewer to 70 more) | 636 |
| Hypoglycaemia/minor hypo (no. of patients) - >6 months | 1 | No serious imprecision | LOW | 41 more per 1000 (from 25 fewer to 107 more) | 823 |
| Hypoglycaemia (episodes/patient/week) - ≤6 months | 1 | No serious imprecision | LOW | MD 0.2 lower (0.3 to 0.1 lower) | 1.1 |
| QoL - DTSQ (score 0-6) - ≤6 months | 1 | No serious imprecision | MODERATE | MD 0.33 lower (0.56 to 0.1 lower) | Not reported |
| QoL - DTSQ (score 0-36) - ≤6 months basal mixed or not stated | 1 | no serious imprecision | MODERATE | MD 2.3 higher (1.29 to 3.31 higher) | 29.7 |

**Table 103: Evidence summary table: Glulisine versus human insulin**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute Difference Glulisine | Control value: event rate (per 1000 patients) or median value Human |
|---|---|---|---|---|---|
| HbA1c (change from baseline) - <6 months | 2 | No serious imprecision | Moderate | MD 0.03 lower (0.13 lower to 0.08 higher) | -0.13 |
| Severe/major hypoglycaemia (no. of patients) - <6 months | 2 | Serious | Low | 16 fewer per 1000 (from 42 fewer to 20 more) | 101 |
| Severe hypoglycaemia (episodes/patient/month) - <6 months | 1 | No serious imprecision | Moderate | MD 0.08 lower (0.2 lower to 0.04 higher) | 0.13 |
| Hypoglycaemia/minor hypo (no. of patients) - <6 months basal once a day | 2 | No serious imprecision | Moderate | 16 more per 1000 (from 25 fewer to 57 more) | 820 |
| Hypoglycaemia (episodes/patient/month) - <6 months | 1 | Very serious | Very low | MD 0.08 higher (0.41 lower to 0.58 higher) | 3.49 |
| Nocturnal hypoglycaemia (no. of patients) - <6 months | 1 | No serious imprecision | Moderate | 0 fewer per 1000 (from 54 fewer to 65 more) | 543 |
| Nocturnal hypoglycaemia (episodes/patient/month) - <6 months | 1 | No serious imprecision | Moderate | MD 0.07 lower (0.24 lower to 0.1 higher) | 0.71 |

### 9.2.2.3 Economic evidence

**Published literature**

Two studies were included with the relevant comparisons.[103] [570] These are summarised in the economic evidence profiles below (Table 104 and Table 105). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

CG15 included one study with the relevant comparison.[154] This study along with one further study[590] that met the inclusion criteria were selectively excluded in the guideline update due to the availability of more applicable evidence– these are summarised in Appendix L, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Update 2015

**Table 104: Economic evidence profile: Insulin aspart versus regular human insulin**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Cameron 2009 [103] [CAN] | Partially[a] | Minor[b] | Used IMS-CDM. This is an abridged version of a report by CADTH[104] | Saves £351 | 0.055 QALYs | Insulin aspart is dominant compared with regular human insulin | Probabilistic sensitivity analysis demonstrated a 52.3% probability that insulin aspart will be cost effective over regular human insulin at a £26K threshold. One-way sensitivity analysis maintained the insulin aspart as the dominant in all analyses except where there was no difference in HbA1c, where the ICER increased to £55,704. |

(a) *Study performed from a Canadian healthcare payer perspective*
(b) *There are discrepancies between the effectiveness data in the clinical review and economic review. However the authors explained this is due to the meta-analysis being updated over time; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trials included had short follow-up times; the report is not completely incremental as it provides the results of four pairwise simulations; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.*

**Table 105: Economic evidence profile: Insulin lispro versus regular human insulin**

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Pratoomsoot 2009 [570][UK] | Directly applicable[a] | Potentially serious limitations[b] | Used IMS-CDM. Treatment effect taken from a Cochrane Review. | Saves £1,953 | 0.105 QALYs | Insulin lispro is dominant compared with regular human insulin | Probabilistic sensitivity analysis demonstrated a 83.9% probability that insulin lispro will be cost-effective over regular human insulin at a 30K threshold. Insulin lispro was dominant over regular human insulin for all sensitivity analyses. In addition, in the base-case analysis, the probability that insulin lispro was more cost- |

| Study | Applicability | Limitations | Other comments | Incremental cost | Incremental effects | Cost effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| | | | | | | | effective than regular human insulin was higher at a £20K threshold than at £30K. |
| Cameron 2009 [103] [CAN] | Partially applicable[c] | Minor limitations[d] | Used IMS-CDM. This is an abridged version of a report by CADTH[104] | £97 | 0.006 QALYs | £15,442[e] | Probabilistic sensitivity analysis demonstrated a 46.1% probability that insulin lispro will be cost effective over regular human insulin at a £26K threshold. One-way sensitivity analysis maintained the insulin lispro was either cost-effective or dominant compared with regular human insulin except where there was no difference in HbA1c, where the ICER increased to £358,432. |

(a) Study performed from a UK NHS perspective

(b) Cohort mean age is higher than may be anticipated; a constant treatment effect of insulin over the long-term is assumed; certain sources of data come from a type 2 diabetes specific population; analysis conducted on the IMS-CDM which has its own limitations

(c) Study performed from a Canadian healthcare payer perspective

(d) There are discrepancies between the effectiveness data in the clinical review and economic review. However the authors explained this is due to the meta-analysis being updated over time; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trials included had short follow-up times; the report is not completely incremental as it provides the results of four pairwise simulations; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

(e) Due to rounding of QALYs, ICERs were not recalculated from the study, only converted into GBP.

Update 2015

**Unit costs**

In the absence of recent UK cost-effectiveness analysis for some insulin regimens, relevant unit costs are provided in Appendix Q to aid consideration of cost effectiveness.

#### 9.2.2.4 Evidence statements

**Clinical**

**Lispro versus human insulin**

Low and Very low quality evidence showed a clinical benefit of insulin lispro compared with human insulin on HbA1c at more than 6 months, in studies where the basal insulin regimen was a mixture of once or twice/day, or not stated. There was no clinical effect on HbA1c at 6 months or more than 6 months in studies in which the basal insulin was taken once a day.

Evidence that was mainly Low and Very low quality, showed a clinical benefit of insulin lispro compared with human insulin on severe hypoglycaemia when measured in terms of 'number of patients', and 'number of episodes', when the basal insulin regimen used by the studies were once/day, and at time-points less than or equal to 6 months. When the basal insulin regimen was mixed or not stated by the studies, there was clinical benefit on severe hypoglycaemia in terms of 'number of episodes' at time-points less than or equal to 6 months, but no clinical difference in terms of 'number of patients' at any time-point.

Evidence that was mainly Low and Very low quality showed that at both less than or equal to 6 months and more than 6 months there was a clinical benefit of insulin lispro compared with human insulin for the outcome of hypoglycaemia when measured in terms of 'total number of episodes'. However there was no clinical difference between the two insulins when hypoglycaemia was measured in terms of 'number of patients experiencing hypoglycaemia', 'episodes/month', 'episodes/patient/month'.

Low quality evidence showed a clinical benefit of lispro compared with human insulin for nocturnal hypoglycaemia when measured in terms of 'number of episodes' and 'episodes/month' at less than or equal to 6 months.

Low quality evidence showed no clinical difference between lispro and human insulin for final body weight at less than or equal to 6 months and more than 6 months, nor for QoL (WED score) at less than or equal to 6 months.

**Lispro versus glulisine**

Evidence that was mostly Moderate and Very low quality, and mostly from a single study, showed that there was no clinical difference between lispro and glulisine for any of the outcomes measured (HbA1c, severe hypoglycaemia, hypoglycaemia, nocturnal hypoglycaemia, and injection site reactions).

**Aspart versus human insulin**

Moderate quality evidence from a single study showed a clinical benefit of aspart compared with human insulin for QoL – DTSQ score at less than or equal to 6 months.

Evidence that was mostly Low and Very low quality evidence showed that there was no clinically significant difference between aspart and human insulin for the following outcomes: HbA1c, severe hypoglycaemia, and hypoglycaemia at both less than or equal to 6 months and more than 6 months;

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and for QoL – DTSQ score 0-6 at less than or equal to 6 months, regardless of the basal insulin regimen used by the studies.

**Glulisine versus human insulin**

Moderate, Low and Very low quality evidence mostly from single studies, showed that there was no clinical difference between glulisine and human insulin for any of the outcomes measured at less than or equal to 6 months (HbA1c, severe hypoglycaemia, hypoglycaemia, and nocturnal hypoglycaemia).

**Economic**

- One cost-utility analysis found that insulin aspart was dominant (less costly and more effective) compared with regular human insulin. This analysis was assessed as partially applicable with minor limitations.
- One cost-utility analysis found that insulin lispro was dominant (less costly and more effective) compared with regular human insulin. This analysis was assessed as directly applicable with potentially serious limitations.
- Another cost-utility analysis found that insulin lispro was cost-effective compared with regular human insulin (ICER; £15,442 per QALY gained). This analysis was assessed as partially applicable with minor limitations.

### 9.2.2.5 Recommendations and link to evidence

| Recommendations | 66. Offer rapid-acting insulin analogues injected before meals, rather than rapid-acting soluble human or animal insulins, for mealtime insulin replacement for adults with type 1 diabetes. [new 2015]<br><br>67. Do not advise routine use of rapid-acting insulin analogues after meals. [new 2015]<br><br>68. If an adult with type 1 diabetes has a strong preference for an alternative mealtime insulin, respect their wishes and offer the preferred insulin.[new 2015] |
|---|---|
| Relative values of different outcomes | Choice of rapid-acting insulin therapy was influenced by the impact of individual insulin therapies on clinical outcomes at <6 months and >6 months, specifically improvement in glycaemic control, assessed by:<br><br>• reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications, and<br><br>• reduction in the incidence of hypoglycaemia. Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes, and an obstacle to improved control. Any therapy that achieves an improvement in glycaemic control without producing hypoglycaemia would be beneficial to patients with diabetes.<br><br>When contemplating the impact of rapid-acting insulin therapies on clinical outcomes, particular focus was given to:<br><br>• Reduction in incidence of severe hypoglycaemia (requiring help from 3rd party for correction), which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. |

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- Reduction in the incidence of nocturnal hypoglycaemia.
- Adverse events; the literature was reviewed for any incidence of neoplastic disease associated with the use of rapid-acting insulins.
- Incidence of diabetic ketoacidosis (DKA); the literature was reviewed to see if any particular choice of insulin regimen was associated with an increased incidence of DKA.
- The impact of particular rapid-acting insulins on quality of life when used in individuals with type 1 diabetes.
- Injection site issues associated with choice of insulin therapy.
- Impact on weight: initiation and intensification of insulin-based therapies are associated with increases in weight. The literature was reviewed to see if weight gain was differently associated with any particular choice of rapid-acting insulin.

| | |
|---|---|
| Trade off between clinical benefits and harms | The GDG reviewed the available evidence from randomised controlled trials that compared clinical outcomes with the use of different rapid-acting insulins.<br><br>**Lispro versus rapid-acting human insulin**<br>Lispro produced a clinically significant improvement in glycaemic control (0.3% improvement in HbA1c) compared with human insulin. This benefit was sustained in studies of >6 months duration, and achieved alongside clinically significant improvements in the incidence of severe/major hypoglycaemia and nocturnal hypoglycaemia. These improvements were achieved irrespective of the choice of basal insulin used.<br>No clinically significant differences in outcomes for weight or quality of life measures were found in the comparison.<br><br>**Aspart versus rapid-acting human insulin**<br>A reduction in HbA1c, and a reduction in the incidence of both major and minor hypoglycaemia, was achieved with use of aspart compared with human insulin but the magnitude of each was not considered to be clinically significant at <6 months or at >6 months.<br>No direct comparison data for the impact of aspart therapy versus human insulin therapy on the incidence of nocturnal hypoglycaemia were available.<br>Evidence assessing impact of treatment on quality of life favoured the use of aspart over rapid-acting human insulin.<br><br>**Glulisine versus rapid-acting human insulin**<br>No data on improvement in glycaemic control were available for the comparison of glulisine therapy to rapid-acting human insulin therapy, and there was no clinically significant difference in hypoglycaemia outcomes (severe/major hypoglycaemia, minor hypoglycaemia, nocturnal hypoglycaemia).<br><br>**Lispro versus glulisine**<br>The available evidence comparing lispro use to glulisine did not demonstrate a clinically significant difference in outcomes assessing glycaemic control (improvement in HbA1c), incidence of hypoglycaemia (severe/major hypoglycaemia, minor hypoglycaemia or nocturnal hypoglycaemia) or injection site difficulties at <6 months and >6 months.<br><br>No data were reported for impact on incidence of neoplastic disease or diabetic ketoacidosis in any of the randomised controlled trials on rapid-acting insulin use. |
| Economic considerations | Two cost-utility analyses, one directly and one partially applicable, with minor limitations were considered. Both analyses used the IMS-CDM model which uses |

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HbA1c levels as a proxy to project the risk of long-term micro and macrovascular complications, amongst others, including the incidence of hypoglycaemia (mild and severe) in assessing cost-effectiveness.

One study, Pratoomsoot et al 2009, a UK cost-utility analysis with minor limitations, compared insulin lispro against regular human insulin.

- A Cochrane meta-analysis provided the difference in HbA1c between the two interventions; a reduction of 0.1% for insulin lispro over regular human insulin. Severe hypoglycaemia was recalculated from the Cochrane meta-analysis to provide rates of 21.8 per 100 patient years for insulin lispro, and 46.1 per 100 patient years for regular human insulin.

- Insulin lispro dominated regular human insulin, with a cost-saving of £1,953 and a 0.105 QALY increase over a lifetime time horizon. At a £20K per QALY threshold, there is a greater than 83.9% probability that insulin lispro is cost-effective.

- The clinical values used for HbA1c reduction and incidence of hypoglycaemia (mild and severe) in this analysis lie at, or slightly below, the lower 95% CI limit as established by the clinical evidence. As such, this analysis is representative of the best treatment effects that can be expected.

The second study, Cameron 2009, a Canadian cost-utility analysis with minor limitations, compared insulin lispro and insulin aspart against regular human insulin in two pairwise analyses.

- Their meta-analysis provided the difference in HbA1c between insulin lispro and aspart compared with regular human insulin; a reduction of 0.01% and 0.12% respectively. The relative risk of severe hypoglycaemia was 0.83 for insulin lispro and aspart compared with regular human insulin.

- Insulin lispro was cost-effective compared with regular human insulin, with an ICER of £15,442 per QALY gained. At a 26K per QALY threshold, there is a 46.1% probability that insulin lispro is cost-effective compared with regular human insulin.

- Insulin aspart was dominant compared with regular human insulin, with a cost-saving of £351 and a 0.055 QALY increase over a lifetime time horizon. At a 26K per QALY threshold, there is a 52.3% probability that insulin aspart is cost-effective compared with regular human insulin.

The clinical values used for HbA1c reduction and incidence of hypoglycaemia (mild and severe) used in this analysis are more consistent with those established from previous clinical studies than those used in Pratoomsoot et al. 2009. However, both insulin lispro and insulin aspart have a less favourable reduction in HbA1c, whilst insulin lispro has a less favourable reduction in severe hypoglycaemia risk compared with regular human insulin, than those in the results of our meta-analysis. As such, the result of this analysis is likely to be conservative and potentially underestimate the true treatment benefit.

In summary, taking these studies in the context of the differences in HbA1c and hypoglycaemia seen in our meta-analysis, it is highly likely that rapid-acting insulin analogues are cost-effective.

| | |
|---|---|
| Quality of evidence | Only UK licensed rapid-acting insulin preparations were considered in the evidence review. Clinical outcomes were assessed from randomised controlled trials (RCT) using rapid-acting insulin as part of a multiple daily injection insulin regimen; trials assessing outcomes from insulin pump studies were not included for this guideline.<br><br>**Lispro versus rapid-acting human insulin studies**<br>• 16 RCT studies compared clinical outcomes with lispro to rapid-acting human insulin (Pfutzner 1996, Anuzzi 2001, Vignati 1997, Gale 2000, Ferguson 2001, |

Holleman 1997, Chan 2004, Heller 1999, Anderson 1997, Lalli 1999, Ciofetta 1999, Lilly 1994, Lilly 1995A, Lilly 1995B, Lilly 1995C, Brunetti 2010).

- The quality of the available evidence was Very low to Moderate, and considered to be at serious to very serious risk of bias.
- 12 of the studies were <6 months duration, 4 of the studies were >6 months duration.
- 15 of the studies used NPH as the basal insulin in the regimen (between once and four times a day; twice a day in most study participants). Only 1 study used glargine and there was no evidence about use of Lispro with other basal insulins.

**Aspart versus rapid-acting human insulin**

- 7 RCT studies compared clinical outcomes with aspart to rapid-acting human insulin (Home 1998, Tamas 2001, Nielsen 1995, Brock 2011, Raskin 200A, Heller 2004, and Home 2000/Bott 2003/Home 2006).
- The quality of the available evidence was Very low to Moderate, and considered to be at serious to very serious risk of bias.
- 6 of the studies were <6 months duration, 1 study was >6 months duration.
- All 7 RCTs used NPH (once or twice a day) as the basal insulin.

**Glulisine versus rapid-acting human insulin**

- 1 RCT study compared clinical outcomes with glulisine to rapid-acting human insulin (Garg et al 2005).
- The quality of the available evidence was Low to Moderate, and considered to be at serious risk of bias.
- The study was of <6 months duration.
- The study used glargine as the basal insulin.
- No comparison of impact on glycaemic control was made in the trials.

**Lispro versus glulisine**

- 2 RCT studies compared clinical outcomes with lispro to glulisine (Dreyer et al 2005, Kawamori et al 2009).
- The quality of the available evidence was Very low to Moderate, and considered to be at serious risk of bias.
- Both studies were of 6 months duration.
- Both studies used glargine as the basal insulin for selected regimens.

The GDG noted that a comparison of lispro use versus aspart was difficult to make, as no RCT data directly comparing the two insulins was available, and the aspart studies included in the evidence review tended to be of shorter duration than the lispro studies.

The GDG considered that the available evidence was sufficient to recommend the use of rapid-acting insulin analogues over rapid-acting human insulins, and that this choice was cost-effective.

The economic evidence was assessed as partially applicable with minor or potentially serious limitations.

| Other considerations | The GDG discussed the timing of administration of rapid acting insulin for meal coverage. There is evidence that injection given 15 minutes after starting to eat a meal gives similar post prandial control to conventional human insulin given immediately before meals (Schernthaner et al, 1998) but agreed that in adults with type 1 diabetes, the advice that rapid acting analigues could routinely be given after was inappropriate. The GDG agreed that adults with type 1 diabetes should be |

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advised to take their rapid-acting insulin before meals, as it is widely accepted that this will provide improved glucose control in comparison to insulin taken during or after meals in adults with type 1 diabetes. This was based on clinical experience that adults with type 1 diabetes may take much longer than 15 minuytes to eat a meal; the suboptimal post-meal glucose profile of human soluble insulin being given immediately before meals (the prescribing advice has been to take these insulins 20 – 40 minutes before eating) and clinical experience that optimal post prandial glucose control (minimal post prandial rise and reduced risk of later hypoglycaemia) is achieved with analogue injections given about 15 minutes before eating. In making this recommendation, the GDG recognised that in some exceptional cases this guidance might not be followed (for example, individuals with gastroparesis, where carbohydrate absorption might be delayed).

Although permitted in the British National Formulary and summary of product characteristics for analogue insulins, in adults with type 1 diabetes, routine use of post-meal injection should therefore be avoided, even with rapid-acting analogues, as it is associated with high post-prandial glucose and increased risk of later hypoglycaemia.

The GDG recognised that some adults with type 1 diabetes may have a personal preference for a particular type or class of rapid-acting insulin over the recommended choice. Historically, some adults with type 1 diabetes reported that they preferred the use of animal insulin over human or analogue insulin. The GDG therefore advise that that an individual's preference for a specific rapid-acting insulin should be respected, even if this choice was against the weight of published evidence, as there is no evidence for major harm with other available fast acting insulins. However, when people are not achieving glycaemic targets with insulins other than those recommended as first line, they should be advised about the potential benefits of these.

### 9.2.2.6 Research recommendation

**14. Research is required into the optimal timing and use of rapid-acting insulin around specific meal compositions and modalities of exercise**

## 9.2.3 Mixed insulin

Although modern flexible insulin therapy mandates independent replacement of basal and meal-related insulin in order to achieve optimal glucose control and support a flexible lifestyle, regimens using a mixture of fast and intermediate acting insulin given twice a day have the attraction of fewer daily injections. The regimen uses a pre-breakfast meal injection to cover breakfast (the fast acting component) and lunch (the delayed acting, isophane insulin) and a second injection before the evening meal from which the fast acting component covers the meal and the delayed acting insulin the overnight requirement. The disadvantage of such regimens include the need for lunch to occur as predicted; frequently, for optimal control, a need for routine between meal and bedtime snacking and a high risk of inadequate overnight control but the idea of less intensive self-management of the insulin regimen remains attractive. Pre-mixed insulins are now available using analogues, as well as human insulin. Given that some people may opt for a pre-mixed insulin regimen, the GDG reviewed the evidence for mixed insulins.

### 9.2.3.1 Review question: In adults with type 1 diabetes, what are the most effective mixed insulins (degludec-aspart versus glargine versus NPH) for optimal diabetic control?

For full details see review protocol in Appendix C.

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**Table 106: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
|---|---|
| Intervention/s | • Mixed insulins<br><br>Only UK licensed interventions and doses will be considered |
| Comparison/s | • Each other<br>• Long plus short-acting insulin (basal-bolus) regimen<br><br>Only UK licensed interventions and doses will be considered |
| Outcomes | Outcomes<br>• HbA1c<br>• Hypoglycaemia<br>• Severe hypoglycaemia<br>• Nocturnal hypoglycaemia<br>• Quality of life – measured by DQoL or any measure used in the studies retrieved<br>• Adverse events – Cancer<br>• Injection site issues<br>• Weight gain/loss<br>• DKA |
| Study design | RCTs |

#### 9.2.3.2 Clinical evidence

We searched for randomised trials comparing the effectiveness of any of mixed insulins versus each other or versus a basal-bolus regimen, in adults with type 1 diabetes.

Fourteen studies[77,112,122,144,183,207,306,311,346,370,593-595,685] were included in the review; see Table 107: Summary of studies included in the review. Evidence from the included studies are summarised in the clinical evidence summary below (Table 107). Some study data was not in a suitable format for including in the meta-analyses, and so has been included separately in GRADE. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix I and exclusion list in Appendix K.

One Cochrane review[652] was found and was used as a source of references for our review, because it contained some studies that were younger age groups and were type 2 diabetes.

#### Outcomes

There was no data reported in any of the studies for the following outcomes:

• Cancer

#### Subgroup analyses for heterogeneity

Where there was heterogeneity between studies in the meta-analyses for the critical outcomes (HbA1c and major/severe hypoglycaemia), it was agreed that this would be explored using pre-specified subgroups in the protocol. These were:

• Baseline HbA1c (differences between studies in baseline HbA1c levels)
• Different doses/regimens (clinically relevant regimens)
• Elderly/older people/frailty (if there were significant differences between studies in subject ages)

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- Baseline weight (if possible, bearing in mind that some studies give BMI and some give weight in kg)
- Baseline hypoglycaemia (if this is known and there are significant differences).

**Nocturnal hypoglycaemia**

For nocturnal hypoglycaemia, a subgroup analysis of the insulins used in each study was performed. This analysis showed that the use of different types of insulins explained the heterogeneity between the studies (see Appendix J).

**HbA1c**

For HbA1c, a subgroup analysis of the insulins used in each study was performed. This analysis showed that the use of different types of insulin did not explain the heterogeneity between the studies (see Appendix J). Other pre-specified sources of heterogeneity were therefore explored, and the results are as follows:

- **Baseline** HbA1c – this was much higher for the Herz study (approximately 11%), but when the Herz study was removed from the meta-analysis, significant heterogeneity remained (that is, baseline HbA1c did not explain the differences in effects between the trials).
- **Dose/regimen** – the studies all used different basal-bolus drugs, and additionally the Fanelli and Janssen studies used different mixed insulin regimens to the other studies in the meta-analysis. The different drugs and regimens used could be one possible explanation for the heterogeneity between the trials.
- **Age of participants** – the mean age of participants in the trials included in the meta-analysis was very similar (late twenties to mid-thirties) and so this would not explain any heterogeneity between the trials.
- **Baseline weight** – baseline weight was not given for most of the studies and so it was not possible to explore this as a source of heterogeneity.
- **Baseline hypoglycaemia** - the Herz study and the Fanelli studies both excluded patients who had a history of severe hypoglycaemia, whereas the other studies in the meta-analysis did not. However, when these studies were removed from the meta-analysis, the heterogeneity still remained statistically significant.

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**Table 107: Summary of studies included in the review**

| Study | Intervention[a] | Comparison[a] | Study type and population | Follow-up | Comments |
|---|---|---|---|---|---|
| **Mixed versus basal-bolus** | | | | | |
| Human mix | | | | | |
| FANELLI 2002[207] | Basal-bolus using mixed evening treatment<br><br>Mixed insulin (Regular plus NPH) at dinner<br><br>Regular insulin at breakfast and lunch | Basal-bolus<br><br>NPH at bedtime<br><br>Regular insulin before all 3 meals. | n=22<br><br>Cross-over RCT<br><br>Type 1 diabetes | 4 months treatment | Patients with hypoglycaemia unawareness or history of severe hypoglycaemia were excluded.<br><br>Mix arm: mixed insulin given part of the insulin basal-bolus treatment |
| KHACHADURIAN 1989[370] | Patient mix: 30% human/70% NPH<br><br>Twice/day<br><br>Patients mixed in syringe, as no pre-mix available at the time. | Basal-bolus: NPH plus Human RA<br><br>NPH (Novolin N) – timing not given in paper<br><br>RA human (Novolin R) could be added if necessary. | n=78<br><br>RCT<br><br>Mixed population: 70% type 1 diabetes/30% type 2 diabetes | 12 weeks treatment | Mix arm: True mixed insulin regimen – mix given twice/day versus basal bolus treatment |
| Lispro mix | | | | | |
| CIOFETTA 1999[122] | Patient mix plus NPH<br><br>NPH at bedtime<br><br>Pre-mixes Lispro plus NPH at meals | Basal-bolus: NPH plus Human regular<br><br>NPH at bedtime<br><br>Human regular at meals<br><br><br>Basal-bolus: NPH plus Lispro<br><br>NPH at bedtime<br><br>Lispro at meals | n=24<br><br>RCT – 3 arms<br><br>Type 1 diabetes | 3 months treatment | >1 episode of severe hypoglycaemia within 6 months of study<br><br>Mix arm: mixed insulin given part of the basal-bolus treatment |
| HERZ 2002[306] | Humalog Mix 50 plus NPH<br><br>Humalog 50 = 50% Lispro/50% Lispro- protamine<br><br>NPH at bedtime | Basal-bolus: NPH plus Human soluble<br><br>NPH at bedtime<br><br>Human insulin pre-meals | n=109<br><br>Cross-over RCT<br><br>Type 1 diabetes | 12 weeks treatment<br><br>(each period | Severe hypo patients (≥2 episodes in past 3 months) were excluded.<br><br>High baseline HbA1c values (Mean 11.1%) |

| Study | Intervention[a] | Comparison[a] | Study type and population | Follow-up | Comments |
|---|---|---|---|---|---|
| | Mix50 pre-meals | | | of cross-over) | Mix arm: mixed insulin given part of the basal-bolus treatment |
| JANSSEN 2000[346] | PT MIX: 75%Lispro/25%NPL Twice/day (before meals) Patients mixed in syringe, as no pre-mix available at the time. | Basal-bolus: NPH plus Human regular SA NPH (Novolin N) Human insulin at all meals. | n=35 RCT Type 1 diabetes | 12-14 weeks treatment | Mix arm: true mixed insulin regimen – mix given twice/day versus basal bolus treatment |
| **Aspart mix** | | | | | |
| CHEN 2006[112] | BIAsp30 plus NPH NPH at bedtime (in some patients) BIAsp30 pre-meals | Basal-bolus: NPH plus Human soluble (ActRapid) NPH at bedtime ActRapid pre-meals | n=27 Cross-over RCT Type 1 diabetes | 12 weeks treatment (each period of cross-over) | Patients with diabetic complications requiring acute treatment were excluded. Mix arm: mixed insulin given part of the basal-bolus treatment |
| HIRSCH 2012B[311] | IDegAsp plus Aspart Once/day (with main meal) Aspart given at other meals. | Basal-bolus: IDet plus IAsp Detemir once/day with evening meal or at bedtime Aspart at all meals. | n=548 RCT Type 1 diabetes | 26 weeks treatment | Patients with recurrent severe hypoglycaemia or hypoglycaemia unawareness were excluded. Patients with proliferative retinopathy or maculopathy requiring treatment were excluded. Mix arm: mixed insulin given part of the basal-bolus treatment |
| TESTA 2012A[685] | LISPRO MIX or ASPART MIX Humalog25 or Novolog30 Humalog25 = 25% Lispro/75% Lispro- protamine Novolog 30 = 30% aspart/70% aspart-protamine. Twice/day | Basal-bolus: Glargine plus Glulisine Glargine once/day Glulisine at all meals. | n=82 type 1 diabetes Cross-over RCT Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis. | 12 weeks treatment | HbA1c between 7.0 and 9.0% Mix arm: true mixed insulin regimen – mix given twice/day versus Basal bolus treatment |

| Study | Intervention[a] | Comparison[a] | Study type and population | Follow-up | Comments |
|---|---|---|---|---|---|
| **Mixed versus mixed** | | | | | |
| BOEHM 2002[77] | BIAsp 30<br>Biphasic Aspart: 30% Aspart/70% Aspart-protamine<br>Twice/day (breakfast and dinner) | BHI 30<br>Biphasic human insulin: 30/70% equivalent of BIAsp<br>Twice/day (breakfast and dinner) | n=104 type 1 diabetes RCT<br>Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis. | 12 weeks treatment | - |
| CUCINOTTA 1991[144] | Actraphane 3/7<br>Actraphane = NPH plus human)<br>Timing not mentioned | Regular mix: 2/8 to 4/6<br>Human regular plus NPH mix<br>Twice/day at breakfast and dinner | n=20<br>Cross-over RCT<br>Type 1 diabetes | 4 months treatment | - |
| DUNBAR 1999[183] | PREMIX (pen)<br>Twice/day (morning and evening)<br>Patients may use different mixtures in morn and eve<br>Penmix (Novo Nordisk) 10/90%, 20/80%, 30/70%, 40/60% and 50/50% | PT MIX (ActRapid plus Human Monotard)<br>Patients continuing their usual/previous treatment | n=100 type 1 diabetes RCT<br>Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis. | 2 months treatment | - |
| ROACH 1999[595] | Lispro Mix25 and Mix50<br>AM before breakfast: Lispro mix50 (50% Lispro/50% NPL)<br>PM before dinner: Lispro mix25 (25% Lispro/75% NPL)<br>Twice/day | Human insulin Mix 50 and 30<br>Twice/day<br>AM before breakfast: Human mix50 (50% regular/50% NPH)<br>PM before dinner: Human mix30 (30% regular/70% NPH) | n=37 type 1 diabetes<br>Cross-over RCT<br>Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis. | 3 months treatment<br><br>(each period of cross-over) | HbA1c between 7.0 and 9.0% |
| ROACH 2001[594] | PT MIX: Lispro plus NPL<br>Twice/day (morning and | PT MIX: Human plus NPH<br>NPH = Humulin N | n=100 type 1 diabetes RCT | 12 months treatment | Recurrent severe hypoglycaemia patients were excluded. |

| Study | Intervention[a] | Comparison[a] | Study type and population | Follow-up | Comments |
|---|---|---|---|---|---|
| | evening) | Human = Humulin R Twice/day (morning and evening) | Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis. | | |
| ROACH 2004[593] | PREMIX (H or M) plus NPH NPH at bedtime Pre-mixes at meals High Mix = 25%Lispro/75% NPL Medium Mix = 50%Lispro/50% NPL | SELF-MIX (H or M) plus NPH NPH at bedtime Pre-mixed Lispro/NPH self-selected ratios | n=89 Cross-over RCT Type 1 diabetes | 8 weeks treatment (each period of cross-over) | >1 episode of severe hypoglycaemia within 6 months of study |

*(a)  In all studies the dose of the intervention and comparison long-acting insulins were titrated*

**Table 108: Evidence summary table: Mixed insulin (human mix) versus basal-bolus insulin (less than or equal to 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference MIX | Final value for control group Basal-bolus |
|---|---|---|---|---|---|
| HbA1c - final value (≤6 months) - True mix (twice/day versus basal-bolus) | 1 | Serious | VERY LOW | MD 0.5 higher (0.17 to 0.83 higher) | 7.0 |
| Nocturnal hypoglycaemia, episodes/patient-day (≤6 months) - Mix part of basal-bolus | 1 | No serious imprecision | LOW | MD 0.02 higher (0.01 to 0.03 higher) | 0.027 |
| Severe/major Hypoglycaemia, number of patients- Mix part of basal-bolus (≤6 months) | 1 | No serious imprecision | LOW | 0 events in each arm | 0 |
| Ketoacidosis, number of patients (≤6 months) - True mix (twice/day versus basal-bolus) | 1 | Very serious | VERY LOW | RR 4.4 (0.19 to 104.42) | 0% |

| Injection site reactions, number of patients (≤6 months) - True mix (twice/day versus basal-bolus) | 1 | Very serious | VERY LOW | 1 fewer per 1000 (from 57 fewer to 317 more) | 70 |

**Table 109: Evidence summary table: Mixed insulin (Lispro mix) versus basal-bolus insulin (less than or equal to 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br>MIX | Final value for control group<br>Basal bolus |
|---|---|---|---|---|---|
| HbA1c - final value (≤6 months) - True mix (twice/day versus basal-bolus) | 1 | Serious | VERY LOW | MD 0.5 higher (0.25 to 0.75 higher) | 6.7 |
| HbA1c - final value (≤6 months) - Mix part of basal-bolus | 3 | Serious | VERY LOW | MD 0.32 lower (0.54 to 0.11 lower) | 6.96 |
| Hypoglycaemia, episodes/patient (≤6 months) - Mix part of basal-bolus | 1 | No serious imprecision | LOW | MD 0.3 lower (1.67 lower to 1.07 higher) | 5.1 |
| Hypoglycaemia, episodes/patient/month (≤6 months) - Mix part of basal-bolus | 2 | Very serious | VERY LOW | MD 0.64 lower (2.53 lower to 1.25 higher) | 6.1 |
| Nocturnal Hypoglycaemia, number of patients (≤6 months) - Mix part of basal-bolus | 1 | No serious imprecision | LOW | 20 fewer per 1000 (from 130 fewer to 117 more) | 651 |
| Severe/major Hypoglycaemia, number of patients (≤6 months) - True mix (twice/day versus basal-bolus) | 1 | Very serious | VERY LOW | 3 more per 1000 (from 52 fewer to 812 more) | 56 |
| Severe/major Hypoglycaemia, number of patients (≤6 months) - Mix part of basal-bolus | 3 | Very serious | VERY LOW | 51 fewer per 1000 (from 104 fewer to 86 more) | 139 |
| Weight change, kg (≤6 months) - Mix part of basal-bolus | 1 | No serious imprecision | LOW | MD 0.7 lower (1.28 to 0.12 lower) | 1.0 |

**Table 110: Evidence summary table: Mixed insulin (aspart mix) versus basal-bolus insulin (less than or equal to 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference MIX | Final value for control group Basal-bolus |
|---|---|---|---|---|---|
| Hypoglycaemia, number of patients - Mix part of basal-bolus (≤6 months) | 1 | No serious imprecision | LOW | 9 more per 1000 (from 37 fewer to 56 more) | 933 |
| Nocturnal hypoglycaemia, number of patients - Mix part of basal-bolus (≤6 months) | 1 | Serious | VERY LOW | 167 fewer per 1000 (from 83 fewer to 229 fewer) | 694 |
| Severe/major hypoglycaemia, number of patients - Mix part of basal-bolus (≤6 months) | 2 | Very serious | VERY LOW | 19 fewer per 1000 (from 54 fewer to 39 more) | 111 |
| SF-36 Physical (≤6 months) - True mix (twice/day versus basal-bolus) | 1 | No serious imprecision | LOW | MD 0.3 higher (0.65 lower to 1.25 higher) | Not reported |
| SF-36 Mental (≤6 months) - True mix (twice/day versus basal-bolus) | 1 | No serious imprecision | LOW | MD 0.1 lower (1.55 lower to 1.35 higher) | Not reported |
| Treatment satisfaction, % (≤6 months - Lispro or Aspart) - True mix (twice/day versus basal-bolus) | 1 | No serious imprecision | LOW | MD 27.7 lower (39.22 to 16.18 lower) | 56.2% |
| Regimen acceptance, % (≤6 months) - Lispro or Aspart - True mix (twice/day versus basal-bolus) | 1 | Serious | VERY LOW | MD 4 lower (7.55 to 0.45 lower) | 64.6% |

**Table 111: Evidence summary table: Mixed insulin versus mixed insulin (less than or equal to 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference MIX | Final value for control group Basal-bolus |
|---|---|---|---|---|---|
| HbA1c, final value (≤6 months) | 2 | no serious imprecision | LOW | MD 0.09 lower (0.33 lower to 0.15 higher) | 9.55 |
| Nocturnal hypoglycaemia, episodes/patient (≤6 months) | 1 | serious | VERY LOW | MD 1.40 lower (3.16 lower to 0.36 higher) | 7.40 |
| Severe/major hypoglycaemia, number of patients (≤6 months) | 1 | Very serious | VERY LOW | 7 more per 1000 (from 32 fewer to 103 more) | 59 |

### 9.2.3.3 Economic evidence

**Published literature**

No relevant economic evaluations comparing pre-mix insulin were identified.

One paper was identified in CG15 that compared pre-mix insulin [180]. Due to severe methodological limitations, it has been excluded. This study is summarised in Appendix L, with reasons for exclusion given.

**Unit costs**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix Q to aid consideration of cost effectiveness.

### 9.2.3.4 Evidence statements

**Clinical**

**Mixed insulin (human mix) versus basal-bolus insulin**

Low and Very low quality evidence from single studies showed a clinically significant harm of human mixed insulin at less than or equal to 6 months compared with basal-bolus insulin in terms of reduction in HbA1c (the mix used was part of a basal-bolus regimen). However there was no clinical difference for either nocturnal hypoglycaemia or severe/major hypoglycaemia (the mix was part of a basal-bolus regimen), nor for the number of patients experiencing ketoacidosis, nor for injection site reactions (the mix used was a clinically relevant regimen, that is, twice/day).

**Mixed insulin (lispro mix) versus basal-bolus insulin**

Low and Very low quality evidence showed a clinically significant harm of lispro mixed insulin at less than or equal to 6 months compared with basal-bolus insulin in terms of reduction in HbA1c (if the mix used was a clinically relevant regimen, that is, twice/day), whereas if the mix used was part of a basal-bolus regimen, there was a clinically significant benefit of lispro mix compared with basal-bolus. However there was no clinical difference for hypoglycaemia episodes (mix was part of a basal-bolus regimen), nocturnal hypoglycaemia episodes (mix was part of a basal-bolus regimen), severe/major hypoglycaemia (regardless of whether the mix used was a clinically relevant regimen, that is, twice/day, or if the mix used was part of the basal-bolus regimen), nor for weight change (mix was part of a basal-bolus regimen).

**Mixed insulin (aspart mix) versus basal-bolus insulin**

Low and Very low quality evidence showed a clinically significant harm of aspart mixed insulin at less than or equal to 6 months compared with basal-bolus insulin in terms of the percentage of patients with treatment satisfaction (the mix used was either lispro or aspart and given as a clinically relevant regimen, that is, twice/day). However, there was no clinical difference for number of patients experiencing measures of hypoglycaemia: hypoglycaemia, nocturnal hypoglycaemia, and severe/major hypoglycaemia (in all measures the mix was part of a basal-bolus regimen), nor for SF-36 Physical or mental, treatment satisfaction, or regimen acceptance (in all measures the mix was given as a clinically relevant regimen, that is, twice/day).

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**Mixed insulin versus mixed insulin**

Low and Very low quality evidence showed no clinical benefit of mixed insulin at less than or equal to 6 months compared with another mixed insulin in terms of HbA1c, episodes of nocturnal hypoglycaemia, and episodes of severe/major hypoglycaemia.

**Economic**

No relevant economic evaluations were identified.

### 9.2.3.5 Recommendations and link to evidence

| | |
|---|---|
| **Recommendations** | **69.Consider a twice-daily human mixed insulin regimen for adults with type 1 diabetes if a multiple daily injection basal-bolus insulin regimen is not possible and a twice-daily mixed insulin regimen is chosen. [new 2015]**<br><br>**70.Consider a trial of a twice-daily analogue mixed insulin regimen if a person using a twice-daily human mixed insulin regimen has hypoglycaemia that affects their quality of life. [new 2015]** |
| Relative values of different outcomes | When considering the use of different insulin regimens in type 1 diabetes, impact on clinical outcomes at <6 months and >6 months were considered in the following order of importance:<br>• Improvement in glycaemic control, assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications.<br>• Reduction in the incidence of hypoglycaemia. Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes, and an obstacle to improved control. Any therapy that achieves an improvement in glycaemic control without producing hypoglycaemia would be beneficial to patients with diabetes.<br>• Reduction in incidence of severe hypoglycaemia (requiring help from 3rd party for correction), which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes.<br>• Reduction in the incidence of nocturnal hypoglycaemia.<br>• Adverse events: the literature was reviewed for any incidence of neoplastic disease associated with the use of mixed insulins.<br>• Incidence of diabetic ketoacidosis (DKA): the literature was reviewed to see if any particular choice of insulin regimen was associated with an increased incidence of DKA.<br>• Quality of life: the impact of particular insulin regimens with varying numbers of insulin injections when used in individuals with type 1 diabetes<br>• Injection site issues associated with choice of insulin therapy<br>• Impact on weight: initiation and intensification of insulin-based therapies are associated with increases in weight. The literature was reviewed to see if weight gain was associated with any particular choice of insulin therapy. |
| Trade-off between clinical benefits and harms | It was recognised by the GDG that insulin regimens requiring a greater number of insulin injections might be considered to be detrimental to quality of life. However, this was not demonstrated in the Diabetes Control and Complications Trial, nor is it found in studies of structured education in flexible insulin therapy. The increased number of injections for many people may be counterbalanced by any improvement in blood glucose control, other aspects of lifestyle such as flexibility of meal timing, and by confidence in managing the regimens. |

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| | |
|---|---|
| | **Multiple daily injection basal bolus insulin regimens versus twice-daily mixed insulin** |
| | Glycaemic control outcomes were better in subjects using basal-bolus regimens in comparison to twice-daily mixed insulin regimens. |
| | No clinically beneficial advantage in the overall incidence of hypoglycaemia or severe hypoglycaemia was seen with use of either insulin regimen. Trials suggested that basal-bolus regimens might produce less nocturnal hypoglycaemia, whilst mixed insulin regimens might have a lower incidence of severe hypoglycaemia. However, the GDG considered the differences were not sufficient to be clinically important. |
| | Incidence of ketoacidosis was markedly less in individuals on basal bolus regimens. |
| | Although no significant difference was obtained between regimens in mental and physical quality of life studies, treatment satisfaction was described as greater in individuals on twice-daily mixed regimens, as was regimen acceptance. |
| | No difference in injection site outcomes was described between groups. |
| | Individuals on mixed insulin regimens gained less weight than those on basal bolus regimens. |
| | **Human mixed insulin versus analogue mixed insulin** |
| | No difference in glycaemic control outcomes was noted between groups and there was no difference in incidence of severe hypoglycaemia. One trial suggested that nocturnal hypoglycaemia incidence might be reduced in individuals using analogue insulins. |
| | No data were available regarding quality of life outcomes, adverse outcomes (including neoplastic disease outcomes), injection site outcomes, weight change or incidence of diabetic ketoacidosis in human mixed insulin versus analogue mixed insulin studies. |
| Economic considerations | No relevant economic evaluations comparing mixed insulin therapies to each other or multiple daily injection insulin regimens were found. |
| | The GDG concluded that the clinical benefits produced by multiple daily injection basal-bolus insulin regimens were sufficient to justify any increase in cost that they might have over twice-daily mixed insulin regimens. |
| | No difference in clinical outcomes was noted when comparing twice-daily human mixed insulins with twice-daily analogue mixed insulin regimens. Twice-daily human mixed insulins are substantially cheaper than analogue twice-daily mixed insulins. Therefore, where a twice-daily mixed insulin regimen is selected for use in an individual with type 1 diabetes, human mixed insulin should be selected in preference to analogue mixed insulin initially. If the individual later experiences an unacceptable frequency of hypoglycaemia whilst using human mixed insulin, this could be substituted with a trial of analogue mixed insulin to see if the frequency of hypoglycaemia episode might be reduced. |
| Quality of evidence | Only UK licensed mixed insulin preparations were considered in the analysis. Only randomised controlled trials were included for assessment of clinical outcome with mixed insulin therapies. It was noted that many of the studies available for analysis using mixed insulin were undertaken in heterogeneous populations containing individuals with type 1 diabetes and individuals with type 2 diabetes. In addition, some studies combined adult and paediatric populations with type 1 diabetes. |
| | Quality of the studies available for analysis ranged from 'Very low' to 'Low' according to GRADE criteria. Caution was given to conclusions reached by studies as the GDG |

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noted that many of the studies had low numbers of participants.

Four studies compared multiple daily injection (MDI) regimens using mixed insulins to basal-bolus regimens using only short-acting insulins and once-daily insulatard in the evening (Ciofetta et al 1999, Fanelli et al 2002, Herz et al 2002, Chen et al 2006). The GDG noted that such MDI mixed insulin regimens have not been commonly used in practice, and have been largely superseded by MDI regimens with twice-daily and/or once-daily longer acting analogue insulins to provide background insulin replacement (see section on MDI). No trial compared MDI with pre-mixed insulin using more modern regimens.

One study compared degludec-aspart mixed insulin therapy with additional aspart insulin injections versus a detemir-aspart basal-bolus regimen (Hirsch et al 2012). Although the study suggested that the incidence of nocturnal hypoglycaemia might be reduced by this regimen, it was noted that patients with recurrent hypoglycaemia were excluded from the study.

Three studies undertook a direct comparison of twice-daily mixed insulin regimens versus basal-bolus regimens (Khachadurian et al 1989, Janssen et al 2000, Testa et al 2012). It was noted that the study reporting greater satisfaction and regimen acceptance with mixed insulin regimens did not include measures of glycaemic control in its outcomes assessment (Testa et al 2012).

Seven studies compared mixed insulin regimens with each other, with three studies comparing analogue mixed insulins with human mixed insulins (Roach et al 1999, Roach et al 2001, Boehm et al 2002). It was noted that in the one study that suggested that analogue insulins may have a beneficial impact on nocturnal hypoglycaemia, glycaemic control was better in the human insulin treated group (Roach et al, 1999).

| Other considerations | The GDG recognised that evidence regarding choice of insulin regimen (basal-bolus versus twice-daily mixed insulin versus basal insulin regimens alone) at the time of diagnosis of type 1 diabetes is insufficient at present to allow a recommendation of a particular regimen. There is evidence that establishing tight glycaemic control soon after diagnosis produces long-term benefits by preserving endogenous insulin production, and that this may have beneficial effects in reducing the risk of vascular complications during the lifetime of an individual with type 1 diabetes. As the current evidence indicates that basal-bolus regimens produce better glycaemic control than twice-daily mixed insulin regimens, this might suggest that basal-bolus regimens should be commenced immediately at the time of diagnosis. However, evidence for this hypothesis is currently lacking. It also does not take into account that some individuals may prefer to use an insulin regimen with fewer injections whilst they come to terms with their diagnosis, at a time when ongoing endogenous insulin production allows good glycaemic control to be achieved with fewer insulin injections. |
|---|---|

After weighing up these issues the GDG agreed that the balance of evidence was in favour of using a basal-bolus regimen as first choice, but acknowledging that there are factors such as limiting the number of injections required which might lead to a different choice in some individuals. Further research is needed to answer whether a particular insulin regimen commenced at the time of diagnosis of type 1 diabetes has any clear advantage over other available regimens.

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71. **For adults with erratic and unpredictable blood glucose control (hyperglycaemia and hypoglycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered:**
    - **injection technique**
    - **injection sites**
    - **self-monitoring skills**
    - **knowledge and self-management skills**
    - **nature of lifestyle**
    - **psychological and psychosocial difficulties**
    - **possible organic causes such as gastroparesis. [2004, amended 2015]**

72. **Give clear guidelines and protocols ('sick-day rules') to all adults with type 1 diabetes to help them to adjust insulin doses appropriately during periods of illness. [2004]**

### 9.2.3.6  Research recommendation

No research recommendations for mixed insulin.

## 9.2.4  Adjunctive non-insulin therapies [2015]

### 9.2.4.1  Introduction

Tight glucose control in type 1 diabetes has been proven to reduce development of microvascular complications (DCCT, 1993). Whilst management is predominantly controlled through insulin treatment there has been recent interest in adjunctive therapies, particularly where insulin resistance has been identified. Insulin resistance in type 1 diabetes is associated with a higher risk of both micro- and macrovascular complications. Improved glycaemic control was shown to reduce these risks. The aim of treatment therefore, is to reduce blood glucose levels and thereby reduce insulin resistance and potential future complications (DCCT, 1993).

Metformin and GLP-1 agonists have both been identified as agents able to reduce insulin resistance (Hamilton, 2003, Parlevliet, 2010). There is limited evidence of use within the type 1 population, although pramlintide, metformin and GLP-1 agonists have all been studied and hold licenses for use in combination with insulin. Pramlintide is the only agent that holds a licence for use in type 1 diabetes. These agents have all been considered for potential use alongside insulin treatment with the aim of improving glycaemic control and reducing insulin resistance.

The evidence review excluded data on other antidiabetic medications as their pharmacology excludes use in type 1 diabetes and therefore falls outside the agreed standard operating procedures for NICE guidelines.

### 9.2.4.2  Review question: In adults with type 1 diabetes, are metformin (with or without insulin), or GLP1-agonists (with or without insulin) as effective as insulin alone for optimal diabetic control?

For full details see review protocol in Appendix C.

**Table 112: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
|---|---|
| | • Adult is defined as aged ≥18 years |
| | • Type 1 diabetes is defined as (if details of diabetes is specified) |
| Intervention/s | • Metformin |

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| | |
|---|---|
| | • Metformin plus insulin<br>• GLP-1 agonists<br>   o exenatide<br>   o pramlintide<br>   o liraglutide<br>• GLP1 plus insulin<br>Note: only UK licensed interventions and doses will be considered |
| **Comparison/s** | Insulin<br>Only UK licensed interventions and doses were considered |
| **Outcomes** | Outcomes<br>• HbA1c (continuous)<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported)<br>• Quality of life – (continuous)<br>• Adverse events – (dichotomous)<br>• Weight loss/change – (dichotomous)<br>• Dose of insulin – (dichotomous) |
| **Study design** | RCTs |

### 9.2.4.3 Clinical Evidence

Sixteen studies were included in the review[184,343,373,387,388,445,529,583,692,693,737 482 741 429 97,371,563,619]. Evidence from these are summarised in the clinical evidence summary below (Table 113). See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix I and exclusion list in Appendix K.

We searched for randomised trials comparing the effectiveness of GLP-1 agonists, Metformin, or amylin analogues (with or without mention of insulin) versus placebo or usual care with insulin in improving diabetic control in adults with type 1 diabetes.

Sixteen randomised trials were identified, reported in 19 published papers. All trials compared the addition of a pharmacological agent to insulin versus insulin alone. Eight trials compared the addition of pramlintide (an amylin analogue), six trials compared the addition of Metformin, one trial compared the addition of liraglutide, and one trial the addition of exenatide.

Studies included participants that were assessed in both inpatient and outpatient hospital settings.

Outcomes reported include:

- Change in glycosylated haemoglobin (HbA1c)
- Hypoglycaemia
- Severe hypoglycaemia
- Insulin dose
- Weight change
- Adverse events
- Quality of life (QoL)

For the purpose of this review, the follow-up periods for the outcomes reported have been grouped into less than or into 6 months and more than 6 months.

*Update 2015*

**Table 113:** **Summary of included studies**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| Pramlintide studies | | | | | |
| Edelman 2006[184] Marrero 2007[459], Kovatchev 2008[396] | Pramlintide 30-60 µg/meal versus placebo<br><br>(TDS or QDS depending on meal pattern) | Adult type 1 diabetes of >1 year using MDI or CSII<br>n= 296<br><br>n=148 Pramlintide<br>(30 µg=41; 60 µg=101; 15-45 µg=5)<br>n=147, Placebo | 29 weeks | HbA1c<br>Hypoglycaemia<br>Quality of Life<br>Gastrointestinal Adverse Events<br>Weight change | Pramlintide initiated at 15 µg/meal and increased weekly to 60 µg/meal. Those unable to tolerate 60 µg were treated with 30 µg/meal for the duration; others were treated with 15 µg and 45 µg doses. Treatment was accompanied by insulin optimization. |
| Ratner 2004 [583] | Pramlintide 60-90 µg/meal TDS versus placebo | Age 16-76 type 1 diabetes of >1 year<br>n=304<br><br>Safety population, n= 631 | 1 year | HbA1c<br>Insulin dose<br>Gastrointestinal Adverse events | Patients randomized to receive different dosing regimens. Placebo based run-in period (4 weeks). Number entering run-in not reported |
| Whitehouse2002 [741] | Pramlintide 30-60 µg/day QDS versus placebo | Aged 16-60 years with type 1 diabetes of >1 year<br>n=480 | 1 year | HbA1c<br>Insulin dose<br>Gastrointestinal Adverse events | At 20 weeks, pramlintide patients with <1% change in HbA1c were re-randomised to 30 or 60 µg QDS |
| Levetan 2003 [429] | Pramlintide 30 µg/meal TDS versus placebo | All people type 1 diabetes of >1 year using CSII<br>n=24<br><br>n=18, Pramlintide<br>n=6, Placebo | 6 weeks | Insulin dose | Treatment was accompanied by insulin optimization. |
| Kolterman 1996[387] | Pramlintide 30-300 µg/meal versus placebo | Adult type 1 diabetes of >2 years C-peptide-negative<br>n= 84 | 2 weeks | Gastrointestinal Adverse Events | Patients randomized to receive different doses. Dose groups analysed separately. |

**Update 2015**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | | n= 62, Pramlintide (30 µg=18; 100 µg=23; 300 µg=21)<br>n=22, Placebo | | | Pre-treatment insulin infusion test prior to randomization. Number of patients entering prerandomization not reported. |
| Nyholm 1999[529]<br>Cross-over RCT | Pramlintide 30 µg QDS versus placebo | Adult men with type 1 diabetes<br>n=14 | 4 weeks with 3-5 week washout | HbA1c<br>Hypoglycaemia<br>Weight change | Treatment was accompanied by insulin optimization. |
| Thompson 1997[692] | Pramlintide 30-60 µg (in four different dosing regimens) versus placebo | Adults with type 1 diabetes<br>n=215<br><br>n=173, Pramlintide (30 µg QDS, n=45; 30 µg TDS (lunch), n=41; 30 µg TDS (snack), n=44; 60 µg BD, n=43)<br>n=42 Placebo | 4 weeks | Hypoglycaemia<br>Gastrointestinal Adverse Events | Placebo based run-in period. Number entering run-in not reported. Four dosing regimens: 30 µg (breakfast, lunch, snack, dinner); 60 µg (breakfast, dinner); 30 µg (breakfast, lunch, dinner) 30 µg (breakfast, snack, dinner) |
| Thompson 1997[693] | Pramlintide 10-100 µg QDS versus placebo | Adults with type 1 diabetes of >1 year<br>n=168<br><br>n=146, Pramlintide (10 µg, n=43; 30 µg, n=41; 100 µg, n=42)<br>n=42, Placebo | 2 weeks | Hypoglycaemia<br>Gastrointestinal Adverse Events | Placebo based run-in period. Number entering run-in not reported. |
| **Metformin studies** | | | | | |
| Burchardt 2013[97] | Metformin (doses up to 2550 mg/day for the most obese) versus insulin alone | Obese adults with type 1 diabetes of >5 years<br>n=68<br><br>n=34, Metformin | 6 months | HbA1c | 1 week insulin dose optimisation period before randomisation.<br><br>Dose of metformin adjusted |

**Update 2015**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | | n=34, Placebo | | | based on level of obesity. |
| Jacobsen 2009[343] | Metformin 1 g BD versus placebo | Adults with type 1 diabetes of >1 year using MDI n=24 n=12, Metformin n=12, Placebo | 24 weeks | HbA1c Gastrointestinal Adverse Events Weight change Dose of insulin | Run-in period of 4 weeks in which glycaemic control was optimised. Number entering run-in period not reported. |
| Khan 2006 [371] Cross-over RCT | Metformin 850 mg TDS versus placebo | All people with type 1 diabetes of >1 year; BMI >27; C-peptide-negative n=15 | 16 weeks | HbA1c Insulin dose Weight change Gastrointestinal Adverse events | Metformin initiated once daily, titrated up. |
| Lund 2008[445] | Metformin 1 g BD versus placebo | Adults with type 1 diabetes of ≥5 years n=100 n=49, Metformin n=51, Placebo | 1 year | HbA1c Hypoglycaemia Dose of insulin Weight change | Placebo based run-in period. Number entering run-in not reported. Metformin dose increased by forced titration weekly as tolerated. |
| Meyer 2002 [482] | Metformin 850 mg BD versus placebo | All people with type 1 diabetes of >1 year using CSII n=62 | 6 months | HbA1c Insulin dose Hypoglycaemia Gastrointestinal Adverse events | Placebo based run-in period (8 weeks). Number entering run-in not reported. |
| Pitocco 2013[563] | Metformin 850 mg TDS versus placebo | Adults with type 1 diabetes of ≥5 years n=42 n=21, Metformin n=21, Placebo | 6 months | HbA1c Insulin dose Hypoglycaemia Weight change | Metformin titrated up. |

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| **Liraglutide studies** | | | | | |
| Kielgast 2011[373] | Liraglutide 0.6-1.2 mg/day versus usual Care | Adults with type 1 diabetes ; C-peptide-negative n=19<br><br>n=9, Liraglutide n=10, Usual Care | 4 weeks | HbA1c Dose of insulin Weight change | C-peptide-positive patients were also included in this study but not randomised, and were subsequently analysed separately |
| **Exenatide studies** | | | | | |
| Sarkar 2014[619] | Exenatide plus/minus daclizumab versus insulin alone | Adults with type 1 diabetes for long duration (mean 21 years) | 6 months (each cross-over treatment period) | HbA1c Dose of insulin Weight change | Analysis in the study showed no effect of daclizumab and so results for all exenatide patients were pooled together; % patients on daclizumab not given.<br><br>2-4 months insulin optimisation period, followed by a run-in period, before randomisation. |

**Update 2015**

**Table 114:** **Clinical evidence summary: Pramlintide plus insulin versus insulin alone (less than or equal to 6 months follow-up)**

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000) |
|---|---|---|---|---|---|
| HbA1c% | 1 | Serious imprecision | LOW | MD 0.3 lower (0.87 lower to 0.27 higher) | 8.2% |
| Severe Hypoglycaemia, no. of patients | 1 | Very serious imprecision | VERY LOW | 6 fewer per 1000 (from 22 fewer to 139 more) | 24 |
| Hypoglycaemia, no. of patients | 2 | Serious imprecision | VERY LOW | 59 more per 1000 (from 66 fewer to 198 more) | 732 |
| Weight Change, kg | 1 | No serious imprecision | MODERATE | MD 1 lower (2.18 lower to 1.18 higher) | -1.3 |

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000) |
|---|---|---|---|---|---|
| Adverse events – Nausea, no. of patients | 1 | No serious imprecision | MODERATE | 190 more per 1000 (from 6 more to 1000 more) | 24 |
| Adverse events – Anorexia, no. of patients | 1 | Serious imprecision | LOW | 40 more per 1000 | 0 |

**Table 115:** **Clinical evidence summary: Pramlintide plus insulin versus insulin alone (more than 6 months follow-up)**

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000) |
|---|---|---|---|---|---|
| HbA1c % | 3 | No serious imprecision | MODERATE | MD 0.26 lower (0.34 lower to 0.18 lower) | Median: -0.12 |
| Hypoglycaemia, no. of patients | 1 | No serious imprecision | MODERATE | 9 more per 1000 (from 55 fewer to 73 more) | 912 |
| Weight Change, kg | 1 | Serious imprecision | MODERATE | MD 2.5 lower (3.25 to 1.75 lower) | +1.2 kg |
| Adverse events – Nausea, no. of patients | 1 | No serious imprecision | LOW | 267 more per 1000 (from 130 more to 443 more) | 361 |
| Adverse events – Vomiting, no. of patients | 1 | Serious imprecision | LOW | 74 more per 1000 (from 2 more to 226 more) | 61 |
| Adverse events – Anorexia, no. of patients | 1 | No serious imprecision | MODERATE | 71 more per 1000 (from 6 more to 294 more) | 20 |

**Table 116:** **Clinical evidence summary: Metformin plus insulin versus insulin alone (less than or equal to 6 months follow-up)**

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute Difference | Control event rate ( per 1000) |
|---|---|---|---|---|---|
| HbA1c % | 4 | Serious imprecision | LOW | MD 0.17 lower (0.44 lower to 0.10 higher) | 7.8% |
| HbA1c % | 1 | Serious imprecision | LOW | MD 0.17 higher (0.36 lower to 0.72 higher) | Not reported |
| Severe hypoglycaemia, | 1 | Serious imprecision | LOW | 65 fewer per 1000 (from 135 fewer to 210 | 161 |

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute Difference | Control event rate ( per 1000) |
|---------|-------------------|-------------|--------------|---------------------|-------------------------------|
| no. of patients | | | | more) | |
| Severe hypoglycaemia – episodes | 1 | No serious imprecision | MODERATE | Zero events in each arm | Not reported |
| Dose of insulin | 3 | Serious imprecision | LOW | MD 4.99 lower (8.35 lower to 1.65 higher) | 1.7 |
| Dose of insulin | 1 | Serious imprecision | LOW | MD 0.027 lower (0.10 lower to 0.51 higher) | Not reported |
| Weight Change, kg | 2 | No serious imprecision | LOW | MD 3.7 lower (5.76 to 1.36 lower) | 45 |
| Weight Change, kg | 1 | No serious imprecision | MODERATE | MD 2.27 lower (3.99 to 0.54 lower) | Not reported |
| Gastrointestinal discomfort, no. of patients | 3 | Serious imprecision | LOW | 148 more per 1000 (from 13 more to 561 more) | 53 |
| Adverse events – Vomiting, no. of patients | 1 | Very serious imprecision | VERY LOW | RR 2.77 (0.12 to 61.65) | 0 |

**Table 117:** **Clinical evidence summary: Metformin plus insulin versus insulin alone (more than 6 months follow-up)**

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute Difference | Control event rate ( per 1000) |
|---------|-------------------|-------------|--------------|---------------------|-------------------------------|
| HbA1c % | 1 | Serious imprecision | MODERATE | MD 0.13 higher (0.18 lower to 0.44 higher) | -0.23 |
| Hypoglycaemia, no. of patients | 1 | No serious imprecision | HIGH | 0 fewer per 1000 (from 59 fewer to 59 more) | 980 |
| Dose of insulin | 1 | No serious imprecision | HIGH | MD 5.7 lower (8.49 to 2.91 lower) | 2.5 |
| Weight Change, kg | 1 | Serious imprecision | MODERATE | MD 1.74 lower (3.31 to 0.17 lower) | 0.53 |
| Gastrointestinal discomfort, no. of patients | 1 | Serious imprecision | MODERATE | 101 more per 1000 (from 47 fewer to 273 more) | 780 |

**Table 118:** **Clinical evidence summary: Liraglutide plus insulin versus insulin alone (less than or equal to 6 months follow-up)**

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute Difference | Control event rate ( per 1000) |
|---|---|---|---|---|---|
| HbA1c% | 1 | Serious imprecision | MODERATE | MD 0.27 lower (0.62 lower to 0.08 higher | -0.2 |
| Dose of insulin | 1 | No serious imprecision | HIGH | MD 0.15 lower (0.23 to 0.06 lower) | 0.017 |
| Weight change, kg | 1 | Serious imprecision | MODERATE | MD 2 lower (3.32 to 0.68 lower) | 0.2 |

**Table 119:** **Clinical evidence summary: Exenatide plus insulin versus insulin alone (less than or equal to 6 months follow-up)**

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute Difference | Control event rate ( per 1000) |
|---|---|---|---|---|---|
| HbA1c | 1 | Very serious imprecision | VERY LOW | MD 0.10 lower (0.52 to 0.32 higher) | 6.37 |
| Dose of insulin | 1 | Serious imprecision | VERY LOW | MD 0.07 lower (0.16 to 0.12 higher) | 0.54 |
| Weight change, kg | 1 | Serious imprecision | VERY LOW | MD 4.20 lower (13.08 to 4.68 higher) | 76.9 |

### 9.2.4.4    Economic evidence

**Published literature**

No relevant economic evaluations comparing adjunctive insulin treatments were identified.

**Unit costs**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

**Table 120: Unit cost of adjunctive insulin treatments**

| Drug | Supplied as | Unit cost | Cost per day |
|------|-------------|-----------|--------------|
| Metformin | 28 x 500 mg tab | £1.32[a] | £0.19[b] |
| Liraglutide | 3 x 3 ml (6 mg/ml) pre-filled pens | £117.72 | £2.62 |

(a)  Source: Drug Tariff 2014
(b)  Assuming dose of 4 times 500 mg per day
(c)  Source: BNF 2014[358]

### 9.2.4.5    Evidence statements

**Clinical evidence statements**

**Pramlintide with insulin versus insulin alone**

**Less than or equal to 6 months follow-up -** Moderate, Low and Very Low quality evidence, mainly from single studies, showed a clinical benefit of pramlintide as an adjunct to insulin for reducing the number of people experiencing episodes of severe hypoglycaemia. However, the evidence also suggested clinical harm in terms of the adverse events of nausea and anorexia. There was no clinical difference between adjunctive pramlintide versus insulin alone for HbA1c, hypoglycaemia, and weight change.

**More than 6 months follow-up -** Moderate and Low quality evidence, mainly from single studies showed a clinical benefit of pramlintide as an adjunct to insulin for reduction in weight, but the evidence also suggested clinical harm in terms of the adverse events of nausea, vomiting, and anorexia. There was no clinical difference between adjunctive pramlintide versus insulin alone for HbA1c, nor for hypoglycaemia.

**Metformin with insulin versus insulin alone**

**Less than or equal to 6 months follow-up -** Low and Very low quality evidence, mainly from several studies pooled together, showed a clinical benefit of metformin as an adjunct to insulin for reducing the number of people experiencing episodes of severe hypoglycaemia, reduction in insulin dose, as well as weight reduction. However, the evidence also suggested clinical harm in terms of the adverse events of GI discomfort and vomiting. There was no clinical difference between adjunctive metformin versus insulin alone for HbA1c.

In a single study of Moderate quality evidence, no clinical difference between metformin as an adjunct versus insulin alone was shown for HbA1c, episodes of severe hypoglycaemia, and insulin dose. However there was a clinical benefit of adjunctive metformin for weight reduction.

**More than 6 months follow-up -** Moderate and High quality evidence from a single study showed a clinical benefit of metformin as an adjunct to insulin for reduction in dose of insulin. However, there

was no clinical difference between adjunctive metformin versus insulin alone for HbA1c, hypoglycaemia, weight change, and the adverse event of GI discomfort.

**Liraglutide with insulin versus insulin alone**

**Less than or equal to 6 months follow-up -** Moderate and High quality evidence from a single study showed no clinical difference between adjunctive liraglutide versus insulin alone for HbA1c, dose of insulin, and weight change.

**Exenatide with insulin versus insulin alone**

**Less than or equal to 6 months follow-up -** Very Low quality evidence from a single study showed a clinical benefit of exenatide as an adjunct to insulin for reduction in weight. However, there was no clinical difference between adjunctive exenatide versus insulin alone for HbA1c, nor for insulin requirement.

**Economic evidence statements**

No relevant economic evaluations were identified.

### 9.2.4.6 Recommendations and link to evidence

| Recommendations | 74. Consider adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m$^2$ or above wants to improve their blood glucose control while minimising their effective insulin dose. [new 2015] |
|---|---|
| Relative values of different outcomes | It is critically important that none of these adjunct therapies are considered appropriate treatment for type 1 diabetes in the absence of insulin as none of them will substitute for insulin deficiency.

When considering the use of adjunct non-insulin therapies in type 1 diabetes, impact on clinical outcomes at <6 months and >6 months was considered in the following order of importance:
• Improvement in glycaemic control, assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications.
• Reduction in hypoglycaemia and severe hypoglycaemia (requiring help from a third party for correction). Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes. Hypoglycaemia occurrence can limit individuals achieving improvements in glycaemic control, and any adjunct therapy that achieves an improvement in glycaemic control without producing hypoglycaemia would be considered beneficial to patients with diabetes.
• Impact on weight – many insulin-based therapies have been associated with increases in weight; any adjunct therapy that can improve glycaemic control with minimal weight gain and/or weight loss might be considered beneficial in patients with type 1 diabetes and an increased body mass index (>25 kg/m$^2$).
• Impact on insulin dose – a reduction in insulin dose may be considered beneficial at least for theoretical reasons and may have a cost benefit by reducing insulin use.
• Side-effects associated with adjunct therapy administration, with particular focus given to gastrointestinal side-effects, nausea, vomiting and anorexia for the agents under review. |

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Weight gain is a common side effect of improving glycaemic control with insulin alone and is undesirable to many people. There was concern that some adjunct therapies might be used for weight loss alone and the GDG considered this inappropriate, where the adjunct therapy is not licensed for weight reduction, nor of proven efficacy in type 1 diabetes, and would be particularly undesirable where BMI was <25 kg/m$^2$. It was also noted that in studies where a reduction in insulin dose was achieved, greater clinical benefit might have been obtained by on-going titration of the insulin dose while on metformin, in order to bring about an improvement in glycaemic control, but the very small numbers recruited in these studies inflects caution and the need for further research and larger studies in this area. Reduction in insulin dose was felt to be of reduced importance in comparison to other clinical outcomes.

| | |
|---|---|
| Trade off between clinical benefits and harms | Impact of adjunct therapies on assessed outcomes:<br><br>**Metformin**<br><br>• Produced no clinically beneficial reduction in HbA1c after <6 months and >6 months therapy.<br><br>• Was associated with a clinically beneficial reduction in severe hypoglycaemia in trials of <6 months duration, although not in trials >6 months duration.<br><br>• Was associated with a clinically beneficial reduction in weight in trials of <6 months duration, although not in trials >6 months duration.<br><br>• Reduced insulin dose requirements in trials after <6 months therapy, and also in trials of >6 months therapy.<br><br>• Metformin was associated with a clinically significant increase in the incidence of vomiting and gastro-intestinal side-effects in trials of <6 months duration.<br><br>**Amylin analogues (pramlintide)**<br><br>• Produced a reduction in HbA1c that could be considered clinically beneficial (0.3%) in trials of <6 months duration and >6 months duration.<br><br>• Was associated with a clinically beneficial reduction in severe hypoglycaemia in trials of <6 months duration, although not in trials >6 months duration.<br><br>• Had no clinically beneficial reduction in weight after <6 months and >6 months therapy.<br><br>• Pramlintide was associated with clinically significant increases in nausea, anorexia and gastro-intestinal side-effects in trials of <6 months duration, and with a clinically significant increase in nausea, vomiting and anorexia in trials of >6 months duration.<br><br>**GLP-1 analogues (liraglutide)**<br>Only one study was available for the GLP-1 analogue Liraglutide. This showed:<br><br>• A reduction in HbA1c that could be considered clinically beneficial (0.3%) No clinically beneficial reduction in weight or insulin dose was achieved.<br><br>• No data on side-effects were reported in this study.<br><br>**GLP-1 analogues (exenatide)**<br>Only one study was available for the GLP-1 analogue Exenatide. This showed:<br><br>• A reduction in HbA1c and dose of insulin, both of which were not considered to be clinically beneficial.<br><br>• A clinical benefit for weight reduction.<br><br>• No data on side-effects were reported in this study.<br><br>The GDG recognised that when treating individuals with type 1 diabetes, an improvement in glycaemic control (HbA1c) is generally considered to be the main |

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| | goal of therapeutic interventions. However, it was also recognised that achieving this goal might lead to an increase in the incidence of hypoglycaemia, and that improvement in HbA1c might be considered to particularly detrimental if it led to an increased incidence of severe hypoglycaemia. |
|---|---|
| Economic considerations | No studies using adjunct non-insulin therapies assessed the cost-effectiveness of the clinical outcomes obtained.<br><br>Metformin is an inexpensive treatment (anticipated cost £18.30 per year for a daily dose of 1.5g), and only a small improvement in clinical benefit might be required to achieve cost-effectiveness. Metformin might also be cost-effective if a reduction in patient insulin dose was achieved. It was recognised that some prescribers may choose to use the metformin glucophage SR preparation, given its propensity to cause less gastro-intestinal side-effects. Glucophage SR is a more expensive preparation (approximately five times the cost of metformin), although this was not felt to be so great that metformin might not still be considered cost-effective if any improvement in clinical outcome was achieved. The GDG therefore considered that the conventional formulation of metformin should be tried first and replaced with Glucophage SR if use of conventional formulations is associated with unacceptable gastrointestinal side effects.<br><br>Amylin analogues and GLP-1 analogues were noted to be considerably more expensive than metformin, and therefore greater clinical benefit would need to be achieved for their use to be considered cost-effective. In the view of the side-effects reported with pramlintide use, the GDG felt that amylin analogue use could be associated with increased co-morbidity with potential to incur additional healthcare costs, and their use was therefore considered less likely to be cost-effective. |
| Quality of evidence | Only randomised controlled trials were included for assessments of clinical outcome with adjunct therapies. It was noted that many of the studies available for analysis using the adjunct therapies identified for this guideline were undertaken in heterogeneous populations containing individuals with type 1 diabetes and individuals with type 2 diabetes. In addition, some studies combined adult and paediatric populations with type 1 diabetes.<br><br>**Metformin studies**<br>Four studies regarding the use of metformin in people with type 1 diabetes were available for analysis. All compared clinical outcomes of metformin versus placebo in people already established on insulin therapy. Only one of the trials was of >6 months duration (Lund et al, 2008): this study was assessed as being of Moderate to High quality. The GDG considered that the available evidence collected in adults with a BMI of >25 kg/m$^2$ was insufficient to be able to recommend its use routinely in this subgroup.<br><br>**Amylin analogues**<br>Eight studies were available on the use of amylin analogues in adults with type 1 diabetes already established on insulin therapy. All the studies used the amylin analogue pramlintide and compared outcomes to the use of placebo. All 8 studies were judged to be at serious risk of bias, and the quality of the available evidence ranged from Very low to Moderate.<br><br>**GLP-1 analogues**<br>Only one study on GLP-1 analogue use in adults with type 1 diabetes was available for analysis (Kielgast et al, 2011).[373] This study used liraglutide in just 9 patients compared with 10 controls. The study did not report side-effects from the medication and was of a duration of <6 months. |

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| Other considerations | The evidence for metformin showed that some reduction in insulin dosage could be achieved together with weight loss, without deterioration in HbA1c. However, the benefits were modest and at the risk of side-effects, particularly gastro-intestinal. The GDG therefore did not recommend metformin should be considered for all patients, but noted that there are some who are particularly concerned about weight and who wish to limit their insulin dose if this is possible. A recommendation was designed to allow a trial of metformin in this group of people. |
|---|---|
| | The amylin analogue pramlintide was not licensed for clinical use in the UK when the evidence was considered. The GDG wished to include data on pramlintide because they understood that a licence for use in the UK might be obtained at a later date, and because they wished to see evidence beyond a single agent (metformin) for the principle of using adjunctive agents with insulin in type 1 diabetes. |
| | Evidence that GLP-1 analogues can improve clinical outcomes in adults with type 1 diabetes is currently insufficient to recommend its use as an adjunct therapy in type 1 diabetes, and further evidence is required prior to recommendations regarding their use in this patient group. |

#### 9.2.4.7 Research recommendations

15. Future studies on the use of metformin as an adjunct to insulin therapy in people with type 1 diabetes should focus on whether improvement in glycaemic control and weight loss (or less weight gain) can be achieved in individuals with a body mass index of more than 25 kg/m$^2$.

16. Further studies on the use of GLP-1 analogues and other potential pharmacological adjuncts to insulin therapy, and their impact on clinical outcomes in people with type 1 diabetes are required prior to recommendations regarding their use in this patient group.

## 9.3 Insulin delivery

This chapter refers primarily to intermittent insulin injection therapy and readers are referred to TA151 for NICE guidance on the use of continuous subcutaneous insulin therapy (CSII, or insulin pump therapy).

### 9.3.1 Introduction

Because it is subject to digestion, exogenous insulin is injected subcutaneously, and for those not using continuous subcutaneous insulin infusion (CSII or insulin pump therapy), this is achieved by intermittent injection using with a needle that is attached to an insulin pen delivery device or an insulin syringe that usually comes with a needle already attached. Needles are disposable and designed for single use and the range of pen needle lengths and diameters (gauges) has increased significantly over recent years.

Injecting insulin into deeper intramuscular tissue can increase the variability of absorption and cause erratic blood glucose levels and hypoglycaemia[365] so choosing an appropriate needle length for the individual patient with regular review is vital.

The recommended injection technique is to insert the needle at a 90 degree angle into the skin, administer the insulin and wait for at least 10 seconds after the plunger is depressed before withdrawing the needle. This is to minimise insulin leakage, which may be detected as dampness around the injection site. With the original longer needle lengths it was advised to lift a skin fold and hold it during insulin administration to minimise the risk of intramuscular injection but this may not always be necessary with use of shorter needles.

Shorter needles are likely to be more attractive to the patient, but the influence of varying needle lengths on long and short term blood glucose control, hypoglycaemic events, bleeding and bruising, insulin leakage and pain perception is uncertain.

Recommended injection sites are the abdomen, buttock, upper outer thigh and upper posterior arm as they generally have ample amount of subcutaneous tissue. Absorption rates may vary according to injection site and type of insulin used and although this problem is reduced with modern analogue insulins, consistency with use of the same area of the body for each daily injection may help stabilise blood glucose levels.

Injection sites should be inspected prior to injection for signs of infection, swelling and lipohypertrophy, which is bulkiness underneath the skin caused by an accumulation of fat tissue caused by overuse of a single site. This can affect the rate of insulin absorption and lead to erratic blood glucose levels, but usually resolves if the site is avoided for several months. Teaching patients to rotate injection sites from the start of insulin therapy can help avoid overuse of sites.

Initial and ongoing provision of accurate advice regarding injection sites and site rotation will enable patients to make informed decisions. With the aim of providing clarity the GDG also asked: in adults with type 1 diabetes what is the optimum injection site and rotation for insulin delivery?

### 9.3.2 Review questions: In adults with type 1 diabetes, what is the optimum needle length for insulin delivery?

For full details see review protocol in Appendix C.

**Table 121: PICO characteristics of review question**

| Population | Adults with type 1 diabetes (over 18 years) |
|---|---|
| Intervention | Insulin – delivered by needle |
| Comparison | As for intervention, but different length of needle |
| Outcomes | • Pain<br>• Discomfort<br>• Patient satisfaction<br>• HbA1c<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported<br>• Quality of life<br>• Adverse events<br>• Adherence |
| Study design | RCTs, observational (retrospective and prospective cohort studies) |

### 9.3.3 Review question: In adults with type 1 diabetes, what is the optimum injection site and rotation for insulin delivery?

For full details see review protocol in Appendix C.

**Table 122: PICO characteristics of review question**

| Population | Adults with type 1 diabetes (over 18 years) |
|---|---|
| Intervention | Insulin – delivered by needle |
| Comparison | As for intervention, but different site of delivery |
| Outcomes | • HbA1c<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported<br>• Quality of life |

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| | • Adverse events |
| | • Adherence |
| **Study design** | RCTs, observational (retrospective and prospective cohort studies) |

### 9.3.4 Clinical evidence

#### 9.3.4.1 Needle length

We conducted an updated literature search and 12 new studies were found that met the inclusion criteria for this review. [44,47,71,247,287,312,340,398,477,485,486,488,497,654]. Five of the studies [312,340,398,477,485] were directly comparing different needle lengths. Evidence from these are summarised in the clinical evidence summary below (Table 123**: Summary of studies included in the review: insulin delivery – needle length**). See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix I and exclusion list in Appendix K. The remainder of the studies were either:

- Conference abstracts (these were included in the review for additional information only, and not pooled in the meta-analysis or GRADE with the fully published RCTs, due to the limited information they provide)

- Studies that assessed a slightly different aspect of needles (the effect of tapering, or needle wall thickness) were also included in the review to be considered as additional information only, and not put in meta-analysis or GRADE, because these were aspects of needles that the GDG were interested in *post-hoc*, and not part of the main review which was specifically looking at needle length.

Due to the paucity of evidence in type 1 diabetes for this review, we have included studies with a mixed population of both type 1 and type 2 diabetes, regardless of the percentages of type 1 or type 2 diabetes, as type of diabetes was not considered to affect several of the outcome measures for this question. No data was reported separately for the population with type 1 diabetes.

Several studies did not report data for some outcomes that was suitable for GRADE, therefore, we have included narrative summaries for these.

The included studies reported the following relevant outcomes:

- HbA1c
- Adverse events
- Hypoglycaemia
- Pain (injection site, during insertion, or VAS pain score)
- Overall satisfaction

The included studies did not report on any of the following outcomes:

- Discomfort
- Adherence
- Severe hypoglycaemia
- Quality of life (QoL)

#### 9.3.4.2 Needle site or rotation sequence

No studies were included in this review which addressed the question of which is the best injection site and rotation. The original 2004 guideline included one RCT[53] which assessed the effects of needle rotation in n=22 people with type 1 diabetes, but this study did report any of our pre-specified outcomes. No new evidence was found to address this in the updated literature search.

**Table 123: Summary of studies included in the review: insulin delivery – needle length**

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| HIRSCH 2010[312] and HIRSCH 2012A[313]<br><br>RCT - cross over | 4 mm x 32G pen needles (PN) versus 5 mm x 31G PN versus 8 mm x 31G PN | n=173 adults with diabetes (37% type 1 diabetes)<br><br>(n= 85: 4mm versus 5mm; n= 83: 4mm versus 8mm) | 3 weeks each needle | Pain (VAS) score<br>Hypoglycaemia<br>Injection site pain<br>Insulin backflow | Mixed population: Type 1 diabetes (37%) and type 2 diabetes<br>No sub-group analysis or data reported separately for type 1 diabetes group<br>OBESE: BMI (kg/m$^2$), mean: 30.6<br><br>Post-hoc subgroup analysis – impact of obesity (BMI of ≥30):<br>The 4 mm PN was statistically significantly less painful in all groups except for the non-obese in the 4 mm versus 5 mm group.<br>Obese patients reported more leakage (regardless of needle size)<br>Less leakage with the 4 mm (versus 5 mm and 8 mm), regardless of BMI. |
| IGNAUT 2012[340],<br>RCT - cross over | 5mm needles versus 8mm needles<br>Both used HumanPen Memoir insulin pen to deliver 20U and 60 U equivalent volume | n=56 adults with diabetes (n=13, 23% type 1 diabetes) | Not reported | Pain (VAS) score<br>Adverse events<br>Insulin leakage | Mixed population: Type 1 diabetes (23%) and type 2 diabetes<br>No sub-group analysis or data reported separately for type 1 diabetes group<br>OBESE: BMI (kg/m$^2$), mean (SD): 35.63 (5.54) |
| KREUGEL 2011[398]<br><br>RCT - cross over | 5mm x 31G PN<br>versus 8mm x 31G PN<br>Both used BD microfine Mini and short insulin pen needles | n=119 adults with diabetes (n=5, 4% type 1 diabetes) | 3 months each needle | HbA1c<br>Hypoglycaemia<br>Pain (VAS)<br>Insulin backflow<br>Adverse events | Mixed population: Type 1 diabetes (4%) and type 2 diabetes<br>No sub-group analysis or data reported separately for type 1 diabetes group<br>OBESE: BMI (kg/m$^2$), mean (range): 36.4 (30 – 62.5) |
| MCKAY 2009[477]<br><br>RCT - cross | 6 mm x 32G PN<br>versus 8mm x 30G PN<br>Both used Novofine needles with FlexPen (NovoNordisk); patients | n=119 adults with diabetes (n=26, 22% type 1 diabetes) | 1-2 weeks each needle | Pain (VAS)<br>Patient preference<br>Adverse events | Mixed population: Type 1 diabetes (22%) and type 2 diabetes<br>No sub-group analysis or data reported separately for type 1 diabetes group<br>Mainly obese: BMI (kg/m$^2$), mean (SD; range): 31 (5.7; |

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| over | injected their usual insulin. | | | | 20 – 48.7) |
| MIWA 2012[485]<br><br>RCT - cross over | 4 mm X 32G needle versus 6 mm X 32G needle | n=41 adults with diabetes (n=5, 12% type 1 diabetes). | 2 months each needle | Pain (VAS) score<br>Adverse events<br>Insulin leakage | Mixed population: Type 1 diabetes (12%) and type 2 diabetes<br>No sub-group analysis or data reported separately for type 1 diabetes group<br>BMI (kg/m$^2$), mean (SD): 23.2 (3.2) |

**Table 124: Summary of additional studies included in the review (not in GRADE or meta-analysis as these are conference abstracts and were used for additional information): insulin delivery – needle length**

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments | Results |
|---|---|---|---|---|---|---|
| Needle length (but not fully published studies) | | | | | | |
| BIRKEBAEK 2008 [71]<br><br>Letter of a case-series | 4 mm pen needles (PN) versus 6 mm PN<br><br>IM Injections using simulated insulin; inserted into abdomen and thigh, perpendicular to the cutis without a skinfold. Volumes equivalent of 10 U and 40 U of insulin. | n=53 diabetic adults and children | Immediate | Risk of IM insulin injections<br>Leakage (backflow) of insulin | Mixed population:<br>diabetes types and % not specified<br>adults and children (60% adults)<br>No sub-group analysis or data reported separately for the type 1 diabetes or the adult group<br>Lean patients (BMI Z score <0) | Statistically significantly more patients injected subcutaneously with the 4 mm versus 6 mm needle at both abdomen and thigh (p<0.032 and 0.001, respectively)<br>Leakage of test medium to skin surface was negligible (regardless of needle length or site)<br>OVERALL: 4 mm needles reduce risk of IM injections without increasing the amount of backflow to the skin surface. |
| HEINEMANN 2009[287]<br><br>Conference abstract of an RCT (cross-over) | ID 1.5 mm x 35G needles versus SC 8mm x 31G needles<br><br>5 arm trial: intradermal versus sc injections of lispro versus regular human insulin, each using the 2 different needle types. And different injection | n=29 young people and adults with type 1 diabetes | Up to 4 hours | Prandial blood glucose | BMI (kg/m$^2$), mean: 25.7 | ID administration resulted in reduction of post-prandial blood glucose with regular insulin and for lispro.<br>However, there was NS difference between SC or ID (for post-prandial blood glucose). |

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| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments | Results |
|---|---|---|---|---|---|---|
| | times (2 and 17 minutes before standard high-carb liquid meal) | | | | | |
| MOK 2012[488]  Conference abstract of a before and after study | 4mm PN versus 5 mm, 6 mm or 8 mm PN (needles that patients were using prior to study of 4 mm PN)  Insulin regimen not reported. | n=34 adults with diabetes (47% type 1 diabetes). | 2-4 weeks | Pain (Likert scale) Leakage | Mixed population: Type 1 diabetes 47% adults and young people (mean age, 18.6 years; range; 13-76 years) No sub-group analysis or data reported separately for the type 1 diabetes or the adult group BMI (kg/m$^2$), mean (SD, range): 24.0 (45.1, 17-45) | Pre- versus post-use of 4 mm insulin PN Leakage: NS difference regardless of site (abdomen or thigh) Pain level: NS difference |

*Abbreviations: IM, intramuscular; ID, intradermal; sc, subcutaneous; RA, rapid-acting; IA, intermediate-acting; LA, long-acting.*

**Table 125: Summary of additional studies included in the review (not in GRADE or meta-analysis as used for additional information post-hoc): thin wall and tapered needles**

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments | Results |
|---|---|---|---|---|---|---|
| Tapered needles | | | | | | |
| ASAKURA 2006[47]  RCT (cross-over) | 3.5 mm micro tapered needle (needle T, Terumo Corp.) versus 5 mm Standard needle (BD Microfine, 31G thin wall)  Injected insulin (no further details given) | n=99 diabetic adults (n=13, 14% type 1 diabetes). | 1 day (2 or more injections) | Pain (VAS) Leakage Bleeding Patient preference | Mixed population: Type 1 diabetes (14%) and type 2 diabetes No sub-group analysis or data reported separately for type 1 diabetes group Weight or BMI not reported. | 44% of patients preferred needle T (19% needle B, 37% had no preference). Pain (VAS): SS less for needle T (P<0.001) Bleeding and leakage: NS difference between needles. |
| MIYAKOSHI 2007[486] | 5 mm x 33G tapered needle (Terumo NanoPass) versus 5 mm x 31G standard | n=40 adults with type 1 diabetes | 1 week each needle | Pain (VAS) Leakage Bleeding | All type 1 diabetes adults. Not obese: BMI (kg/m$^2$), mean: 23.0 (3.1). | Pain (VAS), bleeding, leakage and patient satisfaction, all statistically significantly less for NanoPass. |

**Update 2015**

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments | Results |
|---|---|---|---|---|---|---|
| RCT (cross-over) | needle (BD MicroFine Plus)<br><br>Injected usual insulin (all 4 times a day – RA and IA or LA insulin). | | | Patient satisfaction | | All p<0.001 |
| NAGAI 2012[497] | 5 mm x 33Gbase and 28G tip tapered needle versus 4 mm x 32G standard needle | n=84 adults with type 1 diabetes or type 2 diabetes (11% type 1 diabetes) | 4 weeks each needle | Pain (VAS)<br>Leakage<br>Bleeding | All adults (type 1 diabetes and type 2 diabetes).<br>Not obese: BMI (kg/m$^2$), mean: 24.8 (3.7). | Pain (VAS): statistically significantly less for tapered.<br>Bleeding: less for tapered.<br>Leakage: less for tapered. |
| **Thin wall needles** | | | | | | |
| ARONSON 2013[44] | Extra thin wall (ETW) needles versus patient's usual needle (most patients used 8 mm and 5 mm, and most 31G). | n=216 diabetic adults with type 1 diabetes or type 2 diabetes (10% type 1 diabetes). | 1 week each needle | Pain (VAS)<br>Bleeding<br>Dose delivery<br>Patient preference | All adults - mixed population type 1 diabetes and type 2 diabetes<br>Weight and BMI not reported | Extra thin wall needles were better than regular needles for pain, bleeding, confidence in full dose delivery, and overall patient preference. |
| SIEGMUND 2009[654]<br>Observational cross over trial (not randomised) | 31G thin wall needle (BD microfine PN) versus 31G regular wall needle (Ypsomed optifine)<br><br>Length of needle: not specified in paper. | n=97 diabetic adults (n=27, 28% type 1 diabetes). | 2 weeks each needle | Recurring pain (questions)<br>Skin irritation<br>Bleeding<br>Leakage of insulin<br>Patient | Mixed population: Type 1 diabetes (28%) and type 2 diabetes<br>No sub-group analysis or data reported separately for type 1 diabetes group<br>Obese: BMI (kg/m$^2$), mean (SD): 29.9 (6.0) | Thin wall needles were statistically significantly better than regular needles for pain, bleeding, needle occlusion (p<0.001).<br>Statistically significantly more patients preferred using thin walled needles (78%, p<0.001 versus regular needles). |

Update 2015

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments | Results |
|-------|------------------------|-----------|-----------|----------|----------|---------|
|       |                        |           |           | preference |         |         |

**Additional information: skin thickness**

- One study (Gibney 2010)[247] looked at the differences in skin thickness (ST) and subcutaneous adipose layer thickness (SCT) with patient weight, in n=388 adults with diabetes (28% type 1 diabetes). The study showed that:

- Mean ST (95% CI) was: arm 2.2 mm (2.2, 2.3), thigh 1.9 mm (1.8, 1.9), abdomen 2.2 mm (2.1, 2.2) and buttocks 2.4 mm (2.4, 2.5).

- Multivariate analyses showed body site, gender, BMI, and race are statistically significant factors for ST but effects were small.

Differences of 10 kg/m$^2$ account for 0.2 mm ST variation. Mean SCT was: arm 10.8 mm (10.2, 11.3), thigh 10.4 mm (9.8, 10.9), abdomen 13.9 mm (13.2, 17.7) and buttocks 15.4 mm (14.7, 16.2). Females had 5.1 mm greater SCT. Differences of 10 kg/m$^2$ account for 4 mm SCT variation. These data suggest that needles of less than or equal to 8 mm deliver insulin to the subcutaneous site.

### 9.3.4.3 RCTs – additional data (narrative summary)

The following studies are summarised as narratives because the outcome(s) were not appropriate for GRADE due to incomplete outcome reporting:

**Visual Analogue Scale (VAS) pain score**

- One study (IGNAUT)[340] comparing insulin diluent leakage post injection using two different needle lengths and injection volumes reported "no significant difference between the 5 mm needle versus the 8 mm needle with respect to pain score with either the 20 U or 60 U equivalent volume. Mean ± SD differences in pain score for 20 U and 60 U equivalent volumes were 0.14 ± 2.56 and 0.74 ± 2.49, respectively".

- One study (KREUGEL)[398] reported no significant difference in Pain perception (VAS) between the 5 mm versus 8 mm needles (median value 7 and 9 respectively; p-value not reported).

- One study (McKAY)[477] reported statistically significantly less pain perception (VAS) with the 6 mm/32G versus 8 mm/30G needle needles (p<0.001).

**Adverse events**

- One study (IGNAUT)[340] comparing insulin diluent leakage post injection using two different needle lengths and injection volumes reported "no serious adverse events during the study".

- One study (MIWA)[485] comparing the effects of a new 32-guage X 4 mm pen needle and a 32-guage X 6 mm pen needle on glycaemic control and safety reported "no adverse events during the trials".

- One study (McKAY)[477] reported a similar number of adverse events (bleeding or bruising) for the 6 mm/32G versus 8 mm/30G needle (n=1 event versus n=3 events).

**Hypoglycaemia**

- One study (KREUGEL)[398] reported NS difference in hypoglycaemia between the 5 mm versus 8 mm needles (p=0.337).

**Insulin leakage or backflow**

- One study (HIRSCH 2010)[312] showed that slightly less patients reported leakage when using the 4 mm versus the 5 mm or 8 mm needle (44%, 47% and 56%), and the 5 mm needle was better than the 8 mm needle.

- One study (IGNAUT)[340] reported NS difference in leakage between the 5 mm needle and the 8 mm needle (regardless of injection volume – 20 U or 40 U.)

- One study (KREUGEL)[398] reported SS less insulin backflow for the 8 mm versus 5 mm needles (p=0.01).

- One study (MIWA)[485] reported NS difference in leakage between the 4 mm needle and the 6 mm needle.

**Patient preference**

- One study (McKAY)[477] reported statistically significantly patient preference for the 6 mm/32G versus 8 mm/30G needle (58% versus 27%; p<0.001).

One study (KREUGEL)[398] reported NS in patient preference for the 5 mm versus 8 mm needles (46% versus. 41%; p-value not given).

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**Table 126: Clinical evidence summary tables – Insulin delivery (needle length) - 4 mm x 32G PN versus 5 mm x 31G PN for insulin delivery (less than or equal to 6 months follow-up)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000 patients) |
|---|---|---|---|---|---|
| Hypoglycaemia, no. of patients | 1 study (n=173) | Very serious imprecision | VERY LOW | 29 fewer per 1000 (from 106 fewer to 99 more) | 236 |
| Injection site pain, no. of patients | 1 study (n=173) | Very serious imprecision | VERY LOW | 32 more per 1000 (from 42 fewer to 177 more) | 124 |
| Visual analogue pain score, 150 mm | 1 study (n=173) | No serious imprecision | LOW | MD 11.91 lower (22.91 lower to 0.91 lower) | Not given |

**Table 127: Clinical evidence summary tables – Insulin delivery (needle length) - 4 mm x 32G PN versus 6 mm x 32G PN for insulin delivery (less than or equal to 6 months follow-up)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000 patients) |
|---|---|---|---|---|---|
| Visual analogue pain score, 150 mm | 1 study (n=41) | Serious imprecision | VERY LOW | MD 16.60 lower (25.95 lower to 7.25 lower) | Not reported |

**Table 128: Clinical evidence summary tables – Insulin delivery (needle length) - 4 mm x 32G PN versus 8 mm x 31G PN for insulin delivery (less than or equal to 6 months follow-up)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000 patients) |
|---|---|---|---|---|---|
| Hypoglycaemia, no. of patients | 1 study (n=173) | Very serious imprecision | VERY LOW | 55 fewer per 1000 (from 131 fewer to 68 more) | 262 |
| Injection site pain | 1 study (n=173) | Very serious imprecision | VERY LOW | 25 more per 1000 (from 50 fewer to 168 more) | 131 |
| Visual analogue pain score, 150 mm | 1 study (n=173) | No serious imprecision | LOW | MD 23.26 lower (13.57 lower to 14.95 lower) | Not given |

**Table 129: Clinical evidence summary tables – Insulin delivery (needle length) - 5 mm x 31G PN versus 8 mm x 31G PN for insulin delivery (less than or equal to 6 months follow-up)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000 patients) |
|---|---|---|---|---|---|
| HbA1c (final value) | 1 study (n=130) | No serious imprecision | VERY LOW | MD 0.12 lower (0.35 lower to 0.11 higher) | 7.59 |

### 9.3.5 Economic evidence

**Published literature**

No relevant economic evaluations were identified.

**Unit cost**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

**Table 130: Needle costs[a]**

| Needle Length | 4 mm | 4.5 mm | 5 mm | 6 mm | 8 mm | 10 mm | 12 mm |
|---|---|---|---|---|---|---|---|
| Cost per needle[b] | £0.11 | £0.12 | £0.14 | £0.10 | £0.10 | £0.07 | £0.08 |
| Cost per day | £0.54 | £0.62 | £0.69 | £0.52 | £0.50 | £0.37 | £0.40 |
| Cost per week | £3.81 | £4.31 | £4.86 | £3.61 | £3.52 | £2.61 | £2.82 |
| Cost per month | £15.23 | £17.25 | £19.45 | £14.46 | £14.09 | £10.43 | £11.28 |
| Cost per year | £198.59 | £224.84 | £253.52 | £188.46 | £183.69 | £136.02 | £147.00 |

(a) Assuming five injections a day with single use needles
(b) Average of all needles that length (source: MIMS accessed on October 2013)

### 9.3.6 Evidence statements

#### 9.3.6.1 Clinical [2015]

**Needle length: 4 mm versus 5 mm PN for insulin delivery**

Very Low quality evidence, from a single study, showed a clinically important benefit at less than or equal to 6 months of 4 mm PN compared with the 5mm PN for reducing the number of people experiencing episodes of hypoglycaemia, and reduction in the number of people experiencing injection site pain. However, Low quality evidence from the same study showed that there was no clinical difference between 4 mm and 5 mm PN for pain measured on a VAS.

**Needle length: 4 mm versus 6 mm PN for insulin delivery**

Very Low quality evidence, from a small single study, showed a clinically important benefit at less than or equal to 6 months of 4 mm PN compared with the 6 mm PN for a reduction in pain measured on a VAS.

**Needle length: 4 mm versus 8 mm PN for insulin delivery**

Low and Very Low quality evidence, from a single study, showed a clinically important benefit at less than or equal to 6 months of 4 mm PN compared with the 8 mm PN for reducing the number of people experiencing episodes of hypoglycaemia, reduction in the number of people experiencing injection site pain, and reduction in pain measured on a VAS.

**Needle length: 5 mm versus 8 mm PN for insulin delivery**

Very Low quality evidence, from a single study, showed no clinical difference at less than or equal to 6 months between the 5 mm PN and 8 mm PN for a reduction in HbA1c.

### 9.3.6.2 Economic [2015]

No relevant economic evaluations were identified.

### 9.3.7 Recommendations and links to the evidence

| Recommendations | 75. Offer needles of different lengths to adults with type 1 diabetes who are having problems such as pain, local skin reactions and injection site leakages. [new 2015]<br><br>76. If possible, choose needles with the lowest acquisition cost to use with pre-filled and reusable insulin pen injectors. [new 2015]<br><br>77. Advise adults with type 1 diabetes to rotate insulin injection sites and to avoid repeated injections at the same point within sites. [new 2015] |
|---|---|
| Relative values of different outcomes | To determine the optimum use of needles for insulin delivery in individuals with type 1 diabetes, the GDG reviewed whether the following parameters of needle use in insulin administration had any influence on clinical outcomes:<br>• The length of the insulin needle<br>• The site and frequency of site rotation for insulin delivery<br><br>The impact of these parameters on needle use for insulin delivery was assessed for the following clinical outcomes:<br>• Quality of life: Particular attention was paid to impact of needle length choice on pain, discomfort and patient satisfaction.<br>• Improvement in glycaemic control: assessed by reduction in HbA1c.<br>• Reduction in hypoglycaemia and severe hypoglycaemia (requiring help from 3rd party for correction).<br>• Adverse events.<br>• Adherence to treatment. |
| Trade off between clinical benefits and harms | Studies assessing impact of needle length on clinical outcome reported outcomes using needles for use with pre-filled and reusable insulin pen injectors. Length of needle used in the studies ranged from 3.5 to 8 mm, with gauge 30 to 32 G.<br><br>**Impact on quality of life**<br>One study (Hirsch 2010) investigated the impact of needle size on injection site pain, and found no significant difference in injection site pain with different needle lengths (4 mm versus 5 mm versus 8 mm). Five studies (McKay 2009, Hirsch 2010, Kreugel 2011, Ignaut 2012, Miwa 2012) investigated the impact of needle size on injection site pain scores, including visual analogue pain scores. Two studies (Ignaut 2012, Kreugel 2011) reported no significant difference in visual analogue scale pain scores using needles of different lengths (5mm versus 8mm), whilst three studies (McKay 2009, Hirsch 2010, Miwa 2012) reported that pain perception was less using shorter needles (6 versus 8mm; 4mm versus 5mm; 4mm versus 6mm respectively).<br><br>In studies assessing patient preferences, one study reported that patients had a preference for using shorter needles (6mm versus 8 mm) (McKay 2009), whilst a second study reported no significant difference in preference for needle size (5 mm versus 8 mm) (Kreugel 2011). |

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One study (Asakura 2006) reported that tapered needles produced less pain at the site of injection than thin-walled needles, and two studies (Miyakoshi 2007 and Nagai 2012) reported less pain with tapered needles compared with regular needles.

Two studies (Siegmund 2009 and Aronson 2013) reported that thinner walled needles were better than regular needles for reducing pain.

**Impact on glycaemic control**

One RCT (Hirsch 2010) investigated the impact of 4 mm 32 G needle use versus 5 mm 31 G needle use on glycaemic control – no significant impact on clinical outcome was reported with variation in needle size.

**Impact on frequency of hypoglycaemia**

Two studies (Hirsch 2010, Kreugel 2011) investigated the impact of needle length on frequency of hypoglycaemia, and no clinically important significant difference was found in frequency of hypoglycaemia with variation in needle size.

**Adverse events**

Three studies (Ignaut 2012, Miwa 2012, McKay 2009) reported adverse events; none of the three demonstrated any significant difference between the needle sizes used.

**Impact on leakage of insulin from injection site**

One study (Hirsch 2010) reported that a slightly lower proportion of patients experienced insulin leakage post-injection when using shorter needles (5mm versus 8mm) but a similar mean number of leakage events. A second study reported more leakage with the shorter needle (Kreugel 2011, 5 mm versus 8mm), whilst a third and a fourth study (Miwa 2012, 4 mm versus 6 mm; Ignaut 2012, 5 mm versus 8 mm) reported no significant difference in leakage between needles of different sizes.

One study (Gibney 2010) reported that needles ≥8 mm inserted perpendicularly may frequently enter muscle in the limbs of males and individuals with a body mass index ≤25 kg/m$^2$.

From a review of all of the available evidence, the GDG concluded that there was no evidence to suggest that needle length impacted on biomedical outcomes. There was some evidence to suggest that the use of shorter needles (4 to 5 mm) may have some benefits over longer needles (6 to 8 mm) in terms of quality of life and patient preference, but the evidence was weak and insufficient to make a firm recommendation regarding optimal needle length.

**Insulin injection site rotation**

No studies reporting the influence of injection site or site rotation on clinical outcomes were identified.

All members of the GDG had clinical experience of reviewing patients with lipohypertrophy from repeated administration of insulin in the same skin area without variation of administration site. They had witnessed lipohypertrophy with the whole range of insulin.

In the absence of any clinical trial evidence, the GDG recognised that there was sufficient clinical experience from its members to make a recommendation for insulin injection site rotation so that the incidence of lipohypertrophy might be reduced in adults using insulin for the treatment of type 1 diabetes. The GDG also recognised the need for a research recommendation to be made regarding choice of anatomical site for insulin administration and investigation of injection site rotation.

**Update 2015**

| Economic considerations | No economic evaluations regarding needle length, choice of site and site rotation in the administration of insulin were identified by the GDG. The GDG noted that the prescription cost for needles used for the administration of insulin was £39 million in 2012 (2012 prescription cost analysis)[284] |
| --- | --- |
| | Longer needles tended to be cheaper per unit cost (average cost for an 8 mm 31 gauge needle £0.09 versus £0.13 for a 5 mm 31 gauge needle), and the GDG recognised that a recommendation regarding the use of shorter needles could potentially increase the cost of care in type 1 diabetes management. Evidence supporting the use of shorter needles was felt to be insubstantial given their increased cost, although the GDG also recognised that potential savings regarding brand choice might still allow shorter needle sizes to be selected as the equipment of choice by healthcare professionals. |
| Quality of evidence | Randomised controlled trial evidence alone was insufficient for assessment of needle length choice, site of administration and frequency of rotation on clinical outcomes, and therefore evidence from observational retrospective and prospective cohort studies were also included in the review. |
| | Twelve studies were available for the assessment of needle length on clinical outcome. Five studies were randomised cross-over trials (Ignaut 2012, Miwa 2012, Kreugel 2011, Hirsch 2010, McKay et al 2009), and subsequent GRADE assessment of these RCTs indicated that the quality of the evidence ranged from Moderate to Very low, with some of the evidence at serious risk of bias. Seven further studies (Birkebaek 2008, Heinemann 2009, Mok 2012, Asakura 2006, Miyakoshi 2007, Siegmund 2009, Gibney 2010) were not able to be GRADE assessed as they were not full study reports (conference abstracts, letters) but they provided useful information to the GDG. |
| | No studies were available for review of the impact of choice of needle site and site rotation on clinical outcomes. |
| Other considerations | Patient representatives on the GDG recognised that the majority of individuals with type 1 diabetes would have a preference for shorter needles in the administration of insulin. However, other members of the GDG recognised that there might be theoretical circumstances where a shorter needle option might be inappropriate, for example in individuals with obesity. On reflection, the GDG felt that if an individual with type 1 diabetes was experiencing problems with insulin self-administration that might be related to a pre-selected needle choice, healthcare professionals should support patients in trialling different needle sizes. Healthcare professionals should subsequently balance the cost of a needle against a patient's desired choice prior to a decision on long-term needle use. |
| | The GDG recognised that although choice of needle type may have some influence on clinical outcomes, this was likely to be of secondary importance to clinical education regarding the administration of insulin injections: the teaching of good subcutaneous injection technique is likely to be the most important factor influencing clinical outcome for insulin injections, highlighting the need for structured education to be made available to all individuals with type 1 diabetes. |

**Update 2015**

### 9.3.7.1 Recommendations [2004]

**78.Adults with type 1 diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal wellbeing, often using one or more types of insulin injection pen. [2004]**

79. Provide adults with type 1 diabetes who have special visual or psychological needs with injection devices or needle-free systems that they can use independently for accurate dosing. [2004]

80. Provide adults with type 1 diabetes with suitable containers for collecting used needles. Arrangements should be available for the suitable disposal of these containers. [2004]

81. Check injection site condition at least annually and if new problems with blood glucose control occur. [2004, amended 2015]

### 9.3.8 Research recommendations

17. In adults with type 1 diabetes, what is the clinical and cost effectiveness of basal insulins with longer action profiles compared to existing regimens, particularly in terms of dose adjustment for flexible lifestyles, such as intermittent exercise or alcohol consumption, and their long term safety data?

18. In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of different intensities of glycaemic control (for example, inpatient intravenous insulin management versus outpatient multiple daily dose insulin injection therapies)?

19. In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of using basal-bolus insulin regimens?

20. In adults with type 1 diabetes, what modifications of rapid-acting insulin use (including but not limited to timing of administration, and the nature of the insulin) could be employed to improve glycaemic control around different meal compositions?

21. In adults with type 1 diabetes, what modifications of rapid-acting insulin (including timing of administration and nature of the insulin) could be employed to improve glycaemic control around different modalities of exercise?

22. In adults with type 1 diabetes and a BMI of ≥25 kg/m$^2$, what is the clinical and cost effectiveness of metformin as an adjunct to insulin, particularly in terms of glycaemic control and weight loss (or reduction in weight gain)?

23. In adults with type 1 diabetes, what is the clinical and cost effectiveness of GLP-1 analogues and other potential pharmacological adjuncts to insulin therapy?

24. In adults with type 1 diabetes, what is the optimum needle length and type for administration of exogenous insulin in terms of clinical and cost effectiveness?

25. In adults with type 1 diabetes, what is the optimum injection site and injection site rotation regimen in terms of clinical and cost effectiveness?

Update 2015

# 10 Referral for islet or pancreas transplantation

Islet and pancreas transplantation were not covered in 2004; this is an entirely new section.

## 10.1 Introduction

People with type 1 diabetes rely on insulin replacement therapies to regulate blood glucose. Insulin is usually given by subcutaneous injection, or continuous subcutaneous infusion via an insulin pump. Insulin doses and regimens must be carefully balanced on a continual basis by people with type 1 diabetes against their diet, physical activity, stress, hormonal responses, variations in temperature and a host of other factors in order to minimise blood glucose variation. Many studies [498] demonstrate the benefit of improved blood glucose control in preventing the development of micro- and macro-vascular complications and modern insulin regimens aim to optimise glucose control with this in mind. This requires a high degree of knowledge and engagement by the person with diabetes. Furthermore, a major and persistent risk of exogenous insulin therapy is hypoglycaemia, which for some people can be severe and frequent enough to be disabling.[243,328]

Whole pancreas and islet cell transplantation offer a surgical alternative for sub-cutaneous exogenous insulin replacement, in which insulin is provided by secretion from transplanted beta-cells, and is thus under more physiological control than in conventional exogenous insulin treatments. Whole pancreas transplantation is a more complex procedure which carries significant operative risk. It is most commonly undertaken alongside a kidney transplant but can be carried out in isolation. Islet cell transplantation is a relatively new procedure which involves infusing insulin-producing beta cells isolated from a donor organ into the recipient, currently by infusion into the hepatic portal system. Transplantation allows a person with type 1 diabetes to begin to generate their own insulin in response to carbohydrate and basal insulin requirements without the need to calculate or administer doses manually. Importantly, insulin secretion from transplanted organs or cells ceases in the presence of low blood glucose concentrations preventing hypoglycaemia.

The risks of transplantation include those of the surgeries themselves, and also the potential side-effects of the immunosuppressive medications that need to be taken after transplant. Additionally, long-term insulin independence is difficult to maintain. The transplanted organ or cells may stop working effectively and many people need to re-commence insulin injections or infusion within 5 years.[117,269] Indeed, some do not regain insulin independence at all. However, even partial function of transplanted cells can improve blood glucose control and very successfully protect against severe hypoglycaemia.[92,127,269] Ongoing research is exploring ways of improving transplantation outcomes including stem cell and nano-encapsulation technologies and novel immune-suppressive interactions to protect transplanted cells.

Because of the balance of risks and benefits, transplantation has usually been offered to people who are already taking or will need to be taking immunosuppressive medication, or who have profound problems with blood glucose management and/or a complete lack of hypoglycaemia awareness. However it is a potentially life-changing treatment intervention with proven effectiveness in tackling severe hypoglycaemia.[117,269]

**The GDG asked this question:**

- Which adults with type 1 diabetes are most suitable to be considered for a pancreas transplant, or pancreatic islet cell transplantation?

As already noted, whole pancreas transplantation currently takes place most frequently alongside kidney transplantation in people with end-stage renal failure as a complication of type 1 diabetes. In this situation the major drive to transplant is the renal failure rather than the diabetes per se, and

consideration of suitability for transplantation is therefore beyond the immediate scope of this guideline.

## 10.2 Review question: Which adults with type 1 diabetes are most suitable to be considered for a pancreas transplant, or pancreatic islet cell transplantation?

For full details see review protocol in Appendix C.

**Table 131: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
|---|---|
| Intervention/s | • Whole pancreas transplant<br>• Islet cell transplantation |
| Comparison/s | • Any comparison<br>• No comparison |
| Outcomes | Outcomes<br>• The referral criteria themselves<br>• HbA1c<br>• Severe hypoglycaemia<br>• Longevity of the transplant/organ survival (C-peptide and insulin independence)<br>• Insulin dependence at 1 year and 5 years<br>• Mortality - in-hospital/procedural<br>• Mortality – long-term<br>• Quality of life – any measure used in the paper |
| Review strategy | Strategy for this review is:<br>Use available clinical data for obtaining clinical outcomes. This will be sourced from:<br>• publications of the UK consortia data (National transplant programmes); to see whether patients do well after a transplant which is based on the current UK referral criteria<br>• NICE IPG 257 guidance on transplantation<br>• Report what referral criteria are currently used in the UK. This will be sourced from:<br>• NHS England service specifications document<br>• NICE IPG 257 guidance for any information given on referral criteria.<br>• International criteria: Collaborative Islet Transplant Registry ([CITR] data can be found on their website and any relevant publications) |

## 10.3 Clinical evidence

We looked for UK-specific data on the referral criteria for whole pancreas transplant as well as islet cell transplantation. Our search consisted of looking specifically at data from the CITR as well as the UK National Islet transplant programme, and NHS England data. We also looked at the NICE guidance on allogeneic pancreatic islet cell transplantation (IPG 257).

Data and information from these sources are summarised below.

### 10.3.1    Islet cell transplantation

#### 10.3.1.1    Current listing criteria [2015]

**Islet transplant alone (ITA)**

The standard listing criteria for an ITA are:

- all patients listed should have insulin-treated diabetes
- patients should have type 1 diabetes or diabetes secondary to pancreatectomy or pancreatitis and have confirmed C-peptide negativity in the presence of a glucose level of more than 4 mmol/litre
- at least 2 severe hypoglycaemic episodes in the last 24 months and be assessed by a diabetologist to have disabling hypoglycaemia

**Islet after kidney (IAK) transplant**

The standard listing criteria for an IAK transplant are:

- all patients listed should have insulin-treated diabetes
- should have type 1 diabetes or diabetes secondary to pancreatectomy or pancreatitis and have confirmed C-peptide negativity in the presence of a glucose level of more than 4 mmol/litre
- a history of severe hypoglycaemia within the last 2 years or HBA$_{1c}$ of more than or equal to 53 mmol/mol (7%)

#### 10.3.1.2    2013 NHS England contract A17/S(NHSS)c for islet cell transplantation service – service specifications[521]

**Referral criteria (further described in the Service Standards)**

Referrals are from specialist diabetes services. Referral criteria are described in the service standards. A summary is given below:

**Established type 1 diabetes:**

- children will not ordinarily be considered for transplant given the potential long-term complications of immunosuppression
- insulin dependence for at least 5 years
- negative C-peptide (less than 0.16 nmol/litre with no increment at 6 minutes after 1 mg glucagon IV)

Note: This is because the benefits of islet transplantation are associated with the replacement of C-peptide positivity.

**Intensive diabetes management:**

Evidence of compliance with expert medical advice (with glucose testing 3 or more times daily), formal diabetes self-management, re-education and intensified insulin therapy, including optimised insulin regimens, and where appropriate, continuous subcutaneous insulin infusion pump therapy.

**Absence of insulin resistance**

Current islet replacement techniques are not sufficiently efficient to overcome insulin resistance. This is defined as an insulin requirement of more than 0.7 U/kg body weight per day to achieve a

HbA1c of less than 75 mmol/mol (9%). BMI should not be greater than 28 kg/m$^2$. Chronic treatment with oral steroids is only permissible for those with renal grafts or Addison's disease, and current prednisolone dose should be less than 5 mg daily. Euglycaemic insulin clamps will be used in the early phases to assess insulin sensitivity.

**Absence of contraindications to the use of the immunosuppressants:**

- impaired renal function (creatinine of more than 135 micromoles/litre, or creatinine clearance of less than 80 mls per minute per 1.73 m$^2$)
- macroalbuminuria (albumin excretion rate of more than 300 mg per 24 hours) or overt proteinuria
- uncontrolled hypertension
- uncontrolled dyslipidaemia (fasting LDL of more than 3.4 mmol/litre; triglycerides of more than 2.4 mmol/litre)
- active infection, including hepatitis B virus, hepatitis C virus, HIV, tuberculosis or *Aspergillus* within the previous year
- any history of malignancy except completely resected squamous or basal cell carcinoma of skin
- high index of suspicion of non-compliance with conventional therapy
- pregnancy or plans for pregnancy (including fatherhood)

**Absence of contraindications to surgery:**

- untreated proliferative retinopathy
- recent myocardial infarction or uncorrected myocardial ischaemia
- portal hypertension, gall stones or liver haemangioma on baseline ultrasound
- anaemia/leucopenia/thrombocytopenia; coagulopathy
- on anticoagulants (excluding aspirin)
- active gastric or duodenal ulcer; pancreatitis
- abnormal liver function tests (persistently more than 1.5 times upper limit of normal)
- panel of reactive antibody (more than 20% by flow cytometry)

**Other contraindications:**

- Addison's disease (untreated) or untreated malabsorptive disease
- inability to reach hospital within 2 hours of notification
- evidence of alcohol excess or other drug abuse

**Individuals with severe hypoglycaemia and normal renal function ('Edmonton profile')**

As above but to include:

- experience of at least 2 episodes of severe hypoglycaemia requiring third party intervention within the last 2 years. Usually the rate of severe hypoglycaemia will be higher, but this criterion is used to allow inclusion of patients who begin to experience recurrence of severe hypoglycaemia having previously obtained benefit from optimisation of therapy and those who have relaxed control in an attempt to avoid hypoglycaemia
- evidence of altered hypoglycaemia awareness
- (Clarke score of more than or equal to 4; Ryan HYPO score of more than or equal to the 90$^{th}$ centile; and evidence of presymptomatic biochemical hypoglycaemia on monitoring)

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- or marked glycaemic lability as defined by Ryan Lability Index; continuous subcutaneous glucose monitoring profiles

**Individuals with suboptimal control despite a functional renal graft:**

- islet transplantation may be considered in those at more than 3 months and less than 5 years post-renal transplant who are stable on tacrolimus-based immunosuppression (in combination with mycophenolate mofetil or sirolimus; with prednisolone dose of less than 5 mg daily)
- all with severe hypoglycaemia or altered hypoglycaemia awareness would be eligible
- in addition any person with HbA1c of more than 53 mmol/mol (7%) or marked glycaemic lability
- glomerular filtration rate (GFR) should not be less than 40 ml per minute per 1.73 m and serum creatinine not more than 175 micromoles/litre

This group of patients may also be considered for pancreas after kidney PAK transplantation, but only if without high cardiovascular risk precluding the more major whole organ transplant procedure, or previous prolonged peritoneal dialysis or other abdominal pathology adversely increasing operative risk. Children will not ordinarily be considered for transplant given the potential long-term complications of immunosuppression.

**Exclusion criteria**

See service standards for exclusions.

### 10.3.1.3  2008 NICE IPG 257 for islet cell transplantation [508]

**Recommendation (section 10.3)**

Patient selection for this procedure should involve a multidisciplinary team. Selection criteria should take into account that the procedure is particularly indicated for patients with hypoglycaemia unawareness and/or those already on immunosuppressive therapy because of renal transplantation.

**Outcome data**

Evidence was based on a report using CITR data of 1999-2004 (North American data – second report) – CLOSE 2007[126]. This registry study included n=112 patients. The IPG also focused on efficacy data from 3 case series of n=23, n=36 and n=65 patients[566,609,645] and a non-randomised study of n=99 patients.[698] The results are summarised in Table 132:    Results of the main studies used in IPG257.

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**Table 132: Results of the main studies used in IPG257**

| Outcome | CLOSE 2007[126]. (n=112) CITR Registry data | SHAPIRO 2006[645] (n=36) Case-series | RYAN 2005[609] (n=65) Case-series | TOSO 2007[698] (n=99) Non-randomised CCT | POGGIOLI 2006[566] (n=23) Case-series |
|---|---|---|---|---|---|
| Mortality | None | - | - | - | - |
| Severe hypoglycaemia - episodes | 82% over 1 year pre-transplant 5% over 1 year post-transplant | None at 1-12 years post-transplant (in patients with residual graft function) | Significantly improved severity, up to 4 years from baseline | - | - |
| Insulin independence | 67% at 6 months 58% at 1 year (post-transplant) | 58% during median 41 months 76% of these were insulin dependent again after 2 years 44% at 1 year (post-transplant) | 68% for >1 month (median follow-up 36 months) Median duration of insulin independence was 15 months (post-transplant) | - | - |
| Insulin requirements in insulin dependent people | Reduction from baseline: 57% at 6 months 69% at 1 year (post-transplant) | - | Most patients had to resume taking insulin, but this was lower doses than before transplant | - | - |
| Partial graft function but still insulin dependent | - | 28% at 1 year (post-transplant) | Mean duration of graft function (C-peptide secretion) was 25 months, thus, despite a functioning graft, most people had to resume taking insulin (but lower doses) | - | - |
| Complete graft failure | 13% at 1 year (post-transplant) | 28% at 1 year (post-transplant) | - | - | - |
| Hypoglycaemia unawareness | - | - | Significantly reduced, up to 4 years from baseline | - | - |
| Glycaemic | - | - | Significantly improved, up to | - | - |

| | | | | | |
|---|---|---|---|---|---|
| control | | | 4 years from baseline | | |
| Hypoglycaemia fear | - | - | - | SS improvement post initial transfusion | - |
| QoL | - | - | - | - | SS improvement in DQoL<br><br>SS improvement in only 1/8 domains of HSQ |

**10.3.1.4    CITR data 1999-2010 (BARTON 2012)[57] n=677 patients**

The CITR is the comprehensive islet transplant registry for 27 NIDDK-funded North American and JDRF-funded European and Australian centres since 1999. The CITR consists of 81% of all allogeneic islet transplants conducted as Phase I/II trials or standard of care. In this data set/report there were:

- 214 recipients in 1999–2002 (early), 255 in mid-2003–2006, and 208 in 2007–2010 (recent)
- 423 (62%) came from North America, and 254 (38%) were reported from the European and Australian JDRF sites
- transplants comprised islet alone in 575 (85%) and IAK or simultaneous islet kidney (IAK/SIK) transplant in 102 (15%).
- no cases of islet transplantation after total pancreatectomy

**Recipients**

- typically aged between 18 and 65 years
- all have had type 1 diabetes for more than 5 years
- 95% had documented negative fasting C-peptide (less than 0.3 ng/mL) and
- very problematic diabetes control, including hypoglycaemia unawareness complicated by episodes of severe hypoglycaemia and/or marked glycaemic lability characterized by wide swings of blood glucose levels, often with consistently elevated HbA1c levels (more than 64 mmol/mol [8%]).

**Results**

- Substantial shifts in immunosuppression strategies implemented during the 12-year period:
  - the early and mid-eras dominated by the Edmonton Protocol; which used an IL-2 receptor antagonist (for example, daclizumab) for induction and a mammalian target of rapamycin (mTOR) inhibitor (for example, sirolimus), together with a calcineurin inhibitor ([CNI] for example, tacrolimus) for maintenance immunosuppression.
  - in the most recent era, there has been a shift to induction with a T-cell depleting antibody, with or without a TNF-α inhibitor (for example, etanercept) and maintenance with an mTOR inhibitor or an inosine monophosphate dehydrogenase inhibitor (for example, mycophenolic acid) combined with a CNI.
- Changes in patient characteristics over the 12-year period, suggesting more appropriate patient selection:
  - over time, recipients with C-peptide more than or equal to 0.3 ng/mL have been excluded.
  - increasingly, patients selected at older age and with longer type 1 diabetes duration.
  - requiring slightly less insulin.
  - having better kidney function, as indicated by lower serum creatinine.
  - more people using insulin pumps for insulin delivery (may explain the slightly lower daily insulin requirement).
  - more people taking lipid-lowering medications.
- Increasing levels of missing data for insulin dependence with longer follow-up (7% at 5 years, and 10-20% for other outcomes at 1-3 years).
- Mortality: low events and stable during the 12-year period.
- Life-threatening events: incidence declined with different eras.
- Insulin independence:
  - 1999-2002 era: 51, 36 and 27% (1, 2 and 3 years post-transplant)

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- o 2003-2006 era: 37% (3 years post-transplant)
- o 2007-2010 era: 66, 55 and 44% (1, 2 and 3 years post-transplant)
- o SS (p=0.01) decline during 5 years in all eras.
- Durability of graft function (fC-peptide of more than or equal to 0.3 ng/ml):
  - o improved significantly over the eras (p<0.001).
  - o rate of graft function loss was significantly reduced if insulin independence was previously achieved (effect seen in all eras).
- Islet reinfusion (when first graft loses function completely or declining function proven by declining C-peptide levels:
  - o SS decreased over 12-year period: 48% by 1 year in 2007-2010 versus 60-65% in 1999-2006.
- HbA1c: SS improvement after transplantation.
- Composite HbA1c of less than 48 mmol/mol (6.5%) or a drop by two or more percentage points:
  - o SS improvement from the early era to the mid-era (p 0.03).
  - o no further improvement in the most recent era, with 2–5-year success rates of 50–60% in the recent era.
- Severe hypoglycaemia:
  - o baseline was more than 90% of people (all eras).
  - o more than 90% remained free of SH events through 5 years of follow-up in all eras.

**10.3.1.5 Integrated UK National Islet transplant program (BROOKS 2013)[92] (n=20) islet transplant patients (case series)**

Islet transplants over the first 3 years of the integrated UK islet transplant program (April 2008 – March 2011); 16 ITA and four IAK transplant recipients. Median age was 49 (range, 44–54) years and diabetes duration was 30 (range, 17–39) years with median weight of 61.0 (range, 55.5–76.0) kg.

**Inclusion criteria:**

- C-peptide-negative with type 1 diabetes.
- Complicated by recurrent severe hypoglycaemia (more than or equal to 1 event over the preceding 12 months requiring assistance to actively administer carbohydrate, glucagon or other resuscitative actions) despite optimized conventional management.
- Contraindications included insulin resistance (insulin requirement of more than 0.7 U/kg to achieve HbA1c of less than 75 mmol/mol [9.0%]), body weight of more than 80 kg and any contraindications to immunosuppression therapy (including impaired renal function with isotopic GFR of less than 60 mL per minute per 1.73 $m^2$ or albumin excretion rate of more than 300 mg per 24 hours [unless previous renal transplant]).

**Results**

- SS reduction in severe hypoglycaemia (episodes per patient per year) at 12 and 24 months post-transplant (baseline = 20; 12 months = 0; and 24 months = 0.3; both p<0.001)
- SS reduction in HbA1c (baseline = 64 mmol/mol (8%); 12 months = 45 mmol/mol (6.3%); and 24 months = 44 mmol/mol (6.2%); p<0.001 and p<0.01)
- SS reduction in insulin dose used at 12 and 24 months post-transplant
- graft survival: 80% at both 12 and 24 months post-transplant
- graft survival at 3 years was 70% in patients who had and had not achieved insulin dependence
- insulin independence: 45% of patients; 3 of these 9 patients remained off insulin at 24 months

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### 10.3.2 Whole pancreas transplantation

#### 10.3.2.1 Current listing criteria [2015]

**Simultaneous kidney/pancreas (SPK) transplant**

The standard listing criteria for a SPK transplant are:

- all patients listed should have insulin-treated diabetes
- patients listed with type 2 diabetes must have a BMI of less than 30 kg/m$^2$
- patients listed must be receiving dialysis or have a GFR of less than 20 mls per minute

**Pancreas transplant alone (PTA)**

The standard listing criteria for a PTA are:

- all patients listed should have insulin-treated diabetes
- patients listed with type 2 diabetes must have a BMI of less than 30 kg/m$^2$
- at least 2 severe hypoglycaemic episodes in the last 24 months and be assessed by a diabetologist to have disabling hypoglycaemia

**PAK transplant**

The standard listing criteria for a PAK transplant are:

- all patients listed should have insulin-treated diabetes
- patients listed with type 2 diabetes must have a BMI of 30 kg/m$^2$
- a history of severe hypoglycaemia within the last 2 years or HBA$_{1c}$ of more than or equal to 53 mmol/mol (7%)

#### 10.3.2.2 Data from FRANK 2004[223] (study found in IPG 257); n=30 whole pancreas transplant patients (case series)

**Whole pancreas transplantation**

- continued functioning grafts: 83% (25/30)
- lost graft function or death: 17% (5/30)
- 1 death (11 days after transplant)

## 10.4 Economic evidence

**Published literature**

No relevant economic evaluations were identified. As this question was not aimed at assessing the effectiveness and cost-effectiveness of transplantation, but to identify the referral criteria for being considered for a pancreas transplant, or pancreatic islet cell transplantation, no economic studies could be considered relevant.

## 10.5 Evidence statements

### 10.5.1 Clinical evidence statements

None. Referral criteria and study results have been summarised in the main body of the review.

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**Economic**

No relevant economic evaluations were identified.

## 10.6   Recommendations and link to evidence

| Recommendations | **82. Consider referring adults with type 1 diabetes who have recurrent severe hypoglycaemia that has not responded to other treatments (see Section 11) to a centre that assesses people for islet and/or pancreas transplantation. [new 2015]**<br><br>**83. Consider islet or pancreas transplantation for adults with type 1 diabetes with suboptimal diabetes control who have had a renal transplant and are currently on immunosuppressive therapy. [new 2015]** |
|---|---|
| Relative values of different outcomes | The GDG determined the impact of a whole pancreas transplant and islet cell transplantation in adults with type 1 diabetes by assessing their effect on the following clinical outcomes:<br><br>**Hypoglycaemia, including severe hypoglycaemia** - Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes, and is an obstacle to improved control. Pancreas and islet cell transplantation aims to reduce the incidence of recurrent severe hypoglycaemia in an individual receiving either intervention. Particular focus was given to:<br>• incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a third party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes and their families.<br>• incidence of nocturnal hypoglycaemia.<br><br>**Improvement in glycaemic control** - Assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular and macrovascular complications.<br><br>**Quality of life** – The evidence was reviewed to look at the impact of each transplant intervention on quality of life outcomes. An intervention that reduces the frequency of severe hypoglycaemia episodes and improves glycaemic control should increase quality of life. However, transplantation interventions currently require the recipient to take immunosuppression; immunosuppression carries with it both short- and long-term risks of side effects and requires constant monitoring, all of which may impact on quality of life.<br><br>**Insulin independence rate** – Insulin independence can be achieved with both pancreas and islet transplantation; the data were reviewed to determine which intervention carried the best probability of achieving insulin independence.<br><br>**Graft survival** – An individual undertaking the associated risks with having either intervention would need to be informed of the likely duration of graft survival before considering whether to be referred for the procedure. Note: graft survival may be indicated by biochemical measures of islet function and does not necessarily imply insulin independence. |

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| | |
|---|---|
| | **Hospital admissions** – Recurrent severe hypoglycaemia as a consequence of impaired awareness of severe hypoglycaemia is likely to result in multiple hospital admissions. However, it must also be noted that transplant recipients are at risk of having to attend hospital for admission as a consequence of complications from the transplant procedure or side-effects from having to take long-term immunosuppression.

**Adverse events (including mortality and sudden death)** – Recurrent severe hypoglycaemia carries with it a risk of sudden death. However, transplant interventions aimed at reducing the frequency of severe hypoglycaemia episodes also carry a risk of death as a consequence of the procedure (1-3% for pancreas transplantation in the first year post-transplant) or as a consequence of long-term immunosuppression (including increased risk of renal complications, increased lifetime risk of malignancy and bone marrow suppression). |
| Trade-off between clinical benefits and harms | The GDG considered outcome data from UK and international transplant programmes. Data from the CITR, NHS England and previous NICE Guidance on allogeneic pancreatic islet transplantation [508] were used in writing the guidance.

The original NICE guidance from 2008 was based on data obtained from the CITR in 112 recipients from 1999-2004. The procedure was recommended for individuals with loss of hypoglycaemia awareness and/or patients with diabetes on immunosuppression following renal transplantation.

Both islet and pancreas transplantation achieve their goals of reducing the incidence of severe hypoglycaemia and improving glycaemic control following procedure intervention .[126,609,646]

Insulin independence following islet transplantation has been reported to be between 44 and 66% at 1 year [57,126,609,646], although 76% of patients were reported to be insulin dependent again at 2 years post-transplant.[646] Complete graft failure rate was between 13 and 28% at 1 year post-transplant [126,609,646], with mean duration of graft function reported to be 25 months.[609] Significant improvement in quality of life was reported following islet transplantation (DQoL assessment).[609]

The main aim of islet transplantation is to achieve a reduction in the frequency of severe hypoglycaemia. CITR has shown that improved clinical outcomes have been achieved over the last decade by more careful patient selection[57], including:
- exclusion of patients with C-peptide positivity
- selection of older patients with a longer duration of type 1 diabetes
- avoidance of insulin-resistant patients

The CITR reports that more than 90% of islet recipients are now achieving freedom from severe hypoglycaemia at 5 years post-procedure follow-up.[57]

Evidence for freedom from recurrent severe hypoglycaemia following islet transplantation has been supported by UK study outcomes (Brooks 2013). IN that patient group, 45% achieved insulin independence of variable duration with 1 patient out of 20 continuing insulin independence at 36 months follow-up]) HbA1c had improved to 44 mmol/mol (6.2%) at a median of 24 months follow-up.

Whole-organ pancreas transplantation is associated with a greater short-term risk of morbidity and mortality than islet transplantation. One study (Frank 2004[223]) |

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|  | reported that 1 of 30 pancreas recipients died at 11 days post-transplant, 2 further grafts were lost from vascular thrombosis at 4 and 6 days post-transplant, one graft was lost to perigraft infection at 1 month post-operatively and a further graft was lost through rejection at 24 months post-procedure; function was therefore maintained in 83% of grafts (25/30) at 24 months post-intervention. Insulin independence was achieved in 85% of recipients and an HbA1c of 31 mmol/mol (5%) was attained at 1 year post-transplant.<br><br>The GDG noted that islet transplantation utilised a procedure that carried a lower risk of immediate complications and mortality than pancreas transplantation (Frank 2004, Ryan 2005, Shapiro 2006, Close 2007). Both procedures carry long-term risks from immunosuppression use, although data on complications from immunosuppression use are limited for islet transplantation as the procedure has only been a viable treatment option for patients with type 1 diabetes since the Edmonton trial outcomes of 2000.<br><br>The GDG also recognised that despite the initial short-term morbidity and mortality risks, whole-organ pancreas transplantation was more likely to achieve insulin independence than islet transplantation, and graft function was likely to be more prolonged. However, islet transplantation might be considered for individuals experiencing recurrent severe hypoglycaemia who are not physically fit enough to undergo a major surgical procedure, or for individuals who did not wish to accept the increased short-term morbidity and mortality risks from whole-organ pancreas transplantation. |
|---|---|
| Economic considerations | This review examined referral criteria only and therefore no economic evaluation was considered appropriate for this question.<br>The GDG acknowledged there is a cost associated with specialist referral for transplant. However, this question did not focus on whether referral is effective or cost effective. The GDG observed that both interventions were only likely to be used in a small proportion of individuals with type 1 diabetes experiencing recurrent severe hypoglycaemia that had not responded to other interventions for the management of severe hypoglycaemia. The GDG was mindful that the facilities for transplantation exist and are currently not operating at capacity. It was felt important that the right patients should be put forward for proper assessment in order to maximise the potential benefits of transplantation. |
| Quality of evidence | The only evidence available to the GDG was observational studies that cannot be assessed for quality by GRADE. |
| Other considerations | The GDG considered outcome data from UK and international transplant programmes and found that they supported the current criteria for referral to a specialist centre that can both assess and manage severe hypoglycaemia and offer transplantation options. The GDG noted that it did not have the remit to rewrite referral criteria for pancreas or islet transplantation for adults with type 1 diabetes in the UK. However, the GDG wished to highlight the availability of pancreas and islet transplantation for individuals with type 1 diabetes experiencing recurrent severe hypoglycaemia. At the time of publication, current referral criteria are available at XXXX.[509] |

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# 11 Impaired awareness of hypoglycaemia [2015]

Impaired awareness of hypoglycaemia (IAH) was not covered in the 2004 guideline; these evidence reviews and recommendations are new for 2015.

## 11.1 Identification and quantification of impaired awareness of hypoglycaemia

### 11.1.1 Introduction

Hypoglycaemia is one of the most common complications of the treatment of type 1 diabetes. It is defined as an abnormally low plasma glucose concentration. Cognitive function deteriorates when plasma glucose concentrations decline to less than 3.0 mmol/litre[751] . Mild hypoglycaemia results in a wide variety of symptoms, including hunger, anxiety or irritability, palpitations, sweating or tingling lips and is by definition symptomatic and noted by the patient. As plasma glucose concentrations fall lower patients may experience weakness and lethargy, impaired vision, confusion or irrational behaviour. Severe hypoglycaemia may result in convulsions, loss of consciousness, coma. Between 4 and 10% of deaths in people with type 1 diabetes are attributed to hypoglycaemia[143]. IAH is diagnosed when the adult with type 1 diabetes has poor perception of his/her own hypoglycaemia, depending on glucose monitoring test results or other people's observations to diagnose it. It is likely that most people with type 1 diabetes will experience some form of hypoglycaemia within weeks or months of commencing insulin therapy and throughout their life with diabetes.  In the vast majority of cases people with type 1 diabetes will perceive and successfully treat their own low blood glucose excursions with a small amount of fast-acting carbohydrate (for example, Lucozade, glucose tablets, non-diet fizzy drinks, fruit juice or high glucose, low fat confectionery such as Jelly Babies). Severe hypoglycaemia occurs when patients require treatment by a third party because they are incapable of self-management.[640] The risk for severe hypoglycaemia increases 6-fold if a person has IAH[243]Recent updates to the DVLA guidelines concerning driving and diabetes use instances of 'severe hypoglycaemia' as one determinator of fitness to drive and absence of awareness as another.

Research suggests [151,294] that hypoglycaemic episodes can contribute to a loss of early warning symptoms during subsequent hypoglycaemia, with symptoms beginning to be felt at lower and lower blood glucose concentrations, and recurrent exposure to hypoglycaemia is believed to be the major factor in causing and sustaining hypoglycaemia unawareness. Lack of subjective awareness makes the early self-treatment of mild hypoglycaemia more difficult and episodes of severe hypoglycaemia more likely. Similarly, in research studies, avoidance of exposure to plasma glucose less than 3 mmol/litre has been associated with restored symptom perception[141]. Typically people with diabetes are advised to keep blood glucose levels above 4.0 mmol/litre and to treat levels below 4.0 mmol/litre in order to avoid hypoglycaemia. This advice is clinically sound but defining everything under 4 mmol/litre as hypoglycaemia can lead to over-estimation of mild hypoglycaemia, increased anxiety around hypoglycaemia and inappropriate diagnosis of IAH.

Hypoglycaemia, or the possibility of hypoglycaemia, can have a significant impact on the quality of life of people with type 1 diabetes and also of their families [416,578]. It can affect their ability to drive and their confidence in taking part in a wide variety of activities and careers. On the other hand, mild hypoglycaemia can be so commonplace for some patients that it is easy for them to underestimate its impact or to evaluate whether their hypoglycaemic excursions have become problematic.

**The GDG asked these questions:**

- In adults with type 1 diabetes, how is impaired awareness of hypoglycaemia/hypoglycaemia unawareness best identified and quantified?

- In adults with type 1 diabetes and impaired awareness of hypoglycaemia, what is the most effective strategy for recovering hypoglycaemia awareness?

**11.1.1.1    Summary of the main impaired awareness of hypoglycaemia scores used in studies.**

The following scoring systems for hypoglycaemia awareness assessment were reviewed:

**Gold score[253]**

This scoring system is based on the response to a single question: 'Do you know when your hypos are commencing?'. In validating this score biochemical hypoglycaemia was defined as less than 3 mmol/litre. Results are expressed by a 7-point Likert scale, where 1 = 'always aware' and 7 = 'never aware'. IAH is suggested by a value of more than or equal to 4. This score is based on results from a prospective case-control study with 60 participants and 12 months follow-up (Gold 1994); 29 participants were noted to have impaired awareness and 31 participants had normal awareness of hypoglycaemia. Participants with IAH had an increased frequency of severe hypoglycaemia episodes (more than or equal to 1 severe hypoglycaemia episodes in 66% with impaired awareness versus 26% with normal awareness; higher incidence of severe hypoglycaemia episodes per patient per year: 2.8 with impaired awareness versus 0.5 with normal awareness).

**Clarke score[124]**

This score is made up of 8 questions characterising an individual's exposure to episodes of moderate and severe hypoglycaemia to assess the glycaemic threshold for and symptomatic response to hypoglycaemia. The assessment gives a score where a value of more than or equal to 4 indicates IAH. The scoring system is derived from a prospective case series study in 78 subjects with 9-12 months follow-up (Clarke 1995). The Clarke includes a score for impaired awareness when hypoglycaemia is not detected until blood glucose levels are less than 2.8 mmol/litre. Frequency of severe hypoglycaemia events was increased in subjects with impaired awareness.

**HYPO score**

This is a composite hypoglycaemia score based on the frequency, severity and degree of IAH that provides a measure of the extent of problems with hypoglycaemia to complement an assessment of problems with glucose control.[610] The score is developed from an assessment of glucose readings collected from patients over a 4 week period (minimum of two capillary glucose readings a day), noting details of each hypoglycaemic event (glucose less than 3.0 mmol/litre), the number of occurrences of hypoglycaemia, and a completed questionnaire about the frequency and severity of hypoglycaemia episodes over the previous year (Ryan 2004). In particular, emphasis is placed on which symptoms occur and whether outside help from a third party was obtained to either recognise or treat a hypoglycaemic event. Based on data from a routine clinic and one that assessed people referred for islet transplantation and their experience of hypoglycaemia, a score of more than or equal to 433 is representative of problematic hypoglycaemia, more than or equal to 1047 is indicative of very serious unawareness of hypoglycaemia.

**DAFNE hypoglycaemia awareness rating**

This score is a three question hypoglycaemia assessment that is used in the national DAFNE database. It asks patients to rate their awareness of hypoglycaemia by stating whether they usually recognized that they were hypoglycaemic at a blood glucose concentration of:

1. more than or equal to 3 mmol/litre
2. less than 3 mmol/litre or
3. not at all.

Patients rating themselves in categories 2 and 3 were defined as having impaired awareness and had reported a mean of 3.6 severe hypoglycaemia episodes during the preceding year; compared with 0.87 in patients rating themselves as aware at blood glucose concentrations of 3 mmol/litre or higher[328]

**Pedersen-Bjergaard score[610]**

IAH is assessed by the question 'Can you feel when you are low?', with the respondent selecting one answer of 'always', 'usually', 'sometimes/occasionally' or 'never'. A response of 'usually' implies IAH, whilst the responses of 'sometimes/occasionally' or 'never' imply severely IAH. This scoring system was developed from a questionnaire assessing the occurrence of hypoglycaemia and aspects of hypoglycaemia unawareness in 230 participants, 47% of whom were classified as having impaired awareness (Pedersen-Bjergaard 2001). Groups with impaired awareness were found to have a 5.1 to 9.6 increased risk of severe hypoglycaemia compared with groups defined as having normal awareness.

**Edinburgh Hypoglycaemia Score**

The Edinburgh hypoglycaemia score[295] asks people to rank each of a number of symptoms on an analogue scale from 0 = not at all, to 7 = very severe. The reference is

### 11.1.2 Review question: In adults with type 1 diabetes, how is impaired awareness of hypoglycaemia best identified and quantified?

For full details see review protocol in Appendix C.

**Table 133: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
|---|---|
| Intervention(s) | IAH according to scoring systems (specific names): <br> • Gold score <br> • Clarke score <br> • Ryan score <br> • Pedersen-Bjergaard score |
| Comparison(s) | • Other scoring systems <br> • No scoring system |
| Outcomes | • Ability to predict severe hypoglycaemia (incidence of severe hypoglycaemia) <br> • Ability to predict driving or work related accidents (incidence of accidents) |
| Study design | All study types |

### 11.1.3 Clinical evidence

We searched for studies assessing scoring systems for identifying adults with type 1 diabetes who had IAH. Fourteen full studies[116,124,243,244,251,253,296,316,328,345,551,610,633,670] were included in this review. The GDG also considered seven conference abstracts[11,149,239,362,487,664,680] that met the protocol inclusion criteria, and were used for additional information.

Evidence from these are summarised in Table 134 and Table 135. See also the study selection flow chart in Appendix D, study evidence tables in Appendix G and exclusion list in Appendix K.

All studies were non-comparative observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The

study details and the full results have been summarised in tables below. All of the data was therefore reported narratively in Table 134 and Table 135.

**Table 134: Summary of fully published studies included in the review**

| Study | Intervention/ comparison | Population | Score system used for IAH | Outcomes |
|---|---|---|---|---|
| Choudhary 2010A | Prospective case-series (9-12 months follow-up)<br><br>Weekly 4-point capillary home blood glucose monitoring (HBGM), 5 days of CGM and prospective reporting of severe hypoglycaemia | n=95<br>Type 1 diabetes adults<br>n=74 normal awareness, n=21 IAH | Gold score ratings used to define IAH (≥4) | Patients with IAH versus normal awareness:<br>3 x higher incidence of severe hypoglycaemia<br>1.6 x higher incidence of hypoglycaemia on weekly HBGM<br>NS differences observed with CGM |
| Clarke 1995 | Prospective case-series (9-12 months follow-up)<br><br>Hand held computer (HHC) for BG estimation | n=78<br>Type 1 diabetes adults<br>n=39 IAH | Clarke score (8 questions) versus Question "to what extent can you tell by your symptoms that your sugar is low? (never, sometimes, often, always)." | n=39 with IAH<br>Patients with IAH versus normal awareness had/were:<br>NS difference for age, disease duration, insulin dose, or HbA1c<br>SS less accurate in detecting BG <3.9 mmol/1 (P = 0.001)<br>SS fewer autonomic (p = 0.006) symptoms per subject.<br>SS fewer neuroglycopenic (p=0.004) symptoms per subject.<br>Prospective diary records revealed that reduced-awareness subjects experienced:<br> More moderate (P = 0.026) and severe (P = 0.0062) hypoglycaemic events.<br>The second assessment results were similar to the first and verified the reliability of the data. |
| Geddes 2007 | Prospective case-series (4 weeks follow-up)<br><br>Compares 3 methods of IAH detection:<br>Gold<br>Clarke<br>Pedersen-Bjergaard<br><br>Also filled out Edinburgh Hypoglycaemia Score and 4x/day | n=140 recruited (n=80 completers)<br>Type 1 diabetes adults<br>IAH: Gold = 24%, Clarke = 26%, Pedersen-Bjergaard = 63% | Gold, Clarke and Pedersen-Bjergaard score ratings used to define IAH (≥4, ≥4, always) | IAH: Gold = 24%, Clarke = 26%, Pedersen-Bjergaard = 63%<br>Strong association between Gold and Clarke methods for IAH (p=0.001)<br>If Pederson used 'occasionally and never' as IAH, the % fell to 15.4% - still a poor correlation between this method and Gold or Clarke methods (rs=0.5 for both)<br>Patients with IAH versus normal awareness had/were:<br>SS older (using Gold and Clarke scores). NS difference for Pedersen-Bjergaard score. |

| Study | Intervention/ comparison | Population | Score system used for IAH | Outcomes |
|---|---|---|---|---|
| | HBGM for 4 weeks | | | SS longer duration of diabetes (using all 3 methods) |
| | | | | NS difference in HbA1c (using all 3 methods) |
| | | | | SS more episodes of biochemical hypo over the 4 weeks (using Gold and Clarke scores). NS difference for Pedersen-Bjergaard score. |
| | | | | Lower autonomic symptoms reported during biochemical hypo (using Gold and Clarke scores). NS difference for Pedersen-Bjergaard score. |
| | | | | NS difference in self-reported neuroglycopenic symptoms (using all 3 methods). |
| | | | | SS incidence of severe hypos in previous year (using all 3 methods). |
| Geddes 2008 | Cross-sectional study | n=518 Type 1 diabetes adults n=101 (19.5%) IAH | Gold score ratings used to define IAH (≥4) | Patients with IAH versus normal awareness had/were: |
| | | | | SS older (p<0.001) |
| | | | | SS longer duration of diabetes (p<0.001) |
| | | | | 6 x higher number of episodes of severe hypo (per person) in preceding year p<0.001) |
| | | | | SS lower intensity of autonomic symptoms during episodes of self-treated hypo (p=0.004). |
| | | | | NS difference in intensity of neuroglycopenic symptoms |
| | | | | NS difference for HbA1c |
| | | | | Moderate and SS association between IAH and duration of diabetes (rs = 0.21, p<0.001) and rate of SH (rs = 0.34, p<0.001). |
| Gimenez 2009 | Prospective case-series (72h follow-up)<br><br>Compares 2 methods of IAH detection during an acute induction of hypoglycaemia with regular insulin: Gold Clarke | n=20 Type 1 diabetes adults IAH: 20 on Gold score, 19 also on Clarke score. | Gold and Clarke score ratings used to define IAH (≥4, ≥4) | IAH: Gold 20 of 20 (100%), Clarke = 19 of 20 (95%) |
| | | | | Clarke test score was SS negatively correlated with HbA1c values (that is, lower HbA1c = higher Clarke score, thus IAH). |
| | | | | Ability of score to detect percentage increase in symptoms during an acute induction of hypoglycaemia: |
| | | | | Clarke: sensitivity 100%, specificity 25%, Kappa index[a] 0.35. |
| | | | | CGM from the whole group revealed 18% of measurements <70 mg/dl; this was correlated with Clarke's test score and with |

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| Study | Intervention/ comparison | Population | Score system used for IAH | Outcomes |
|---|---|---|---|---|
| | | | 376 | increase in % of signs/symptoms during induced hypo. In patients with abnormal response of symptoms during hypo, CGM % of values <70 mg/dl was higher (23% versus 8%) than in those with a normal response (10%; p<0.028). |
| Gold 1994 | Prospective case-control study (12 months follow-up) | n=60 Type 1 diabetes adults n=29 IAH and n=31 normal awareness. | Gold score | IAH versus normal awareness: SS more patients had 1 or more episodes of SH (66% versus 26%) SS higher incidence of SH episodes/patient/year (2.8 versus 0.5) SS more patients had greater worry/fear of hypoglycaemia, but did not modify their behaviour accordingly. |
| Hendrieckx 2014 | Retrospective case-series | n=422 completers Type 1 diabetes adults IAH (Gold): 20.5% | Gold | IAH (Gold ≥4): = 20.5% Intact awareness (Gold = 1): 27% Most patients (52.4%) had Gold score 2 or 3. SH: 18.5% at least one event in past 6 months (mean 0.5; that is, 1 event/year) 46% of patients who reported severe hypoglycaemia episode in past 6 months also reported IAH; only 7% had intact awareness. Patients with severe hypoglycaemia were more likely to have IAH, experienced fewer symptoms of hypo, and relied more often on others to recognise a hypo event. Multivariate analyses: <br>• Greater IAH was SS associated with occurrence of SH <br>• IAH was SS associated with more frequent SH. |
| Hoi-Hansen 2010 | Cross-sectional study<br><br>3 methods compared: Gold (A) Clarke (B) Pedersen-Bjergaard (C) | n=470 (n=372 responders) Type 1 diabetes adults IAH: Gold = 75%, Clarke = 51% and Pedersen-Bjergaard = 41% | Gold (A) Clarke (B) Pedersen-Bjergaard (C) | Normal awareness: 75% (A), 51% (B) and41%(C) Impaired awareness/unawareness (C): 25% (A), 28%(B) and 13% were unaware (C) 46% belonged to intermediate group of impaired awareness (C) and 21% not classifiable (B) Higher rates of severe hypo in patients with impaired awareness (A,B)/unawareness (C) versus aware patients |

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| Study | Intervention/ comparison | Population | Score system used for IAH | Outcomes |
|---|---|---|---|---|
| | | | 377 | Patients with impaired awareness (C) had more severe hypoglycaemia than aware patients, and less severe hypoglycaemia than unaware patients. <br><br> A lower rate of severe hypo was reported by aware patients classified by method C versus method A <br><br> Fractions of patients with normal awareness without an event of severe hypo were 0.81, 0.86, 0.91 <br><br> All 3 methods of assessment of hypoglycaemia awareness are feasible in clinical practice since degree of awareness is associated with risk of severe hypo. Method C (trisected method) identifies and intermediate group with impaired awareness and with a risk of severe hypo that is SS different from those of aware and unaware patients. |
| Hopkins 2012 | Retrospective case-series - data from DAFNE audit (baseline and 1 year follow-up) | • n=539 responders <br> • Type 1 diabetes adults | IAH = those reporting symptom onset <3 mmol/litre or not at all | Pre-DAFNE: <br> • IAH: 40%, Hypo aware: 60% <br> • SH: 25% had ≥1 event in past 1 year; 16% ≥1 episode in past year. <br> Post-DAFNE <br> 62% of those who had experienced SH remained free of further episodes at follow-up <br> 10% of those who had been free of SH in the preceding year experienced ≥1 episodes. <br> Overall mean SH rate fell from 1.93 (range 0–99) to 0.61 (0–70) episodes/person/year after DAFNE (difference 1.15 [95% CI 0.73 to 1.57]; p<0.001) <br> At follow-up, 43% of those with IAH at enrolment reported restoration of the ability to detect hypoglycaemia at a blood glucose >3 mmol/litre. <br> The rate of SH fell significantly in both groups. |
| Janssen 2000A | Prospective case-series (2-4 weeks follow-up) | n=19 <br> Type 1 | Clarke score | The composite self-report score agreed reasonably well with the hypoglycaemia clamp measure |

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| Study | Intervention/ comparison | Population | Score system used for IAH | Outcomes |
|---|---|---|---|---|
| | Clarke questionnaire<br><br>Hand held computer to assess their recognition of hypo episodes occurring during 2-4 weeks<br><br>Underwent stepped hypoglycaemic clamp, so could study response to standardised hypoglycaemia. Diagnosis of IAH was based on the self-report questions, a composite self-report score and 3 different cut-off levels for the % of accurately recognised hypo episodes during the field study. Agreement with the hypoglycaemia clamp measure was tested by kappa, sensitivity and specificity. | diabetes adults | | (kappa 0.49, sensitivity 66.7, specificity 85.7%) and showed a better agreement than the separate self-report questions.<br><br>The hand help computer criterion of IAH did not agree with the hypoglycaemia clamp criterion at any of the cut-off levels tested. |
| Pedersen-Bjergaard 2003 | Prospective case-series (1 year follow-up)<br><br>Questionnaire based on Pramming and Deary studies for occurrence of hypo, aspects of hypo unawareness and sections on demographic issues and lifestyle. | n=230<br>Type 1 diabetes adults<br>IAH: 47% | Pedersen-Bjergaard score: questionnaire: can you feel when you are low?<br><br>Cut-off: usually = IAH, occasionally or never = severe IAH (unawareness). | Almost 90% of patients correctly recalled whether they had had SH over the previous year. Those with high recorded numbers of episodes had incomplete recall, resulting in 15% underestimation of overall rate.<br>Question: do you recognise symptoms when you have a hypo? 40% normal awareness, 47% impaired awareness and 13% unawareness.<br>Groups with IAH had 5.1 and 9.6 x higher rates of SH versus normal awareness groups (p<0.001). |
| Ryan 2004 | Prospective case-series (4 weeks follow-up) | n=100<br>Type 1 diabetes adults | Hypo score<br><br>IAH = median score ≥850; | Group with IAH had:<br>• median 8.0 versus 2.0 episodes of hypoglycaemia per patient in previous 4 weeks (p<0.001), |

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| Study | Intervention/ comparison | Population | Score system used for IAH | Outcomes |
|---|---|---|---|---|
| | Prospective monitoring of blood glucose ≥2x/day for 4 weeks. Frequency of SH over preceding year also estimated. | | intact awareness = median score 91. | • 0.4 versus 0.0 SH episodes per patient in previous 4 weeks (p-value not reported). |
| Schopman 2011 | Prospective case-control study (4 weeks follow-up) Prospective monitoring of blood glucose 4x/day for 4 weeks. Frequency of SH over preceding year also estimated. | n=38 Type 1 diabetes adults Normal awareness (n=19) patients and IAH (n=19) patients. | Gold score | IAH patients versus normal awareness: 2 x frequency of all episode of hypo over 4-week monitoring period (SS; p=0.003) NS difference in total no of symptomatic hypo episodes. 7 x higher incidence of symptomatic hypo (SS, p=0.001) – comprised 47% of all glucose values <3.0 mmol/litre versus 14% in normal group. Higher annual prevalence of SH: 53% versus 5% SS higher incidence of severe events (p=0.001). |
| Streja 2005 | Prospective case-series (2-4 weeks) SMBG and clinical data collected 72hr CGMS Questionnaire | n=60 Type 1 diabetes adults HUN = 42% | Adapted Janssen questionnaire (3/5 questions answered yes = HUN) | HUN by Questionnaire: 42% Best predictor of HUN was maximal duration of hypo, as determined by CGMS (p=0.001) Detection of hypo episodes with duration >90 minutes identified patients with HUN (sensitivity, 75%, specificity, 885) HUN was SS associated with used of ACEs or ARBs (p=0.003), and longer duration of diabetes (p=0.008) |

*Abbreviations: HUN, hypoglycaemia unawareness; IAH, impaired hypoglycaemia unawareness; SH, severe hypoglycaemia*
*(a)* Kappa index of 1.0 = complete agreement.

**Table 135: Summary of conference abstracts considered by the GDG**

| Study | Intervention/ comparison | Population | Outcomes |
|---|---|---|---|
| ACAMPO 2012 | Conference abstract Cross-sectional study Dutch translation of the Clarke | n=486 Type 1 diabetes adults | • HUN: n=158 patients (33%) and n=103 patients (21%) recalled SH in the year before the Clarke questionnaire. • HUN was associated with male sex, lower HbA1c, duration of diabetes, autonomic neuropathy and estimated GFR <60 ml/minute/1.73m$^2$ (all p<0.05). • After adjustments, duration of diabetes, estimated GFR <60 ml/minute/1.73m$^2$ and lower HbA1c were still SS associated with HUN. • SH was independently associated with the presence of autonomic neuropathy (3.62; 1.65-7.94) and the use of |

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| Study | Intervention/ comparison | Population | Outcomes |
|---|---|---|---|
| | questionnaire : score ≥3 out of 5 was assumed to indicate HU. SH was assessed on the basis of the same questionnaire . | | benzodiazepines (4.59; 1.80-11.73), but not with HbA1c or diabetes duration.<br><br>• No association with SH or HUN: use of insulin analogues, insulin pump therapy, ACE inhibitors or beta-blockers<br><br>Conclusion: HUN is still highly prevalent in type 1 diabetes patients despite advances in insulin therapy. Diabetes duration, lower HbA1c level and kidney dysfunction were independent risk factors for HU. Autonomic neuropathy and use of benzodiazepines were risk factors for SH. Clinicians treating patients with type 1 diabetes should be aware of the still high prevalence of HUN and its risk factors. (Table presented). |
| CZYEWSKA 2012 | Conference abstract | n=238<br><br>Type 1 diabetes adults and young people | HUN was assessed by Clarke and Gold.<br>HUN: CLARKE = 58 patients (24.4%), GOLD = 68 patients (28.5%).<br>Patients split into 3 groups:<br>Group I- patients with Hypo awareness confirmed by both tests (n = 142)<br>Group II- patients with HUN confirmed by one test (n = 66)<br>Group III- patients with HUN confirmed by both tests (n = 30).<br>Patients with HUN versus awareness patients:<br>were older (P = 0.040)<br>had longer diabetes duration (P = 0.014)<br>NS difference in lipid level, waist circumference, creatinine level, BMI, arterial pressure and HbA1c.<br>More glycaemia level below 55 mg/dl (p=0.016).<br>Performed measurements of glycaemia more frequently (p=0.049).<br><br>Conclusion: Hypoglycaemia unawareness was observed in 40% type 1 diabetic patients. The severity of hypoglycaemia unawareness was associated with longer diabetes duration. The patients with hypoglycaemia unawareness had more frequent low glycaemia level. |
| GANDHI 2013 | Conference abstract | n=100<br><br>Type 1 diabetes (age not given) | HUN assessed by Clarke, Gold and Pederson and the Edinburgh Hypoglycaemic Score, questions on causes and worry for hypoglycaemia scored on a seven-point Likert scale.<br>Clarke score was used to assess HUN.<br>HUN: Clarke = 18%, Gold = 19% and Pederson = 7%.<br>HUN:<br>were SS older (p = 0.0018)<br>Had SS longer duration of diabetes (p = 0.0015)<br>Had SS increased prior severe hypoglycaemic episodes (p = 0.024) |

| Study | Intervention/ comparison | Population | Outcomes |
|---|---|---|---|
| | | | Giving the insulin dose twice was increased (p = 0.011) Were SS more worried about night-time hypoglycaemia (p = 0.041) Felt significantly less empowered to avoid future hypoglycaemic episodes (p = 0.047). There was very poor correlation between the Pederson questionnaire and the other two methods used to assess HU. There was moderate agreement between the Clarke and Gold scores (kappa = 0.503). Conclusion: This report demonstrates lower prevalence of HU compared with the literature and may reflect recent improvements in type 1 diabetes management, most notably education. It highlights opportunities to improve education to avoid hypoglycaemia. The findings of this study are in keeping with a previous report suggesting that Clark and Gold questionnaires are better discriminators for HU than Pederson |
| KANC 2010 | Conference abstract | n=114 type 1 diabetes (n=53) and type 2 diabetes insulin treated | Hypoglycaemia awareness status by Clarke's questionnaire Confirmed high internal consistency reliability of the translated questionnaires (Cronbach's alphas were 0.93, 0.94, and 0.49 for HFS, PAID, and Clarke's questionnaire, respectively). SS correlation found between HFS score and Clarke's score in general (r = 0.20, p = 0.030), type 2 diabetes (r = 0.27, p = 0.036), type 1 diabetes (r = 0.17, p = 0.217), meaning that patients with type 2 diabetes experience an increase in Fear of Hypoglycaemia as their awareness decreases (but NS for type 1 diabetes). SS association of HbA1c with HFS score (r=0.23, p=0.015) and PAID score (r=0.47, p<0.001), indicating worse glucose control with increasing FoH and diabetes problems. On the contrary, four patients had very high PAID and HFS score and low HbA1c. Conclusion: In particular MDI-treated women with type 1 diabetes, bad glycaemic regulation and lower awareness of hypoglycaemia need clinical attention, focused on hypoglycaemia. Patients with excellent glycaemic control, combined with great FoH and pronounced diabetes-related problems, but should not be overlooked |
| MOHEET 2012 Additional info | Conference abstract | n=18 Type 1 diabetes adults with IAH (Clarke score) | History of severe HG and high total score on CQ (Clarke questionnaire/ Clarke score) is significantly related to reduced CR response to HG in patients with type 1 diabetes. Therefore, such responses on the CQ may indicate those patients with the most profound IAH, which can be of value in both the research and the clinical setting |
| SPEIGHT 2011 | Conference abstract | n=14 Type 1 diabetes adults | Patient input identified the need for separate questions about: |

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| Study | Intervention/ comparison | Population | Outcomes |
|---|---|---|---|
| | Patient, physician and psychologist discussions drafting new items to the Clarke Score. | tested the new items of score Score = The Hypo Awareness Questionnaire | hypoglycaemia when awake and asleep ways to improve specificity/acceptability. 18 items assess recall of hypoglycaemic events, blood glucose thresholds at which symptoms occur, awareness of symptoms, altered awareness, and frequency of checking blood glucose when 'feeling low'. Completion time: average 7 minute (range 5-15 minutes), shorter following each revision. Authors' Conclusion: A comprehensive, collaborative and iterative design process has generated a detailed measure of IAH with good face and content validity. The Hypo Awareness Questionnaire is likely to be useful in clinical trials and enable improved recognition of IAH together with more accurate evaluation of medical fitness for activities including driving. |
| TAN 2012A | Conference abstract | n=30 Type 1 diabetes | Clarke and Gold scores for IAH IAH: GOLD = 8 patients (27%) IAH versus aware patients: NS difference in HbA1c SS longer mean duration diabetes Discussed IAH during their consultation with a specialist (88% versus 64%). Conclusion: The prevalence of IAH was higher in this study than in previous work suggesting that the problem may still be underestimated. It was appropriately recognised, and treatment strategies documented for the majority, on attendance at specialist clinics. |

*Abbreviations: HFS, Hypoglycaemia Fear Score; PAID, Problem Areas in Diabetes*

## 11.1.1 Economic evidence

### Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

## 11.1.2 Evidence statements

### Clinical

Low quality evidence from observational studies showed that the Gold Score and the Clarke score were the best performing scores, and were equally effective at identifying IAH. These score were also good predictors of episodes of hypoglycaemia and severe hypoglycaemia in adults with type 1 diabetes.

The evidence also showed that adults with type 1 diabetes and IAH had higher rates of hypoglycaemia and severe hypoglycaemia compared with those with intact or normal hypoglycaemia awareness. People with type 1 diabetes with IAH were more likely to have a longer duration of diabetes.

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**Economic**

- No relevant economic evaluations were identified.

### 11.1.3 Recommendations and link to the evidence

| | |
|---|---|
| **Recommendations** | **84. Assess awareness of hypoglycaemia in adults with type 1 diabetes at each annual review. [new 2015]**<br><br>**85. Use the Gold score or Clarke score to quantify awareness of hypoglycaemia in adults with type 1 diabetes, checking that the questionnaire items have been answered correctly. [new 2015]**<br><br>**86. Explain to adults with type 1 diabetes that impaired awareness of the symptoms of plasma glucose levels below 3 mmol/litre is associated with a significantly increased risk of severe hypoglycaemia. [new 2015]** |
| Relative values of different outcomes | The GDG reviewed the evidence for assessment of IAH to discover how it might be best identified and quantified. The aim of the review was to determine the effectiveness of current scoring systems in predicting IAH and increased risk of severe hypoglycaemia. The principal outcomes of interest are the sensitivity and specificity of the scores for predicting hypoglycaemia.<br><br>Comparison of the scoring systems was undertaken by the GDG, with particular focus given to studies that assessed correlation between the scoring systems and their ability to predict severe hypoglycaemia. |
| Trade off between clinical benefits and harms | The GDG considered information from 14 fully published studies as well as 7 conference abstracts.<br><br>The benefits and harms of completing the scores are related almost entirely to their accuracy. Some of the scores are more complex than others and are therefore more time consuming.<br><br>Correlation between scoring systems for assessment of IAH<br><br>Four studies undertook comparison of scoring systems for IAH.[149,239,244,316]<br><br>Three studies undertook direct comparison of the Clarke, Gold and Pedersen-Bjergaard scores (Geddes 2007, Hoihansen 2010, Gandhi 2013).[239,244,316] Gold and Clarke scores defined 18-29% of study participants as having IAH and both scores correlated well in all three studies. The Pedersen-Bjergaard scoring defined 7-15% of subjects as having IAH. However, correlation with Clarke and Gold score assessments was poor. The studies suggested that Clarke and Gold questionnaires might be better discriminators for IAH in comparison to the Pedersen-Bjergaard questionnaire.<br><br>A fourth study undertook correlation of Gold and Clarke scores in 238 study participants (Czyewska 2012)[149]: Gold and Clarke scores defined 24% and 29% of participants as having IAH respectively, with both scores again correlating well.<br><br>Scores as predictors of hypoglycaemia and severe hypoglycaemia<br><br>One study reported that more episodes of biochemical hypoglycaemia were predicted with use of Clarke and Gold scoring, but not with the Pedersen-Bjergaard score (Geddes 2007).[244] Gold and Clarke scores predicted reduced autonomic warning symptoms during biochemical hypoglycaemia but again this was not noted with Pedersen-Bjergaard scoring. All three testing methods predicted an increased rate of severe hypoglycaemia episodes.<br><br>In a second study in 518 study participants (Geddes 2008)[243], the Gold score |

| | classified 101 participants as having impaired awareness: rate of severe hypoglycaemia per person was increased six-fold in this group, with lower intensity of autonomic symptoms reported. Two further studies reported that Gold scoring (Schopmann 2011)[633] and Clarke scoring (Moheet 2012)[487] predicted Increased rates of severe hypoglycaemia in study participants. |
| | A further study of 95 adults with type 1 diabetes of at least 5 years duration found that people defined as having impaired awareness by Gold score showed increased rates of hypoglycaemia on home blood glucose monitoring by finger prick tests and an increased incidence of severe hypoglycaemia in the year following assessment, although no increase in time spent hypoglycaemic during five days of continuous glucose monitoring (CGM) was recorded (Choudhary 2010A).[116][251]In a study of 20 people reporting more than four non-severe hypoglycaemic episodes per week over 8 weeks, and at least 2 severe hypoglycaemic episodes in the previous 3 years, impaired awareness was found in 20 (100%) study participants by Gold score and 19 out of 20 by Clarke score. The Clarke score correlated with % time spent under 3.9 mmol/litre on 72 hours of continuous glucose monitoring (Giminez 2009). Clarke scoring has also been found to correlate with clamp study findings in 19 study participants (Janssen 2000).[346] |
| Economic considerations | No economic evaluations regarding identification and quantification of the IAH were identified by the GDG. |
| | The GDG recognised that there were unlikely to be any substantial cost differences between the use of each of the available scoring systems, and that use of any of the scoring systems was likely to involve minimal cost. |
| | IAH is associated with an increased risk of severe hypoglycaemia (requiring help from 3rd party for correction); a reduction in the incidence of severe hypoglycaemia has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. The GDG recognised that the use of scoring systems to identify individuals with IAH would be cost-effective if the identified individuals were subsequently able to undergo education or other interventions that might reduce their risk of severe hypoglycaemia. |
| Quality of evidence | Fourteen full studies and seven conference abstracts assessing scoring systems for identifying adults with type 1 diabetes with IAH were included for review by the GDG. Meta-analysis and GRADE were not conducted for this review as the study types and data available were not appropriate for this type of assessment. The GDG therefore made a subjective assessment on the quality of each of the available studies before reaching any conclusions on the data and concluded that the quality of the available evidence was sufficient to allow recommendations to be made. |
| Other considerations | The GDG observed that the Gold and Clarke scores correlated well in studies and had a high concordance with increased frequency of severe hypoglycaemia episodes. The Pedersen-Bjergaard score had less correlation with Gold and Clarke scores and not such a good concordance with prediction of severe hypoglycaemia episodes. |
| | There was little evidence reporting the use of other scoring systems but their possible use in clinical practice was considered by the GDG. The HYPO score was noted to have good concordance with frequency of severe hypoglycaemia. However, the baseline data required and the method of its interpretation for the score's calculation was considered to be too complex for regular use in clinical practice outside of the research environment. The hypoglycaemia assessment used by the DAFNE studies was felt to be a viable alternative to the Gold and Clarke scores. However, given the greater weight of available evidence, the GDG made the recommendation of utilising the Gold score or the Clarke score for assessment of IAH in clinical practice. The GDG noted that patients make errors in completing |

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questionnaires that could lead to their awareness status being misclassified, leading to the recommendation that scores be checked by the clinician against clinical presentation.

The GDG debated whether all adults with type 1 diabetes should be assessed for IAH or only those individuals who had previously experienced a severe hypoglycaemia episode. Annual prevalence of severe hypoglycaemia has been reported to be 30% in individuals with type 1 diabetes (Frier 2008)[226], and higher in those with IAH. The GDG recognised that measures should be taken to assess risk of hypoglycaemia and avoid the potentially dangerous consequences of a severe hypoglycaemia episode, with just one episode having potential implications regarding lifestyle choices and driving. The GDG therefore recommended that all adults with type 1 diabetes should be assessed for IAH, and that this should take place at the individual's annual care review.

The GDG noted that whilst studies often asked study participants to list their symptoms when they felt hypoglycaemic, there was not a consensus regarding the level of glucose at which hypoglycaemia symptoms might be experienced and which labels an individual as having 'impaired awareness' of hypoglycaemia. The GDG recognised that once hypoglycaemia resulted in cognitive impairment, this was significant as it was likely to result in a reduced ability to self-manage a hypoglycaemia episode and increase the risk of accident. The Clarke Score included assessment of symptoms at less than 3.9 mmol/litre but scored for impaired awareness of 50 mg/dl or less, which converts to a value of 2.8 mmol/litre; whilst the HYPO score assessment stated that study participants with a glucose of <3.0 mmol/litre were considered to be hypoglycaemic and asked subjects to list their symptoms at this level of blood glucose. The DAFNE questionnaire refers to a glucose level of 3.0 mmol/litre with recognition of hypoglycaemia at higher blood glucose levels constituting normal awareness. Glucose levels of <3.0 mmol/litre have also been found to be associated with the onset of cognitive impairment during glucose clamp studies [457]. The GDG concluded that if an individual reaches a glucose concentration of <3.0 mmol/litre without symptoms of hypoglycaemia, then they should be considered to have an IAH., The GDG recognised that scoring systems for the assessment of IAH might provide more detail about an individual's risk of severe hypoglycaemia episodes than a single absolute cut-off level of blood glucose for all adults with type 1 diabetes. The GDG therefore recommended the use of scoring systems for the assessment of IAH in its recommendations.

## 11.2 Strategies for the management of impaired awareness of hypoglycaemia

### 11.2.1 Introduction

Adults with IAH have a six-fold increase in risk for severe hypoglycaemia and if their unawareness is complete[243], and/or they experience more than one severe hypoglycaemia in a 12 month period, they may lose privileges such as the right to drive. Severe hypoglycaemia and hypoglycaemia unawareness also damage quality of life and cause stress not just for the person with diabetes but also for their family.[416,578] Restoring awareness of hypoglycaemia is therefore a key therapeutic goal.

Research carried out with adults with type 1 diabetes and IAH shows that avoidance of low plasma glucose concentrations leads to restoration of symptomatic responses to a subsequent episode[141] and this has led to a recognition of the importance of always defining lower limits as well as upper limits when setting targets for self-monitoring of plasma glucose. Participants in the research were

helped to avoid hypoglycaemia in daily life through very frequent contact with researchers who were healthcare professionals with experience in insulin dose adjustment. Helping adults with type 1 diabetes avoid hypoglycaemia routinely can be difficult. Anecdotally, not everyone who regained hypoglycaemia awareness during a research study was able to maintain it after the study ended.

It is important, when helping people with diabetes avoid hypoglycaemia, not to achieve that aim at the expense of a rise in glycated haemoglobin, as that replaces one problem (asymptomatic and severe hypoglycaemia) with another, increased risk of long term vascular complications. Modern methods of teaching adults with type 1 diabetes skills in flexible insulin therapy through structured education are able to reduce HbA1c and severe hypoglycaemia risk and in the case of the DAFNE programme also reduce IAH.[139,300,328,624] Exposure to such education and support in implementing its learning is thus considered the first step in treating people with IAH (see Section 7.2). However, as the DAFNE national audit shows, a significant number of people remain or have developed IAH one year after education. There are other education programmes that more specifically target hypoglycaemia.[439] Other strategies that have been shown to reduce hypoglycaemia experience include use of technologies for insulin delivery and glucose monitoring, such as insulin pumps and interstitial glucose monitoring devices, and these might be expected to help restore awareness too. Ultimately, transplantation therapies that remove the need for exogenous insulin may be the most effective treatment. However, there is evidence that some people exhibit a resistance to changing behaviour that will help avoid hypoglycaemia, with reduced ability to change treatment regimens after consultation with healthcare professionals.[659] This group may have unhelpful beliefs related to their hypoglycaemia experience.[599]

**The GDG therefore asked this question:**

- In adults with type 1 diabetes and impaired awareness of hypoglycaemia, what is the most effective strategy for recovering hypoglycaemia awareness?

### 11.2.2 Review question: In adults with type 1 diabetes and impaired awareness of hypoglycaemia, what is the most effective strategy for recovering hypoglycaemia awareness?

For full details see review protocol in Appendix C.

**Table 136: PICO characteristics of review question**

| Population | Adults with type 1 diabetes (this covers type 1a diabetes and type 1b diabetes) with IAH |
|---|---|
| | • Adult is defined as aged ≥18 years |
| | • Type 1 diabetes is defined (WHO definition and NICE 2004 GL) |
| Intervention(s) | • Adjusting treatment/adjusting insulin regime/less intensive glycaemic control |
| | • Pancreas/islet cell transplant |
| | • Hypoglycaemia avoidance |
| | • Adjusting monitoring of blood glucose, for example CGM |
| | • Education interventions |
| | • Psychological interventions |
| | |
| | Only intervention durations of ≥1 month will be considered |
| Comparison(s) | • Any |
| | • None |
| Outcomes | • HbA1c (continuous) |
| | • Autonomic symptoms/symptom scores during hypoglycaemia clamp study |
| | • Hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) |
| | • Severe hypoglycaemia (dichotomous or continuous outcome, depending how it is |

| | reported) |
|---|---|
| | • Nocturnal hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) |
| | • Hospital admissions (dichotomous or continuous, depending how it is reported) |
| | • Hypoglycaemia unawareness or awareness (dichotomous or continuous, depending how it is reported) |
| | • Quality of life – measured by DQoL, DSQoL, PAID, HADS, fear of hypoglycaemia, anxiety, depression, cognitive function (continuous) |
| | • Road traffic accidents and work related accidents |
| **Study design** | • RCTs: unit of randomisation: individual patient, cluster randomised trials |
| | • Observational studies |

### 11.2.3    Clinical evidence

Twenty studies were included in the review[92,118,139,141,163,205,206,211,227,250,300,304,328,422,426,440,481,609,611,690], these are summarised in Table 137 and Table 138 below. See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J and excluded studies list in Appendix K.

Five studies were RCTs or observational cohort studies[139,205,211,300,690]. Evidence from these studies is summarised in the GRADE clinical evidence profile in Appendix I. Outcomes were reported for the following interventions in patients with IAH or recurrent severe hypoglycaemia:

- Structured education and hypoglycaemia avoidance intervention (3 studies[139,205,300]): severe hypoglycaemia; nocturnal hypoglycaemia; hypoglycaemia unawareness (Gold score, Clarke score); HbA1c and symptom scores during hypoglycaemic clamp.
- Insulin regime interventions (2 studies[211,690]): severe hypoglycaemia; HbA1c; hypoglycaemia unawareness and QOL.

Fifteen studies were observational case-series[92,118,141,163,206,227,250,304,328,422,426,440,481,609,611]. Data from these studies cannot be combined in a meta-analysis or assessed in GRADE as there is no comparison control group. Data from these studies are summarised narratively in Table 138. Outcomes were reported for the following interventions in patients with IAH or recurrent severe hypoglycaemia:

- Hypoglycaemia avoidance intervention (5 studies[141,206,227,422,440]): HbA1c; severe hypoglycaemia; hypoglycaemia unawareness (Gold score) and symptom scores during hypoglycaemic clamp.
- Educational intervention (three studies[163,304,328]): severe hypoglycaemia; IAH; HbA1c; QOL (DQol, TDQ, HADS, PAID); hospitalisation and driving incidents.
- Continuous glucose monitoring intervention (2 studies[118,611]): severe hypoglycaemia; HbA1c and hypoglycaemia unawareness (Gold score, modified HYPO score).
- Insulin regime intervention (one study[250]): severe hypoglycaemia; HbA1c; hypoglycaemia unawareness (clarke score); symptom score during hypoglycaemic clamp and QOL (DQoL, SF-12 health survey)
- Islet transplantation intervention (four studies[92,426,481,609]): HbA1c; severe hypoglycaemia; IAH and symptom scores during hypoglycaemic clamp.

The non-comparative observational studies were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below.

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**Table 137: Summary of included studies: RCTs and observational cohort studies**

| Study | Intervention | Comparison | Population | Outcomes |
|---|---|---|---|---|
| **Structured education and hypoglycaemia avoidance** | | | | |
| COX 2004[139]<br><br>RCT | SMBG plus HAATT (structured education designed to reduce occurrences of low BG, increase awareness and improve treatment of low BG)<br><br>n=30 | SMBG (standard care in Bulgaria at the time did not routinely employ SMBG)<br><br>n=30 | n=60<br><br>History of ≥2 episodes of SH (inability to treat oneself due to hypoglycaemic stupor or unconsciousness) in the past year. | • Severe hypoglycaemia – reported as frequency/subject/6 months (unable to put into meta-analysis as no variance reported – ANCOVA summary reported in GRADE table)<br>• Nocturnal hypoglycaemia – reported as frequency/subject/6 months (unable to put into meta-analysis as no variance reported – ANCOVA summary reported in GRADE table) |
| HERMANNS 2007[300]<br><br>RCT | HyPOS training programme (focusing on avoiding low BG values, causes of HU, improving detection and recognition of warning symptoms and need for treatment of low BG values).<br><br>n=84 | Control (Education programme aimed at optimising intensive insulin therapy without regard to hypoglycaemia problems)<br><br>n=80 | n=164<br><br>At least one episode of SH in the past 12 months (requiring 3rd party assistance) or IAH and tight glycaemic control (HbA1c <6.5%) | • Hypoglycaemia awareness questionnaire (HAQ; Clarke score)<br>• Gold score<br>• Severe hypoglycaemia – reported as frequency/patient-year<br>• HbA1c, %, final values<br>• QOL – PAID<br>• QOL - ADDQoL |
| FANELLI 1994[205]<br><br>Observational cohort study | Hypoglycaemia avoidance by change in regime and counselling. To prevent hypoglycaemia, insulin doses aimed at fasting, preprandial and bedtime BG of ~7.2-8.3 mmol/litre.<br><br>n=16 | Continued therapeutic regime on at entry<br><br>n=5 | n=21<br><br>Consistent history of frequent hypoglycaemia (BG<3 mmol/litre) in the absence of autonomic warning symptoms for at least 6 months before the study | • Autonomic symptom score during clamp, mean (SE) at 2 weeks (not reported at 3 months or 1 year)<br>• Neuroglycopenic symptom score during clamp, mean (SE) at 2 weeks (not reported at 3 months or 1 year) |
| **Insulin regime** | | | | |
| FERGUSON 2001[211]<br><br>RCT (Open label | Insulin Lispro and human NPH insulin for 6 months | Regular human insulin and human NPH insulin for 6 months | n=40<br><br>Reported a reduction in their warning | • Severe hypoglycaemia<br>• HbA1c %<br>• QOL (DTSQ and HFS) – unable to put into meta-analysis as no mean and variance reported – |

| crossover) | | | symptoms for hypoglycaemia for at least 2 years; had ≥2 episodes of SH in the 2 years preceding and self-scored on Likert scale | ANCOVA summary reported in GRADE table |
|---|---|---|---|---|
| THOMAS 2007[690]<br><br>RCT | Education alone – re-education with relaxation of BG targets<br><br>n=7 | ANALOGUE; lispro/glargine n=7<br><br>continuous subcutaneous insulin infusion therapy (CSII; lispro) n=7 | n=21<br><br>At least one episode of SH according to ADA criteria in the preceding 6 months. Recurrent severe hypoglycaemia confirmed in all participants. Questionnaire confirmed altered hypoglycaemia awareness in all participants (score ≥4 out of 7 on validated questionnaire) | • HbA1c %<br>• Altered hypoglycaemia awareness (score ≥4 out of 7 on validated questionnaire), reported as number of patients<br>• QOL(DTSQ and HFS) |

**Table 138: Summary of included studies: Observational case-series (not suitable for meta-analysis or GRADE)**

| Study | Intervention | Population | Outcomes |
|---|---|---|---|
| Hypoglycaemia avoidance | | | |
| CRANSTON 1994[141] | Hypoglycaemia avoidance (treatment programme designed to achieve 3 weeks without BG<3.5 mmol/litre – achieved by diet review, advice about exercise, redistribution of insulin) | n=12<br>Group A: good control HbA1c <7%, n=6<br>Group B: poor control, swung from one extreme of hypoglycaemia to the other<br><br>History of hypoglycaemia without warning. At least three BG <3mmol/litre per 2 weeks in the month before the study | • HbA1c %, mean (SD)<br>• Group A: Before: 6.5 (0.2); After 6.9 (0.3). Reported as NS<br>• Group B: Before: 8.2 (0.2); After 8.7 (0.3). Reported as NS<br>• Hypoglycaemia (<3 mmol/litre) – reported as frequency/month<br>• Group A: Before: 21; After 0<br>• Group B: Before:14; After 0<br>• Total autonomic symptoms scores during hypoglycaemia clamp<br>• Reported as higher after intervention for both groups (data reported graphically only) |
| FANELLI 1993[206] | Hypoglycaemia avoidance by | n=8 | • Severe hypoglycaemia |

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| | | | |
|---|---|---|---|
| | change in regime and counselling. To prevent hypoglycaemia, insulin doses aimed at fasting, pre-prandial and bedtime BG of ~7.2- 8.3 mmol/litre. | Consistent history of frequent hypoglycaemia (BG<3 mmol/litre) in the absence of autonomic warning symptoms for at least 6 months before the study | <ul><li>One year before: 2/8; three month study period: 0/8</li></ul><ul><li>HbA1c %, mean (SE)<ul><li>Before: 5.8 (0.3); After 6.9 (0.2). Reported as SS</li></ul></li><li>Autonomic symptom score during clamp, mean (SE)<ul><li>Before: 2.2 (0.9); After 5.8 (0.6). Reported as SS</li></ul></li><li>Neuroglycopenic symptom score during clamp, mean (SE)<ul><li>Before: 5.4 (1.5); After 9.4 (1.1). Reported as SS</li></ul></li></ul> |
| FRITSCHE 2001[227] | Avoidance of hypoglycaemia. Target pre-prandial BG levels increased from 5.6 mmol/litre to 8.3 mmol/litre and at bedtime from 5.6 mmol/litre to 10 mmol/litre | n=10<br><br>Self-reported IAH and a history of SH as defined by DCCT (SH resulting in coma or seizure, requiring assistance from another person and treatment with glucagon or IV glucose | <ul><li>Severe hypoglycaemia – reported as episodes/patient, mean (SD)<ul><li>Four months before: 2.0 (0.5); four month study period: 0.0 (0.0)</li></ul></li><li>HbA1c %, mean (SD)<ul><li>Before: 6.8 (0.9); After 7.7 (0.9). Reported as SS</li></ul></li><li>Autonomic symptom score during clamp, mean (SE)<ul><li>Before: 1.8 (0.6); After 3.3 (0.7). Reported as SS</li></ul></li><li>Neuroglycopenic symptom score during clamp, mean (SE)<ul><li>Before: 2.2 (0.7); After 3.7 (0.7). Reported as SS</li></ul></li></ul> |
| LEELARATHNA 2013[422] | Hypoglycaemia avoidance (6 months): HypoCOMPaSS education tool (individualised education session aimed at avoidance and early detection of BG <4 mmol/litre). Followed by 24-week using either MDI plus SMBG; MDI plus SMBG and RT-CGM; CSII plus SMBG; CSII plus SMBG and RT-CGM<br><br>PRIMARY GOAL OF INSULIN DOSE | n=18<br><br>IAH (Gold score ≥4 with or without history of SH in preceding 12 months defined by ADA) | <ul><li>Severe hypoglycaemia, annualised rate, median (IQR)<ul><li>Before: 4 (0-7); After 0 (0-0). Reported as SS</li></ul></li><li>Gold score, mean (SD)<ul><li>Before: 5.2 (0.2); After 4.3 (0.4). Reported as SS</li></ul></li><li>Edinburgh Hypo score during clamp study. Total AUC<ul><li>Before: 500 (365-685); After 650 (365-1285). Reported as SS</li></ul></li></ul> |

| | TITRATION THROUGHOUT THE 24-WEEK RCT PERIOD WAS ABSOLUTE AVOIDANCE OF ALL BG LEVELS <4 mmol/litre | | |
|---|---|---|---|
| LIU 1996[440] | Hypoglycaemia avoidance by 3 months less strict glycaemic control aimed at increasing daily mean BG to 8-10mmol/litre | n=7<br><br>Recurrent hypoglycaemia (BG<3 mmol/litre more than twice a week for 5 months and at least one SH requiring assistance during the last 2 years. | • HbA1c %, mean (SE)<br>○ Before: 6.9 (0.3); After 8.0 (0.3). Reported as SS<br>• Symptom scores on VAS 0-10 scale, mean (SE)<br>○ Sweating: Before: 1.1 (0.4); After 5.2 (1.9). Reported as SS<br>○ Lack of concentration: Before: 0.2 (0.2); After 4.0 (1.1). Reported as SS<br>○ Hunger; palpitation; tremor; fatigue: all reported as NS |
| **Education** | | | |
| DE ZOYSA 2014[163] | DAFNE-Hypoglycaemia Restoration Awareness Training (DAFNE-HART). 6 week intervention, follow-up 12 months | n=23<br><br>Persistent IAH assessed clinically and Gold score ≥4. | • Severe hypoglycaemia (<3.5 mmol/litre requiring assistance), events/patient-year, median (range)<br>○ Before: 3.0 (0-104); After: 0 (0-3)<br>• HbA1c, %<br>○ Before: 7.8 (1.2); After: 7.8 (1.1)<br>• Gold score, range 1-7, ≥4 = impaired awareness<br>○ Before: 5.6 (1.4); After: 4.5 (1.9)<br>• Clarke score, ≥4 = impaired awareness<br>○ Before: 5.4 (1.2); After: 3.8 (1.8)<br>• Ryan score, hypoglycaemia burden (<423 considered to indicate hypoglycaemia not a major clinical concern)<br>○ Before: 948 (831); After: 372 (466)<br>• Anxiety, HADS (score >8 indicates clinically relevant psychological distress)<br>○ Before: 5.9 (5.0); After: 6.0 (5.7)<br>• Depression, HADS (score >8 indicates clinically relevant psychological distress)<br>○ Before: 5.2 (4.6); After: 5.1 (4.7)<br>• PAID, score ≥40 indicates clinically relevant psychological distress<br>○ Before: 30.7 (22.6); After: 24.7 (20.5) |
| HERNANDEZ 2008[304] | Self-awareness educational intervention (reported at 6, 12 and 18 months – outcomes reported here as end-of-study, 18 months) | n=23<br><br>Previously diagnosed with HU by an endocrinologist and verified with the Clarke score | • Severe hypoglycaemia, number of events<br>○ Before: 13.3 (17.4); After 7.1 (11.6). Reported as NS<br>• QOL – The Diabetes Questionnaire (TDQ)<br>○ Before: 75.3 (7.8); After 79.7 (7.0). Reported as SS<br>• QOL – DQoL<br>○ Before: 93.3 (18.7); After 120.9 (22.3). |

| | | | Reported as SS<br>• Hospitalisation, number of events<br>  ○ Before: 0.8 (2.2); After 0.2 (0.4). Reported as NS<br>• Driving incidents, number of events<br>  ○ Before: 0.3 (0.7); After 0.1 (0.5). Reported as NS |
|---|---|---|---|
| HOPKINS 2012[328] | DAFNE (Dose adjustment for normal eating) – 5 day course focusing on adjustment of insulin for carbohydrate intake and reflective use of home BG monitoring data.<br><br>Follow-up 1 year | n=215 (only including subgroup of patients with impaired awareness before intervention)<br><br>Those reporting symptom onset at BG <3 mmol/litre or not at all were considered to have IAH. | • Number of patients with IAH (reporting symptom onset at BG <3 mmol/litre or not at all)<br>  ○ Before: 215/215 (100%); After: 97/215 (45%)<br>• Severe hypoglycaemia – reported as episodes/patient- year, mean (SD)<br>  ○ Year preceding: 3.6 (13.6); Year post-DAFNE: 1.3 (5.9) |
| **Monitoring** | | | |
| CHOUDHARY 2013[118] | CGM for 12 months (in addition to usual CSII or MDI) | n=35<br><br>Ongoing problematic hypoglycaemia leasing to limitation of daily activities and Gold score >4 despite structured education with or without CSII | • Severe hypoglycaemia – reported as episodes/year, mean (SD)<br>  ○ Before: 8.1 (13); After 0.6 (1.2). Reported as SS<br>• HbA1c %, mean (SD)<br>  ○ Before: 8.1 (1.2); After 7.8 (1.0). Reported as SS<br>• Gold Score (range of values 1-7), mean (SD)<br>  ○ Before: 5.0 (1.5); After 5.0 (1.9). Reported as NS |
| RYAN 2009[611] | CGM for 2 months (in addition to MDI) | n=16<br><br>Elevated baseline HYPO-score >75th percentile for type 1 diabetes population (>423) and had at least one SH within the last year | • Modified HYPO score (higher scores = worse), mean (SE)<br>  ○ Before: 857 (184); After: 444 (92)<br>• HbA1c %, mean (SE)<br>  ○ Before: 8.4 (0.3); After: 8.2 (0.3) |
| **Insulin regime** | | | |
| GIMENEZ 2010[250] | CSII (reported at 6, 12 and 24 months – outcomes reported here as end-of-study, 24 months) | n=20<br><br>Presenting more than 4 mild hypoglycaemia events per week (in the last 8 weeks) and more than 2 SH events (in the last 2 years) | • Severe hypo – reported as episodes/patient/year, mean (SD)<br>  ○ Before: 1.3 (0.4); After 0.1 (0.2). Reported as SS<br>• HbA1c %, mean (SD)<br>  ○ Before: 6.6 (1.1); After 6.3 (0.9). Reported as NS<br>• Clarke score, number of patients with HU (score≥4) |

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|  |  |  | o Before: 19/20; After: 3/20 |
|---|---|---|---|
|  |  |  | • Clarke score, mean (SD) |
|  |  |  | o Before: 5.5 (1.2); After: 1.6 (2.0). Reported as SS |
|  |  |  | • Hypoglycaemia symptom score during clamp, mean (SD) |
|  |  |  | o Before: 31.6 (16.4); After: 62.3 (23.6). Reported as SS |
|  |  |  | • QOL, DQoL |
|  |  |  | o Reported as SS better for all four subscales after intervention |
|  |  |  | • SF-12 health survey, mean (SD) |
|  |  |  | o Before: 34.1 (3.9); After 37.0 (2.9). Reported as SS |
| **Islet transplantation** | | | |
| BROOKS 2013[92] | Islet transplantation | n=20<br><br>Recurrent severe hypoglycaemia (≥1 event over the preceding 12 months requiring assistance to actively administer carbohydrate, glucagon or other resuscitative actions) despite optimized conventional management. | • Severe Hypoglycaemia, number of patients<br>o Baseline 12 months: 20/20 (100%); During 24 month follow-up: 8/20 (40%)<br>• Severe hypoglycaemia, episodes/patient-year, median (IQR)<br>o Before: 20 (7-50); 12 months: 0 (0-1); 24 months: 0.3 (0-1.6)<br>• HbA1c %, median (IQR)<br>o Before: 8.0 (7.0-9.6); 12 months: 6.3 (5.8-7.1); 24 months: 6.2 (5.7-8.4)<br>• Gold score, range 1-7, ≥4 = impaired awareness, median (IQR)<br>o Before: 6 (5-7); 24 months: 3 (1.5-4.5) |
| LEITAO 2008[426] | Islet transplantation | n=31<br><br>Having islet transplantation (not all patients classified as having HU before intervention, 87% had HU before) | • Clarke score, number of patients with HU (score≥4)<br>o Before: 27/31 (87%); After: 4/31 (13%)<br>• Clarke score, mean (SD)<br>o Before: 5.29 (1.51); After: 1.35 (1.92) |
| MEYER 1998[481] | Islet transplantation | n=3<br><br>Multiple episodes of protracted SH requiring hospitalisation and glucagon or IV glucose | • HbA1c %, mean (SD)<br>o Before: 8.0 (0.5); After 8.2 (0.3). Reported as NS<br>• Severe hypoglycaemia, number of patients<br>o Before: 3/3; After: 0/3<br>• Autonomic symptom score during clamp, mean (SD)<br>o Before: 2.3 (1.5); After 7.0 (1.7)<br>• Neuroglycopenic symptom score during clamp, mean (SD)<br>o Before: 2.7 (2.5); After: 5.0 (1.7) |
| RYAN 2005[609] | Islet transplantation | n=65<br><br>Having islet | • Problematic hypoglycaemia (frequent recurrent episodes of hypoglycaemia, usually associated with HU and more |

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| | | transplantation (not all patients classified as having HU before intervention). 80% classified as having problematic hypoglycaemia before intervention (frequent recurrent episodes of hypoglycaemia, usually associated with HU and more recently quantified with HYPO score ≥1047). | recently quantified with HYPO score ≥1047):<br>o Before: 52/65 (80%); After: reported to improve significantly post-transplant |
|---|---|---|---|

**Update 2015**

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**Table 139: Clinical evidence summaries: structured education and hypoglycaemia avoidance versus standard care**

| Outcome | No. of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000) | Control event mean (continuous outcomes) |
|---|---|---|---|---|---|---|
| Hypoglycaemia unawareness ≤6months: HAQ (Clarke) | 1 | Serious | VERY LOW | MD 0.7 lower (1.3 to 0.1 lower) | - | 3.0 |
| Hypoglycaemia unawareness ≤6months: Gold Score modified VAS | 1 | Serious | VERY LOW | MD 0.8 higher (0.2 to 1.4 higher) | - | 5.3 |
| Severe Hypoglycaemia ≤6months: events/patient-year | 1 | Serious | LOW | MD 0.3 lower (1 lower to 0.4 higher) | - | 1.2 |
| Severe Hypoglycaemia ≤6months: events/patient/6 months | 1 | Very serious | VERY LOW | Unable to calculate MD[a,b] | - | 1.7 |
| Nocturnal Hypoglycaemia ≤6months: events/patient/6 months | 1 | Very serious | VERY LOW | Unable to calculate MD[a,c] | - | 1.6 |
| HbA1c % (final values) ≤6months | 1 | No serious imprecision | MODERATE | MD 0.1 higher (0.18 lower to 0.38 higher) | - | 7.1 |
| Quality of Life ≤6months: PAID | 1 | Very serious | VERY LOW | MD 0.7 higher (3.2 lower to 4.6 higher) | - | 23.3 |
| Quality of Life ≤6months: ADDQoL | 1 | No serious imprecision | LOW | MD 0.1 lower (0.3 lower to 0.1 higher) | - | 1.1 |
| Autonomic symptom score during clamp ≤6months | 1 | Serious | VERY LOW | MD 5.0 higher (3.0 to 7.0 higher) | - | 1.9 |
| Neuroglycopenic symptom score during clamp ≤6 months | 1 | Serious | VERY LOW | MD 3.6 higher (1.14 to 6.06 higher) | - | 6.1 |

(a) SD not given, therefore, unable to calculate MD and 95% CI
(b) Data given: SE and avoidance 0.4, Control 1.7; p=0.03
(c) Data given: SE and avoidance 0.8, Control 1.6; p=0.06

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**Table 140: Insulin Lispro versus regular Human Insulin**

| Outcome | No. of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000) | Control event mean (continuous outcomes) |
|---|---|---|---|---|---|---|
| Severe Hypoglycaemia ≤6 months, number of patients | 1 | Very serious | VERY LOW | 0 fewer per 1000 (from 197 fewer to 300 more) | 545 per 1000 | - |
| HbA1c % ≤6 months | 1 | Serious | VERY LOW | MD 0.2 lower (0.64 lower to 0.24 higher) | - | 9.3 |
| Quality of Life ≤6 months: DTSQ | 1 | Very serious | VERY LOW | Unable to calculate MD[a,b] | - | Unable to calculate[a,b] |
| Quality of Life ≤6 months: HFS | 1 | Very serious | VERY LOW | Unable to calculate MD[a][b] | - | Unable to calculate[a,b] |

(a)  *Mean values and SD not given therefore unable to calculate MD and 95% CI*
(b)  *Data given: No differences between Lispro and human insulin*

**Table 141: Education and relaxation of BG targets versus analogue insulin lispro/glargine**

| Outcome | No. of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000) | Control event mean (continuous outcomes) |
|---|---|---|---|---|---|---|
| HbA1c % ≤6 months | 1 | Serious | LOW | MD 0.7 higher (0.2 lower to 1.6 higher) | - | 7.6 |
| Altered hypoglycaemia awareness, number of patients ≤6 months | 1 | Very serious | VERY LOW | 285 fewer per 1000 (from 497 fewer to 514 more) | 571 per 1000 | - |
| Quality of Life ≤6 months: DQOL | 1 | Serious | VERY LOW | MD 12 lower (26.38 lower to 2.38 higher) | - | 70 |
| Quality of Life ≤6 months: HFS | 1 | Very serious | VERY LOW | MD 2 lower (23.88 lower to 19.88 higher) | - | 83 |

**Table 142: Clinical evidence summary: Education and relaxation of BG targets versus CSII**

| Outcome | No. of studies | Imprecision | GRADE rating | Absolute difference | Control event rate (per 1000) | Control event mean (continuous outcomes) |
|---|---|---|---|---|---|---|
| HbA1c % ≤6months | 1 | Serious | LOW | MD 0.9 higher (0.15 lower to 1.95 higher) | - | 7.4 |
| Altered hypoglycaemia awareness, number of patients ≤6 months | 1 | Very serious | VERY LOW | 142 fewer per 1000 (from 360 fewer to 789 more) | 429 per 1000 | - |
| Quality of Life ≤6 months: DQOL | 1 | Serious | VERY LOW | MD 16 lower (34.97 lower to 2.97 higher) | - | 74 |
| Quality of Life ≤6 months: HFS | 1 | Serious | VERY LOW | MD 17 higher (1.25 to 32.75 higher) | - | 64 |

### 11.2.4    Economic evidence

**Published literature**

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

### 11.2.5    Evidence statements

**Clinical**

**RCT and cohort study evidence**

**Structured Education and Hypoglycaemia Avoidance versus Standard Care**

Evidence that was mostly Low and Very low quality from single studies showed a clinical benefit at less than or equal to 6 months of structured education and hypoglycaemia avoidance compared with standard care in people with type 1 diabetes and IAH for severe hypoglycaemia (events/patient-year), and for both autonomic and neuroglycopenic symptom scores during clamp. However the evidence showed no clinical difference for the outcomes of hypoglycaemia unawareness (in terms of HAQ- Clarke, and Gold modified VAS), severe hypoglycaemia and nocturnal hypoglycaemia (both measured by events/patient/6 months), HbA1c, and QoL (measured by PAID and by ADDQoL)

**Insulin Lispro versus Regular Human Insulin**

Very low quality evidence from a single study showed no clinical difference at less than or equal to 6 months between insulin lispro and regular human insulin in people with type 1 diabetes and IAH for the outcomes of severe hypoglycaemia (number of patients), HbA1c, and for QoL (measured by DTSQ, and HFS)

**Education and relaxation of BG targets versus analogue insulin lispro/glargine**

Low and Very low quality evidence from a single study showed a clinical benefit at less than or equal to 6 months of education and relaxation of BG targets compared with insulin lispro/glargine in people with type 1 diabetes and IAH for QoL (DQOL). However the evidence showed clinical harm of education and relaxation of BG targets for HbA1c, and the number of patients with altered hypoglycaemia awareness. There was no clinical difference between the two interventions for QoL (HFS).

**Education and relaxation of BG targets versus CSII**

Low and Very low quality evidence from a single study showed a clinical benefit at less than or equal to 6 months of education and relaxation of BG targets compared with CSII in people with type 1 diabetes and IAH for: QoL (DQOL). However the evidence showed clinical harm of education and relaxation of BG targets for HbA1c, and the number of patients with altered hypoglycaemia awareness, and for QoL (HFS).

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**Observational case-series evidence**

**Hypoglycaemia avoidance programmes**

Low quality evidence from several case-series showed consistently that, compared with baseline, hypoglycaemia avoidance programmes in people with type 1 diabetes who had IAH resulted in improved hypoglycaemia awareness in terms of symptom scores, reduction in the rate of severe hypoglycaemia, and reduction in Gold and Clarke scores. However there were increases in HbA1c levels.

**Education programmes**

Low quality evidence from several case-series showed consistently that, compared with baseline, education programmes (particularly those aimed at improving awareness) in people with type 1 diabetes who had IAH, resulted in improved hypoglycaemia awareness in terms of reporting symptom onset at BG of less than 3 mmol/litre or not at all, reduction in the rate of SH, improvement in several (but not all) QoL scores and reduction in Gold and Clarke scores.

**CGM**

Low quality evidence from two case-series showed that, compared with baseline, monitoring using CGM in people with type 1 diabetes who had IAH, resulted in a small reduction in HbA1c, reduction in the rate of SH, and improved hypoglycaemia awareness in terms of HYPO score. However there was no difference in terms of Gold score for improved awareness.

**CSII**

Low quality evidence from a single case-series showed that compared with baseline, insulin therapy using CSII in people with type 1 diabetes who had IAH, resulted in a reduction in HbA1c, reduction in the rate of SH, and improved hypoglycaemia awareness in terms of worse symptom scores, and lower Clarke score and Gold scores. There was also improvement in QoL measures.

**Islet transplantation**

Low quality evidence from several case-series showed that, compared with baseline, islet transplantation in people with type 1 diabetes who had IAH or recurrent SH, resulted in a reduction in HbA1c, reduction in the rate and number of people experiencing SH or problematic hypoglycaemia, and improved hypoglycaemia awareness in terms of symptom scores, and lower Clarke and Gold scores.

**Economic**

No relevant economic evaluations were identified.

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### 11.2.6    Recommendations and link to evidence

| Recommendations | 87. Ensure that adults with type 1 diabetes with impaired awareness of hypoglycaemia have had structured education in flexible insulin therapy using basal-bolus regimens and are following its principles correctly. [new 2015]<br><br>88. Offer additional education focusing on avoiding and treating hypoglycaemia to adults with type 1 diabetes who continue to have impaired awareness of hypoglycaemia after structured education in flexible insulin therapy. [new 2015]<br><br>89. Avoid relaxing individualised blood glucose targets as a treatment for adults with type 1 diabetes with impaired awareness of hypoglycaemia. [new 2015]<br><br>90. Review insulin regimens and doses and prioritise strategies to avoid hypoglycaemia in adults with type 1 diabetes with impaired awareness of hypoglycaemia, including:<br>• reinforcing the principles of structured education<br>• offering continuous subcutaneous insulin infusion (CSII or insulin pump) therapy<br>• offering real-time continuous glucose monitoring. [new 2015]<br><br>91. If impaired awareness of hypoglycaemia is associated with recurrent severe hypoglycaemia despite these interventions, consider referring the person to a specialist centre.[new 2015] |
|---|---|
| Relative values of different outcomes | The GDG reviewed the evidence for the most effective strategy for recovery of IAH in adults with type 1 diabetes. Only interventions with an evidence base to reflect an effect of ≥ 1 month duration were reviewed<br><br>The following outcomes were considered:<br><br>• Recovery of hypoglycaemia scores/autonomic/neuroglycopenic warning symptoms, reflecting an objective improvement in hypoglycaemia awareness.<br>• Reduction in the incidence of severe hypoglycaemia.<br><br>The GDG acknowledged that even if interventions could not restore awareness of hypoglycaemia, they might still be able to reduce incidence of severe hypoglycaemia. When contemplating the impact of interventions on clinical outcomes, particular focus was given to:<br><br>• A reduction in the incidence of severe hypoglycaemia (requiring help from 3rd party for correction), which has been recognised as having a significant impact on quality of life in individuals with type 1 diabetes.<br>• A reduction in the incidence of nocturnal hypoglycaemia.<br>• Change in glycaemic control, assessed by HbA1c.<br><br>Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications. Any therapy that achieves a reduction in the frequency of hypoglycaemia and improvement in awareness of hypoglycaemia without worsening glycaemic control would be beneficial.<br><br>**Improvement in quality of life.**<br><br>It would be anticipated that a reduction in the incidence of severe hypoglycaemia |

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would result in an improvement in quality of life. However, in order to achieve a reduction in the rate of severe hypoglycaemia, some lifestyle constraints or greater regularity of glucose monitoring might be required. In addition, transplant interventions require immunosuppression therapy, which can produce side-effects and impact on quality of life by their effect on the immune system.

Reduction in the incidence of hospital admissions.

Ultimately, the aim of any intervention would be to reduce the incidence of severe hypoglycaemia episodes, and this might be reflected in a reduction in the incidence of hospital attendances for the treatment of severe hypoglycaemia.

Reduction in the incidence of road traffic accidents and work-related incidents as a consequence of hypoglycaemia.

| | |
|---|---|
| Trade off between clinical benefits and harms | **Evidence for hypoglycaemia avoidance by relaxation of blood glucose control:**<br><br>A number of research studies reported that if hypoglycaemia is avoided by intensive supervision of patients' insulin regimens, hypoglycaemia awareness can be re-established with time (Fanelli 1993, 1994, Cranston 1994, Liu 1996, Fritsche 2001). However, the GDG noted that this achievement was sometimes at the expense of an elevation in mean blood glucose reflected by increased HbA1c. There are a number of currently available interventions which report improvement in hypoglycaemia awareness without deterioration in glycaemic control.<br><br>**Evidence for structured education interventions:**<br><br>Three RCTs used structured education interventions for IAH and reported a reduction in the frequency of severe hypoglycaemia episodes and an improvement in hypoglycaemia awareness following attendance by adults with type 1 diabetes.<br><br>Hypoglycaemia Anticipation, Awareness and Treatment Training (HAATT) is a structured education programme designed to reduce occurrence of low blood glucose in adults with type 1 diabetes. An RCT in 60 participants (Cox 2004) reported that incidence of severe hypoglycaemia per subject reduced from 2.0 to 0.4 episodes and frequency of nocturnal hypoglycaemia from 1.1 to 0.8 episodes in individuals receiving HAATT education, whilst no change in clinical outcomes was reported for controls not receiving the education. In addition, improved awareness of symptoms accompanying hypoglycaemia was reported in the trial.<br><br>HyPOS training (Hermanns 2007) was a structured education programme focusing on avoidance of low blood glucose levels, causes of IAH, improvement in detection and recognition of hypoglycaemia warning symptoms and recognition of the need to treat low blood glucose levels. An RCT in 164 participants showed that education resulted in an improvement in Clarke and Gold scores for hypoglycaemia awareness and a reduced incidence of severe hypoglycaemia; no change in HbA1c or quality of life scores was observed.<br><br>Four observational studies of education programmes provided further support for their use as an intervention in the management of individuals with IAH. A self-awareness educational intervention in 23 participants with IAH showed that incidence of severe hypoglycaemia and hospitalisation could be reduced, even if hypoglycaemia symptoms, HbA1c and quality of life remained unchanged (Hernandez 2008).<br><br>DAFNE (Diabetes Adjustment for Normal Eating) education has been shown to reduce the incidence of severe hypoglycaemia in attendees and improve |

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hypoglycaemia awareness, with 43% of those entering the programme with impaired awareness reporting recovered awareness one year later and an overall improvement in the prevalence of impaired awareness (Hopkins 2012). The DAFNE-HART study (Dose Adjustment For Normal Eating Hypoglycaemia Awareness Restoration Training, De Zoysa 2014) was a pilot study in 23 participants with IAH who underwent a six week education intervention aimed at reducing their incidence of hypoglycaemia. At reassessment one year later, Gold, Clarke and HYPO scores improved and incidence of severe hypoglycaemia was reduced, quality of life as measured by the PAID score improved, whilst HbA1c and anxiety and depression HADS scores were unchanged.

The HypoCOMPaSS education tool for avoidance of hypoglycaemia in patients with IAH has been shown to produce an improvement in autonomic and neuroglycopenic warning symptoms during clamp studies, with increased self-awareness of hypoglycaemia, an improvement in Gold scores and a reduction in the incidence of severe hypoglycaemia (Leelarathna 2013).

**Evidence for Insulin analogue use and CSII pump therapies:**

An RCT in 40 participants comparing lispro insulin and neutral protamine hagedorn (NPH) insulin use with regular human insulin and NPH use over six months reported that use of the analogue insulin lispro had no impact on severe hypoglycaemia rate, HbA1c, or quality of life in study participants (Ferguson 2001). A further RCT compared lispro and glargine analogue use to lispro CSII, whilst a third intervention group received education and relaxation of glucose targets. Whilst treatment with insulin analogue therapies and CSII improved HbA1c and reduced incidence of severe hypoglycaemia, there was no difference between the two treatment strategies and no impact on hypoglycaemia awareness or quality of life (Thomas 2007). A fall in severe hypoglycaemia rate also occurred in the group treated by education and relaxation of glucose targets alone, but the mean rate remained higher as did HbA1c, although the trend did not reach significance in this small study (7 subjects per group).

An observational study reported that 24 months CSII therapy reduced Clarke score, improved autonomic scoring during a hypoglycaemic clamp, decreased the incidence of severe hypoglycaemia and improved quality of life alongside maintenance of a stable HbA1c in 20 study participants (Gimenez 2010).

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**Evidence for CGM usage:**

A study in 16 participants with IAH reported a reduction in modified HYPO scoring after 2 months CGM use (Ryan 2009). However, a larger observational study assessing impact of CGM in 35 participants over 12 months showed that whilst a reduction in the frequency of severe hypoglycaemia episodes was achieved alongside a small reduction in HbA1c (8.1 to 7.8 %), no impact Gold score was achieved (Choudhary 2013).

**Evidence for transplant interventions:**

Early observational studies in islet transplant recipients reported that autonomic and neuroglycopenic symptoms were improved during a hypoglycaemic clamp in post-transplant recipients (Meyer 1998). Subsequent larger studies in islet transplant recipients reported a reduction in HbA1c and frequency of severe hypoglycaemia alongside an improvement in awareness of hypoglycaemia assessed by HYPO score (Ryan 2005), Clarke score (Leitao 2008, Brooks 2013) and Gold score (Brooks 2013).

The GDG were aware of an observational study that did not meet the review protocol inclusion criteria (too short follow-up time), but they thought it was useful for their consideration, as no other suitable evidence on pancreas transplantation was found. The study was conducted in 13 pancreas transplant recipients and matched controls with IAH assessed responses to a stepped hypoglycaemic clamp protocol (Kendall 1997). Successful pancreas transplantation improved adrenaline response and normalised hypoglycaemia symptom recognition in recipients with established autonomic neuropathy.

The GDG recognised that both pancreas transplantation and islet transplantation were viable treatments for the restoration of hypoglycaemia awareness, and that both interventions might also improve HbA1c and reduce frequency of severe hypoglycaemia. However, the risk of complications from immunosuppression therapy and its possible impact on quality of life led the GDG to recommend the use of transplant interventions only in individuals experiencing recurrent severe hypoglycaemia episodes with ongoing IAH despite efforts with alternative interventions.

| | |
|---|---|
| **Economic considerations** | No economic evaluations regarding strategies for the management of IAH were identified by the GDG. |
| | Cost-effectiveness of structured education, analogue insulin therapies, CSII and CGM have been considered in Chapter 7. |
| | The likely high cost of transplant interventions and the ongoing need for post-operative immunosuppression contributed to the GDG decision to recommend transplant interventions only if alternative strategies for the management of IAH had been unsuccessful. Discussion on referral for transplant interventions is reported in chapter 18. |
| **Quality of evidence** | Twenty studies were included in this review. |
| | Six studies were RCTs or observational cohort studies. Evidence from these studies was GRADE assessed. The quality of this evidence for the structured education RCTs (Cox 2004, Schachinger 2005, Hermanns 2007) was Moderate to Very low; for the insulin regimen RCT (Ferguson 2001) it was Very low; for the studies on education and relaxation of blood glucose targets it was low to Very low (Fanelli 1994, Thomas 2007). |

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| | Fifteen studies were observational case-series. Meta-analysis and GRADE were not conducted for these studies as they were not appropriate for this type of assessment as there were no comparison control groups. The GDG noted that many of the studies were small in size, making it hard for study outcomes to achieve significance. However, the GDG were satisfied that recommendations could be made from the available evidence regarding interventions for the management of individuals with IAH. |
|---|---|
| Other considerations | The GDG noted that in both the HAATT and HyPOS training programmes, participants had not received any previous formal structured education before their participation in the education programmes. However, the GDG recognised that educational interventions aimed specifically at individuals with IAH could improve clinical outcomes in adults with diabetes, even if they had previously received other forms of structured education. |

### 11.2.7    Research recommendations

**26.For adults with type 1 diabetes, what are the optimum technologies (such as insulin pump therapy and/or continuous glucose monitoring, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions) and how are they best used, in terms of clinical and cost effectiveness, for preventing and treating impaired awareness of hypoglycaemia?**

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## 11.3    Prevention, problems related to hypoglycaemia, and management of symptomatic hypoglycaemia [2004]

This section of the guideline was not updated by the GDG in 2015. Content and recommendations are from the 2004 guideline. The blood glucose awareness training section originally featured in 2004 has been removed as it has been superseded by new evidence reviewed by the 2015 GDG (see Chapter 8). The original content can be found in Appendix S.

### 11.3.1    Rationale

Hypoglycaemia is, for most people using insulin therapy, an inevitable consequence of the erratic absorption of insulin from subcutaneous tissue after depot injection or infusion, coupled with absence of feedback to insulin need when changes in planned activity or eating occur once the injection has been given. Hypoglycaemia is usually unpleasant, often becomes a source of fear, and can be an embarrassment as well as a safety risk. Accordingly while careful choice of insulin regimen (Section 9.2) informed by self-monitoring (Section 9) is important in ameliorating this problem, other preventative measures are of importance. A higher level of optimised management is needed when hypoglycaemia and its related problems do occur.

### 11.3.2    Evidence statements

**Management of hypoglycaemia**

Canadian clinical practice guidelines reported four studies supporting the use of 15 g glucose (monosaccharide) (orally) for the treatment of moderate hypoglycaemia.[753] Two studies within the guidelines explored a 20 g oral glucose dose for recovery of blood glucose levels. Recovery was

slower following treatment with milk and orange juice. The use of glucose gel also delivered slower recovery in the latter study and required swallowing to have a significant effect. A further study showed no support for buccal administration of glucose (**Ia**).

One study within the Canadian guidelines[753] reported on the special needs of people taking alpha-glycosidase inhibitors when treating hypoglycaemia, recommending the use of glucose (dextrose) tablets, or milk or honey if these are unavailable (**IV**).

**Nocturnal hypoglycaemia**

A bedtime snack may be needed to avoid nocturnal hypoglycaemia. Two studies from a systematic review showed prepared corn starch snack bars have some benefit in overnight reduction of hypoglycaemia, but the number of events were not significantly reduced (**Ia**).[753]

**Hypoglycaemia unawareness**

Canadian clinical practice guidelines[753] report one paper on the link between incidence of prior hypoglycaemic episodes and worsening in the defect of the hormonal responses to hypoglycaemia, leading to a reduction in the self-detection of hypoglycaemia. Eight papers report the benefits of strict avoidance of hypoglycaemia in improving recognition of severe hypoglycaemia or the responses of counter regulatory hormones (**Ia**).

**Long term complications of hypoglycaemia**

Evidence on the impact of hypoglycaemia on cognitive function is not clear. Two prospective studies reported within the Canadian guidelines , which did not find association between intensive diabetes management and cognitive function.[753] However, six retrospective studies found subjects with recurrent hypoglycaemia performed more poorly in a range of intellectual tests (**IIa**).

**Medical intervention of hypoglycaemia**

Two randomised studies compared the use of glucagon and dextrose in the treatment of severe hypoglycaemia. One study compared intramuscular administration of 1 mg glucagon with 50 ml 50 % IV dextrose in people with hypoglycaemic coma.[548] A second study compared intravenous administration of 1 mg glucagon versus 50 ml 50 % dextrose in people with hypoglycaemic coma.[128] Both studies showed a significantly slower recovery to a normal level of consciousness in the glucagon treated group (**Ib**).

Two glucagon-treated patients in each study (7 and 4 % respectively) and two dextrose-treated patients in the second study (4 %) required additional administration of 12.5 g IV dextrose following failing to recover consciousness after 15 minutes. In the first study average duration of hypoglycaemic coma was not different between the two treatment groups (**Ib**).

No correlation was seen between time taken to recovery of consciousness and initial plasma glucose concentration or duration of hypoglycaemia in either of the studies. Side effects were similar among the treatment groups (**Ib**).

These two small studies suggest that intravenous glucose gives a clinically non-significant advantage over intra-muscular glucagon in time to recovery of consciousness in people with type 1 diabetes in hypoglycaemic coma (**Ib**).

### 11.3.3 Health economic evidence

No health economic evidence on the prevention or management of hypoglycaemia was identified in the literature review.

### 11.3.4 Consideration

The group noted this was an area of considerable importance to people with type 1 diabetes, but that prevention of hypoglycaemia was considered appropriately under insulin therapy recommendations, and secondarily under education and lifestyle issues. The Group noted issues related to absorption and ingestion of free carbohydrate in people with decreased conscious level. They were concerned that recurrent hypoglycaemia was properly considered in a medical context, and not simply attributed to lifestyle problems secondary to insulin therapy.

Hypoglycaemia unawareness was also noted to be an important issue, and be partially reversible and capable of useful management, as now is nocturnal hypoglycaemia (it was noted that the recommendations on insulin therapy and clinical monitoring addressed other aspects of such management). No useful hard evidence was available for cognitive decline occurring in people with type 1 diabetes, but the possibility of recurrent severe hypoglycaemia being a contributory factor was felt worth mentioning.

The group noted that the ease and safety of administration of glucagon compared to IV glucose (risk of extravasation) meant that in most situations it was the treatment of choice. While it was recognized that there were groups of people to whom the identified studies do not apply (starvation, alcohol toxic), and that these people would not be expected to respond well to glucagon, it was agreed that the best means of detecting this was by absence of a response to glucagon at 10 minutes. Safe follow-up management after either therapy should include oral carbohydrate and awareness of risk of relapse. Users of glucagon injections need appropriate education and training.

### 11.3.5 Recommendations [2004]

92. Explain to adults with type 1 diabetes that a fast-acting form of glucose is needed for the management of hypoglycaemic symptoms or signs in people who are able to swallow. [2004, amended 2015]

93. Adults with type 1 diabetes with a decreased level of consciousness as a result of hypoglycaemia and so are unable to take oral treatment safely should be:
   - given intramuscular glucagon by a family member or friend who has been shown how to use it (intravenous glucose may be used by healthcare professionals skilled in obtaining intravenous access)
   - monitored for response at 10 minutes, and then given intravenous glucose if their level of consciousness is not improving significantly
   - then given oral carbohydrate when it is safe to administer it, and placed under continued observation by a third party who has been warned of the risk of relapse. [2004, amended 2015]

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94. Explain to adults with type 1 diabetes that some hypoglycaemic episodes are an inevitable consequence of insulin therapy in most people using any insulin regimen, and that it is advisable that they should use a regimen that avoids or reduces the frequency of hypoglycaemic episodes while maintaining as optimal a level of blood glucose control as is feasible. Make advice available to all adults with type 1 diabetes to assist in obtaining the best such balance from any insulin regimen (see 'Insulin regimens' Section 10.2 and 'Insulin delivery' Section 10.3). [2004]

95. If hypoglycaemia becomes unusually problematic or of increased frequency, review the following possible contributory causes:

- inappropriate insulin regimens (incorrect dose distributions and insulin types)
- meal and activity patterns, including alcohol
- injection technique and skills, including insulin resuspension
- injection site problems
- possible organic causes including gastroparesis
- changes in insulin sensitivity (including drugs affecting the renin-angiotensin system and renal failure)
- psychological problems
- previous physical activity
- lack of appropriate knowledge and skills for self-management. [2004]

96. Manage nocturnal hypoglycaemia (symptomatic or detected on monitoring) by:

- reviewing knowledge and self-management skills
- reviewing current insulin regimen, evening eating habits and previous physical activity
- choosing an insulin type and regimen that is less likely to induce low glucose levels at night. [2004, amended 2015]

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97. Explain to adults with type 1 diabetes that late postprandial hypoglycaemia may be managed by eating snacks between meals or by using rapid-acting insulin analogues before meals. [2004]

98. If early cognitive decline occurs in adults on long-term insulin therapy, supplement normal investigations by the consideration or investigation of possible brain damage resulting from overt or covert hypoglycaemia, and the need to ameliorate this. [2004]

# 12 Ketone monitoring and management of diabetic ketoacidosis (DKA)

The 2015 GDG updated self-monitoring and in hospital monitoring of ketones. The 2004 content that has been superseded by the 2015 update can be found in Appendix S. Management of DKA was not in the scope for the 2015 update and therefore the original recommendations and content from CG15 are reproduced in this chapter.

## 12.1 Ketone monitoring [2015]

### 12.1.1 Introduction

Ketosis and ketonuria reflect a greater degree of insulin deficiency than hyperglycaemia alone. The presence of ketones indicates that insulin concentrations are too low not only to control blood glucose concentrations but also to prevent the breakdown of fat (lipolysis). Because ketones are acid substances, high ketone concentrations in the blood may create acidosis. Diabetic ketoacidosis (DKA) is a medical emergency and in its established state carries a 0.7–5% mortality in adults.[436,453,750]

High ketones in the blood are associated with high levels of fatty acids and together create insulin resistance. The patient with significant ketonaemia will require more insulin than usual to control the blood glucose.

Traditionally, ketonaemia has been assessed by urine testing. This has been applied in three main settings: it is recommended as part of guidance for patient self-management of acute illness at home, when patients are advised to increase their usual corrective insulin doses in the presence of significant ketonuria; in the assessment of patients presenting to emergency services with hyperglycaemia, where presence of ketonuria may influence management decisions, including need for admission and in the management of established DKA, where resolution of ketonuria is an important indication of recovery. However, not all ketone bodies are detected by urine testing, for example, beta-hydroxybutyrate (β-OHB) is not detected with current strip tests and if there is a high β-OHB:acetoacetate ratio, urine testing may give a falsely low estimate of ketosis. Furthermore, after an episode of ketoacidosis, where measurement of blood ketones may provide a more accurate assessment of re-insulinisation than blood glucose measurements alone, urine tests, measuring lipid soluble acetone, may continue positive for 48 hours as acetone leaks from fat tissue although ketogenesis and lipolysis have stopped.

Recent advances in technology have included the development of faster, more accurate blood tests for ketones, including strip and meter tests for measuring ketonaemia as β-OHB from a finger prick blood sample. There is a need to assess the evidence base for the use of blood ketone measurement, both laboratory- and strip-based, in three settings:

- Use of self-assessment of blood ketones as part of home monitoring when hyperglycaemia is detected and the patient is feeling unwell to see if it can improve a patient's ability to manage intercurrent illness at home, reduce hospital admissions and/or reduce the severity of ketoacidosis when someone presents to the emergency services.

- Use of blood rather than urine ketone measurement in the assessment of patients presenting to emergency services with hyperglycaemia.

- Use of blood rather than urine ketone measurement in the inpatient management of established ketoacidosis to reduce morbidity and length of stay in either high dependency care and/or the hospital.

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**The new review questions included in this chapter are:**

- In adults with type 1 diabetes (including atypical ketosis-prone diabetes), does patient self-monitoring of blood (and urine) ketones reduce the incidence of DKA and hospital admissions?

- In adults with type 1 diabetes, does inpatient monitoring of blood ketones by the healthcare professional reduce the length of hospital stay, exposure to IV insulin and the development of in-hospital complications:

  o  in patients with suspected DKA?

  o  in patients admitted with DKA and/or those that get it in hospital?

The evidence and text from the previous guideline, CG15, that has been superseded by this update is in Appendix S.

### 12.1.2  Review question: In adults with type 1 diabetes (including atypical ketosis-prone diabetes), does patient self-monitoring of blood (and urine) ketones reduce the incidence of DKA and hospital admissions?

**Table 143: PICO characteristics of review question - self-monitoring**

| Population | Adults with type 1 diabetes |
|---|---|
| Intervention/s and comparison/s | • Blood ketone versus urine ketone measurements<br>• Any or no comparison |
| Outcomes | • Hospital admissions – for DKA if specified<br>• Duration of admission/length of hospital stay<br>• DKA<br>• HbA1c<br>• Hypoglycaemia<br>• Quality of life – measured by PAID, anxiety<br>• Severity of acidosis at admission - duration of acidosis and degree of acidosis |
| Study design | All study types |

### 12.1.3  Review question: In adults with type 1 diabetes, does inpatient monitoring of blood ketones by the healthcare professional reduce the length of hospital stay, exposure to IV insulin and the development of in-hospital complications:

- **in patients with suspected DKA?**

- **in patients admitted with DKA and/or those that get it in hospital?**

**Table 144: PICO characteristics of review question - inpatient monitoring**

| Population | Adults with type 1 diabetes and DKA |
|---|---|
| Intervention/s | Blood Ketone monitoring |
| Comparison/s | • Urine ketone<br>• No monitoring |
| Outcomes | • Length of hospital stay (continuous)<br>• In-hospital complications of the admission – for example, cerebral oedema, mortality, serious electrolyte imbalance (dichotomous)<br>• Exposure to IV insulin (dichotomous)<br>• Sensitivity of DKA diagnosis<br>• Specificity of DKA diagnosis<br>• How often admission occurs |

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| Population | Adults with type 1 diabetes and DKA |
|---|---|
| | • Hypoglycaemia<br>• Quality of life (continuous) |
| Study design | All study types |

## 12.2  Clinical evidence

We searched for studies published since the original type 1 diabetes guideline (2003 onwards).

Five studies were included in the review [45,62,281,407,676] One of the studies was a randomised controlled trial (RCT)[407]. All other studies were non-comparative observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. Evidence from these studies has therefore been summarised narratively, with an overview in Appendix I. See also the study selection flow chart in Appendix D, and study evidence tables in Appendix G and exclusion list in Appendix K.

One study, the RCT [407], looked at ketone self-monitoring. All other studies involved inpatient ketone measurement (point of care testing in the emergency department).

There were no data reported in any of the studies for the following outcomes:

- length of hospital stay
- in-hospital complications of the admission
- quality of life
- hypoglycaemia

The terms β-OHB and β-HBA have been used throughout the review, according to what was reported in the studies. These are alternative acronyms representing the same ketone, beta-hydroxybutyric acid.

**Table 145: Summary of studies included in the review (self-monitoring)**

| Study | Intervention/ comparison | Frequency of ketone monitoring | Setting | Population | Follow-up | Outcomes/results |
|---|---|---|---|---|---|---|
| LAFFEL 2006[407] | RCT<br><br>Blood vs. urine ketone (β-OHB) monitoring | No. of checks overall was not significantly different between groups (1866 blood vs. 1798 urine checks).<br><br>Frequency of checks during hyperglycaemia was similar.<br><br>Frequency of checks during sick days SS higher in | Sick day management (home monitoring) | n=123<br>type 1 diabetes<br><br>Children, adolescents and young people | 6 months | Blood β-HBA is best<br><br>Monitoring of blood (capillary) β-HBA resulted in less ER use, hospitalisations and greater change in HbA1c than with urine β-HBA monitoring<br><br>HbA1c change from baseline: no significant difference between groups or within groups |

<div style="writing-mode: vertical-rl">Update 2015</div>

| Study | Intervention/ comparison | Frequency of ketone monitoring | Setting | Population | Follow-up | Outcomes/results |
|---|---|---|---|---|---|---|
| | | blood vs. urine group (91% vs. 61%; p<0.001) | | | | Patient preference: blood ketones (easier to perform) VERY LOW quality[a] |

(a) Quality rating from GRADE table, see Appendix I for details.

**Table 146: Summary of studies included in the review (inpatient monitoring)**

| Study | Intervention/ comparison | Frequency of ketone monitoring | Setting | Population | Follow-up | Outcomes/results |
|---|---|---|---|---|---|---|
| ARORA 2011[45] | Ketone (β-OHB) measurement in blood and urine Observational study (prospective case series) | Not reported | ED patients Point of care testing | n=516 Blood glucose ≥250 mg/dL | 2 years | Blood β-HBA is best Blood (capillary) β-HBA was as sensitive and more specific than urine β-HBA for detecting: DKA (98/79 vs. 98/35) VERY LOW quality[a] |
| BEKTAS 2004[62] | Ketone (β-HBA) measurement in blood and urine Observational study (prospective case series) | Weekly | ED patients Point of care testing | n=139 Diabetic newly diagnosed or known Adults | 6 months | Blood β-HBA is best Blood (capillary) β-HBA was more sensitive and specific than urine β-HBA for detecting: DK (91/56 vs. 82/54) DKA (72/82 vs. 66/78) VERY LOW quality[a] |
| HARRIS 2005[281] | Ketone (β-OHB) measurement in blood and urine Observational study (retrospective case series) | Not reported | ED patients Near patient testing | n=50 Hyperglycaemia Blood glucose >11 mmol/litre | n/a | Blood β-OHB (>3 mmol/litre) is best Blood (capillary) β-OHB >3 mmol/litre was as sensitive and more specific than urine β-OHB for detecting: DKA (100/88 vs. 100/52) Patients requiring IV insulin treatment (100/100 vs. 100/65) VERY LOW quality[a] |
| TABOU | Ketone (β- | Frequency | ED | n=529 | 32 | Blood β-OHB is best |

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| Study | Intervention/ comparison | Frequency of ketone monitoring | Setting | Population | Follow-up | Outcomes/results |
|---|---|---|---|---|---|---|
| LET 2007[676] | OHB) measurement in blood and urine  Observational study (retrospective case series) | not mentioned, but nurses instructed to measure as often as possible, and both blood and urine samples were always taken together in order for comparison. | patients  Point of care/near patient testing | Hyperglycaemia Blood glucose >13.75 mmol/litre | months (retrospectively in patients records) | Blood (capillary) β-OHB was significantly better than urine β-OHB for predicting: ketoacidosis hospitalisation hospitalisation for ketoacidosis VERY LOW quality[a] |

(a) Data is from case series, mostly of retrospective design. The quality has been rated as VERY LOW because these study designs are associated with a high risk of bias.

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**Table 147: Clinical evidence summary: Blood β-HBA versus urine β-HBA ketone measurement (less than or equal to 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Blood ketones | Control event rate (per 1000 patients)<br><br>Urine ketones |
|---|---|---|---|---|---|
| HbA1c | 1 study (n=123) | Serious | VERY LOW | MD 0.7 higher (0.12 to 1.08 higher) | 8.3 final value in urine group |
| ER use | 1 study (n=123) | Serious | VERY LOW | 101 fewer per 1000 (from 172 fewer to 55 more) | 230 |
| Hospitalisation | 1 study (n=123) | Very serious | VERY LOW | 83 fewer per 1000 (from 118 fewer to 43 more) | 131 |

## 12.3 Economic evidence

**Published literature**

No relevant economic evaluations comparing either self-monitoring of blood ketones with urine ketones, or hospital-monitoring of blood ketones with urine ketones were identified.

**Unit costs**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

**Table 148: Unit costs for self-monitoring of ketones**

| Self-monitoring ketone tests | Usage | Cost | Quantity | Cost per unit |
|---|---|---|---|---|
| Ketostix | Urine test | £3.00[a] | 50 | £0.06 |
| Mission Ketone | Urine test | £2.50[a] | 50 | £0.05 |
| FreeStyle Optimum ß-Ketone Test Strips | Blood test | £20.63[a] | 10 | £2.06 |
| Optimum Xceed | Monitor | Free[b] | 1 | Free[b] |
| GlucoMen LX Ketone Test Strips | Blood test | £20.32[a] | 10 | £2.03 |
| GlucoMen LX | Monitor | Free[b] | 1 | Free[b] |

*(a) Electronic Drug Tariff[517]*
*(b) GDG opinion – Monitors are given away free by medical devices companies. Normal cost ranges around £10 to £15*

**Table 149: Unit costs for in-hospital ketone monitoring**

| In-hospital ketone monitoring tests | Usage | Cost | Quantity | Cost Per Unit |
|---|---|---|---|---|
| Biochemistry Blood Test | Blood test | £1.26[a] | 1 | £1.26 |
| FreeStyle Optimum ß-Ketone Test Strips | Blood test | £20.63[a] | 10 | £2.06 |
| GlucoMen LX Ketone Test Strips | Blood test | £20.32[a] | 10 | £2.03 |
| Ketostix | Urine test | £3.00[b] | 50 | £0.06 |
| Mission Ketone | Urine test | £2.50[b] | 50 | £0.05 |
| Nurse time | Administer test | £40 an hour[c] | 5 minutes | £3.33 |

*(a) NHS Reference Cost[166]*
*(b) Electronic Drug Tariff[517]*
*(c) PSSRU 2011[147]- 14.3 – Cost of a band 5 nurse on a standard day ward (plus qualification cost)*

**Table 150: Pooled average cost of non-elective inpatient care for management of DKA**

| Age range | Average | Lower quartile | Upper quartile |
|---|---|---|---|
| Under 69 years | £828 | £611 | £953 |
| 70 and above years | £1,532 | £1,102 | £1,775 |

*Source: NHS Reference Costs[166]. This includes excess bed days.*

**Table 151: Pooled average cost of non-elective excess bed care days for management of DKA**

| Age range | Average | Lower quartile | Upper quartile |
|---|---|---|---|
| Under 69 years | £230 | £184 | £263 |
| 70 and above years | £207 | £174 | £249 |

*Source: NHS Reference Costs[166]*

### 12.3.1 Evidence statements

**Clinical**

**Self-monitoring of β-HBA ketones: blood capillary versus urine**

Very low quality evidence from one RCT (n=123) showed:

- clinical benefit of blood monitoring in reducing both ER use and hospitalisations
- no clinical benefit of blood monitoring for HbA1c
- patients preferred blood measurements and found them easier to perform

In the case of ER use and hospitalisations the direction of the estimate of effect favoured blood measurement, with no impact on HbA1c.

**Inpatient monitoring**

Low quality evidence from four observational studies (n=50 to n=529) showed that point-of-care testing of blood (capillary) β-OHB or β-HBA (in people admitted to the emergency department) was better than urine β-OHB or β-HBA in terms of:

- sensitivity and specificity of detecting DK and detecting DKA.
- patients requiring IV insulin treatment.
- predicting ketoacidosis and hospitalisation

**Economic**

No relevant economic evaluations were identified.

### 12.3.2 Recommendations and link to evidence

| Recommendations | 99. Consider ketone monitoring (blood or urine) as part of 'sick-day rules' for adults with type 1 diabetes, to facilitate self-management of an episode of hyperglycaemia. [new 2015]<br><br>100. In adults with type 1 diabetes presenting to emergency services, consider capillary blood ketone testing if :<br><br> • DKA is suspected or<br><br> • the person has uncontrolled diabetes with a period of illness, and urine ketone testing is positive. [new 2015]<br><br>101. Consider capillary blood ketone testing for inpatient management of DKA in adults that is incorporated into a formal protocol. [new 2015] |
|---|---|
| Relative values of different outcomes | To determine whether ketone monitoring might be beneficial to individuals with type 1 diabetes, the GDG reviewed the evidence for the use of capillary blood ketone measurement in adults with type 1 diabetes in three clinical settings:<br>Patient self-assessment of capillary blood ketones as part of home-monitoring during acute illness, when hyperglycaemia is detected and the patient is feeling unwell. Ketone monitoring here might improve the patient's ability to manage intercurrent illness at home, with the possibility of reducing hospital admissions. It could also |

*Update 2015*

| Recommendations | **99. Consider ketone monitoring (blood or urine) as part of 'sick-day rules' for adults with type 1 diabetes, to facilitate self-management of an episode of hyperglycaemia. [new 2015]**<br><br>**100. In adults with type 1 diabetes presenting to emergency services, consider capillary blood ketone testing if :**<br>• **DKA is suspected or**<br>• **the person has uncontrolled diabetes with a period of illness, and urine ketone testing is positive. [new 2015]**<br><br>**101. Consider capillary blood ketone testing for inpatient management of DKA in adults that is incorporated into a formal protocol. [new 2015]** |
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| | ensure that patients present to emergency services at the appropriate time, reducing the severity of ketoacidosis at presentation to emergency services<br><br>Comparison of capillary blood ketone measurement versus urine ketone measurement undertaken by healthcare staff at the time of patient presentation to the emergency services with hyperglycaemia, to determine whether one might be superior in determining the need for patient admission to hospital.<br><br>Comparison of blood ketone measurement versus urine ketone measurement in the inpatient management of established ketoacidosis, with the aim of determining which might lead to morbidity reduction and decreased length of stay in hospital in patients with established DKA.<br><br>Based on assessment from these three clinical settings, the following outcomes for the use of ketone monitoring were assessed:<br>Mortality and morbidity – High ketone levels in the blood result in acidosis, and DKA is a medical emergency that in its established state carries a 0.7 to 5 % mortality (MacIsaac et al., 2002, Lin et al., 2005, Wright et al., 2009). Ketone testing should allow earlier diagnosis and management of ketosis in individuals with type 1 diabetes and therefore, prevention of complications from DKA.<br>Emergency admission rates to hospital – Early identification of ketosis in individuals with type 1 diabetes might allow corrective measures to be taken and subsequent treatment at home, potentially avoiding the need for presentation as a medical emergency to healthcare services. Access to ketone testing may allow more effective self-management of intermittent illness associated with hyperglycaemia and subsequent morbidity may be reduced, especially if timely referral to emergency services is enabled.<br>Assessment of ketonaemia in hospital – Ketonaemia assessment might influence clinical decision making, enabling earlier diagnosis and management of established DKA. Ketone testing might guide insulin dosing in the management of ketoacidosis, and could conceivably reduce admission times for DKA.<br>Sensitivity and specificity of capillary blood strips versus urine testing for ketones assessment - Ketone testing has traditionally been assessed by urine testing, although, not all ketone bodies are detected by this method of testing. β-OHB is not detected with current urine test strips, and there is the possibility that urine testing can give a falsely low estimate of ketosis.<br>Recent advances in technology have included the development of capillary blood testing strips for ketonaemia, which measure β-OHB from a finger prick blood sample – The evidence was reviewed to assess their sensitivity and specificity in |

Update 2015

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| **Recommendations** | **99.Consider ketone monitoring (blood or urine) as part of 'sick-day rules' for adults with type 1 diabetes, to facilitate self-management of an episode of hyperglycaemia. [new 2015]**<br><br>**100. In adults with type 1 diabetes presenting to emergency services, consider capillary blood ketone testing if :**<br>• **DKA is suspected or**<br>• **the person has uncontrolled diabetes with a period of illness, and urine ketone testing is positive. [new 2015]**<br><br>**101. Consider capillary blood ketone testing for inpatient management of DKA in adults that is incorporated into a formal protocol. [new 2015]** |
| | comparison with urine ketone sticks.<br>Ease of capillary blood testing versus urine testing for ketones assessment.<br>Ease of test use is likely to determine frequency of use by both patients and healthcare staff; patients are more likely to be compliant with testing, and healthcare professionals are more likely to adopt the test in management-driven protocols if it is easy to use. |
| Trade-off between clinical benefits and harms | Mortality and morbidity<br>The GDG looked for published outcomes on whether monitoring for ketones had any impact on electrolyte imbalances, cerebral oedema and mortality during the management of ketoacidosis, but no studies were available for review following evidence searches.<br><br>Emergency admission rates to hospital<br>A single study from the USA showed that the use of blood rather than urine ketone monitoring during home management of intercurrent illness was associated with a reduced attendance rate to the Emergency Room. Although this difference did not achieve statistical significance, the GDG considered this to be of substantial clinical benefit and an important clinical outcome favouring the use of blood ketone monitoring (Laffel et al., 2006).<br><br>Assessment of ketonaemia in hospital<br>Four studies (Bektas et al., 2004, Harris et al., 2005, Taboulet et al., 2007, Arora et al., 2011) showed that capillary blood ketone testing might have advantages over urine ketone testing, and that they could be used as a rapid bedside test to accurately measure blood concentrations of ketones in an emergency department setting. The studies suggested that this might be useful for making early management decisions in patients presenting to emergency departments with suspected DKA.<br>One study (Ray et al., 2013) showed that length of hospital stay for the management of DKA was reduced from 3.0+/-1.4 days to 1.8+/-0.7 days by the introduction of capillary blood ketone monitoring to an inpatient DKA management protocol. The GDG observed that this protocol followed the Joint British Diabetes Associations (JBDS) DKA management protocol[622], and were wary of what influence the combined aspects of the protocol, as opposed to ketone measurement alone, might have had on influencing duration of admission in this study. However, the GDG also recognised that one of the main monitoring tests used in the JBDS protocol was the use of blood ketone monitoring to dictate management decisions, and therefore, it was likely that blood ketone monitoring did influence the duration of hospital admission in this |

*Update 2015*

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| **Recommendations** | **99. Consider ketone monitoring (blood or urine) as part of 'sick-day rules' for adults with type 1 diabetes, to facilitate self-management of an episode of hyperglycaemia. [new 2015]**<br><br>**100. In adults with type 1 diabetes presenting to emergency services, consider capillary blood ketone testing if :**<br><br>• **DKA is suspected or**<br>• **the person has uncontrolled diabetes with a period of illness, and urine ketone testing is positive. [new 2015]**<br><br>**101. Consider capillary blood ketone testing for inpatient management of DKA in adults that is incorporated into a formal protocol. [new 2015]** |
| | study.<br><br>Sensitivity and specificity of capillary blood strips versus urine testing for ketones assessment<br>Capillary blood ketone assessment was felt to be more sensitive than urine testing in two studies (Bektas et al., 2004, Arora et al., 2011), and more specific in three studies (Bektas et al., 2004, Harris et al., 2005, Arora et al., 2011), while a further study concluded that blood ketones were able to better predict ketoacidosis, hospitalisation and hospitalisation for ketoacidosis management than urine ketones assessment (Taboulet et al., 2007).<br><br>Ease of capillary blood testing versus urine testing for ketones assessment<br>Patients in one study expressed a preference for ketone monitoring over urine ketone monitoring (Laffel et al., 2006). As a patient testing for ketones is likely to be already testing their blood for glucose levels, no additional finger pricking is required. The GDG recognised that more frequent measurements of blood ketones were relatively easy to undertake in comparison to urine ketone monitoring. |
| Economic considerations | No relevant economic evaluations comparing either self-monitoring or hospital-monitoring of blood ketones with urine ketones were identified.<br>In the absence of UK cost-effectiveness analysis, the GDG considered the relevant unit costs of blood and urine monitoring to reach its own conclusion regarding cost-effectiveness.<br><br>Home monitoring<br>Blood ketone test strips are approximately forty times more expensive (£20.32 for a pack of 10) than urine ketone test sticks (£2.50 for a pack of 50). However, blood ketone test strips have a longer shelf-life (12-18 months) compared with urine test sticks (3 months). As individuals with type 1 diabetes are likely to test for ketones on an infrequent basis, it is possible that only a fraction of the ketone testing strips or sticks might be used from a provided container before they have passed their expiry date. This wastage will be greater for urine sticks, which partially offsets the lower unit cost. The GDG recognised that companies making test strips should provide a lower number of strips or sticks per container to reduce the risk of wastage.<br>The clinical review showed that blood strip ketone testing rather than urine ketone monitoring during home management of intercurrent illness was associated with a reduced attendance rate to the Emergency Room in individuals with type 1 diabetes. This was considered clinically significant by the GDG and they recognised that allowing adults with type 1 diabetes access to home blood strip ketone monitoring |

Update 2015

| Recommendations | **99.Consider ketone monitoring (blood or urine) as part of 'sick-day rules' for adults with type 1 diabetes, to facilitate self-management of an episode of hyperglycaemia. [new 2015]**<br><br>**100. In adults with type 1 diabetes presenting to emergency services, consider capillary blood ketone testing if :**<br>• **DKA is suspected or**<br>• **the person has uncontrolled diabetes with a period of illness, and urine ketone testing is positive. [new 2015]**<br><br>**101. Consider capillary blood ketone testing for inpatient management of DKA in adults that is incorporated into a formal protocol. [new 2015]** |
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|  | could have substantial cost-saving implications if it resulted in a reduction in hospital admission rates for the management of DKA.<br>The GDG acknowledged that there would be additional cost implications in that individuals would need education from healthcare staff on how to test for blood ketones and how to interpret the result.<br><br>Presentation to emergency services and hospital monitoring<br>Given the cost of individual blood ketone test strips, the GDG was keen that capillary blood testing did not replace the use of urine testing when screening for ketones. This was with the aim of preventing capillary blood ketone testing becoming ubiquitous amongst healthcare professionals even when suspicion of ketosis is low.<br>The biochemistry blood test for ketones assessment costs £1.26 per unit, which is cheaper than capillary blood strip ketone testing. However, the GDG recognised that in clinical practice the result would be available less readily than capillary blood ketone results when making management decisions for insulin infusion rates in the management of DKA.<br>For the use of capillary blood ketones for inpatient management of DKA, the GDG were presented with the cost of the average length of hospital stay of 3.4 days for the management of DKA (Hospital Episode Statistics 2011-12). The GDG found that provided discharge was safe and would not lead to a recurrence of DKA, capillary blood ketone monitoring would have to reduce length of stay in hospital by more than 0.074 days (or 100 minutes) in order to be cost-saving in comparison to urine ketone monitoring. The GDG observed that one study in the clinical review had shown that switching to a protocol using capillary blood ketone testing in place of urine ketone testing as per the JBDS protocol had reduced length of hospital stay by 1.2 days, and therefore, capillary blood ketone monitoring was likely to be cost-effective for use in the inpatient management of DKA. However, in making its recommendation, the GDG wanted to state explicitly that blood ketone monitoring should only be used as part of an approved protocol for the management of DKA, rather than being used in isolation. |
| Quality of evidence | Six studies were identified for the review.<br>Only one of the studies was a RCT, and this assessed self-monitoring of ketones at home and its impact on emergency admission rates (Laffel et al., 2006). The population participating in this study was young (age ≤22 years - a mixture of children, young people and young adults) and therefore, caution was taken in interpreting the results from this study and applying the results to the adult population with type 1 diabetes.<br>The GRADE quality of the study was 'Very low', and the GDG expressed concerns |

Update 2015

| Recommendations | 99. Consider ketone monitoring (blood or urine) as part of 'sick-day rules' for adults with type 1 diabetes, to facilitate self-management of an episode of hyperglycaemia. [new 2015]<br><br>100. In adults with type 1 diabetes presenting to emergency services, consider capillary blood ketone testing if :<br>• DKA is suspected or<br>• the person has uncontrolled diabetes with a period of illness, and urine ketone testing is positive. [new 2015]<br><br>101. Consider capillary blood ketone testing for inpatient management of DKA in adults that is incorporated into a formal protocol. [new 2015] |
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| | about the effect of the study protocol impacting on the final result. Individuals in the trial underwent training on blood ketone monitoring, and had 24 hour access to advice from a physician, and therefore, may have been better able to manage intercurrent illness for reasons other than just ability to monitor ketonaemia. The study also specifically excluded individuals with a previous history of high admission rates for DKA, who would arguably be the target group for assessing the effectiveness of home ketone monitoring.<br><br>The other studies for the evidence review were non-comparative observational studies, and therefore, could not be assessed by meta-analysis or GRADE assessment. All five studies assessed the impact of ketone monitoring on inpatient management (Bektas et al., 2004, Harris et al., 2005, Taboulet et al., 2007, Arora et al., 2011, Ray et al., 2013). These studies were given a 'Low quality' rating by the GDG, and therefore, conclusions were drawn with caution when interpreting the data. |
| Other considerations | Members of the GDG recognised that the most recent national guidance for DKA management (JBDS guidelines) advised the use of capillary blood ketone testing to facilitate management decisions, and that this guidance was being used in hospitals across the country.<br><br>The GDG recognised that the quality of the available evidence regarding capillary blood ketone testing was low, and that there were no RCT data to support the use of capillary blood ketone strips in the emergency department setting. The GDG therefore made a recommendation that research into whether the use of blood ketone strips improves clinical outcome should be undertaken.<br><br>Patient members on the GDG expressed a preference for access to capillary blood ketone monitoring over urine ketone monitoring, as it provided a means of testing for ketones that was of greater convenience and the evidence suggested that it provided a more accurate result. |

**Update 2015**

### 12.3.3 Research recommendations

**27. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the management of DKA?**

28. **In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the prevention of DKA?**

29. **In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of pre-empting admissions) of self-monitoring blood ketones compared to urine ketones?**

## 12.4 Management of DKA [2004]

The management of DKA is a topic which has attracted considerable attention over 40 years because it can carry a high fatality risk if suboptimally managed. If optimally managed, the fatality and morbidity rates are very low. The topic is not easily addressed within a general diabetes guideline, being large enough for a guideline of its own. The approach below is to address some broad principles and specific topics of contention, rather than present a detailed protocol.

### 12.4.1 Evidence statements [2004]

**Insulin therapy**

Continuous versus intermittent insulin therapy for DKA was evaluated in one small randomised study.[562] Insulin was administered as bolus injections (50 U per 2 hours) compared with continuous insulin infusion (10 U per hour) and low-dose continuous insulin infusion (2 U per hour) with an initial loading dose. To reduce plasma glucose concentrations, continuous infusion is as effective as intermittent insulin therapy at 10 U per hour, with reduction to 5 U per hour when plasma glucose is less than 300 mg/100 ml. DKA recovery rate was significantly reduced following the very low dose continuous infusion regimen (Ib).

Another small study showed that low doses of insulin given by intermittent intramuscular (IM) injection or by constant intravenous (IV) infusion after an initial IV loading dose are similarly effective in controlling DKA.[614] Time to recovery of DKA and total insulin dose required did not differ between the two treatment groups (Ib).

A comparison of different possible routes of insulin delivery in treating DKA showed similar efficacy for IV, IM and subcutaneous administered insulin therapy.[217] No significant differences were seen for the time to metabolic recovery or total insulin dose or fluid replacement requirements. Patients receiving IM insulin were most likely to require an additional insulin loading dose to achieve an adequate initial response. In this report, a significantly higher rate of decrease in glucose and ketone bodies was observed in the first 2 hours following IV insulin, but these differences were not maintained over the rest of the recovery period (Ib).

No significant differences in recovery rates were seen following the administration of human and porcine insulin for the treatment of DKA in a prospective trial with a small study population of people with both type 1 and type 2 diabetes (Ib).[669]

Continuation of insulin administration past the usual cut-off point of near-normoglycaemia versus conventional insulin regimen (rehydration, electrolyte replacement and insulin at 5 U per hour to near-normoglycaemia, that is blood glucose less than or equal to 10 mmol/litre, and then at a reduced rate until clinical recovery) in one small study, significantly increased the resolution of ketosis, measured as duration of elevated blood 3-hydroxybutyrate levels, and acidosis (Ib).[742]

**Bicarbonate therapy**

IV sodium bicarbonate therapy added to the treatment regimen for DKA was shown in a randomised trial with small sample size to increase recovery of arterial pH and bicarbonate levels in the first

2 hours, but did not effect $pCO_2$ or blood glucose levels.[234] All patients in the bicarbonate group developed hypokalaemia (Ib).

One study compared the effect of two different IV bicarbonate doses (adjusted to initial arterial pH) on the recovery rate of DKA, with placebo.[491] No significant differences were seen between the groups treated with bicarbonate or placebo (Ib).

In agreement with these studies, one small trial showed that IV bicarbonate therapy had no additional beneficial effect when compared with standard DKA therapy without bicarbonate supplementation (IIa).[722]

No significant differences were seen after the addition of phosphate therapy to treatment for DKA in a small trial.[216] A protective effect against hypophosphataemia was seen following phosphate treatment compared with placebo, but only on the first day of treatment (Ib).

An additional paper also reported no evidence of clinical benefit of phosphate therapy compared with placebo (Ib).[747]

**Somatostatin therapy**

One small study concluded that addition of the somatostatin analogue, octreotide, to low-dose insulin therapy reduced the time taken for correction of ketonuria.[760] However, no such effect was seen on the recovery rate of hyperglycaemia and acidosis (Ib).

### 12.4.2 Health economic evidence [2004]

The health economic searches found only one US-based costing study.[352] As such, no specific health economic guidance can be provided here.

### 12.4.3 Considerations [2004]

DKA management was noted to be based on a mixture of types of evidence, pathological, pharmacokinetic, clinical outcomes, cohorts and trials.

It was noted that DKA management is:

- quite detailed
- often performed under the supervision of diverse groups of specialists
- dependent on careful monitoring if catastrophic outcome is to be avoided

There was broad consensus on issues of management, which largely seem to revolve around ameliorating the acidosis and hyperglycaemia without inducing the possibly fatal complications of cerebral oedema, hypokalaemia or aspiration pneumonia. Moderation in the speed and methods of correcting dehydration, hyperglycaemia and ketosis is combined with a high intensity of the monitoring of the changing condition of the patient.

The group noted that there was no evidence at all for the use of bicarbonate in any situation, and that the consensus recommendations for its use below a pH of 6.9 were poorly grounded in either clinical experience or any kind of evidence.

The group noted that the nature of insulin pharmacokinetics and pharmacodynamics suggested that the detailed studies of ways of starting insulin infusions had no logical basis.

Clinical experience of management in adults suggested that acute respiratory distress syndrome ('fluid on the lung') was seen not infrequently in addition to cerebral oedema. While the evidence

that either of these could be ameliorated by using lower rates of saline replacement was not good, nor was there any impression that in the non-shocked patients such lower rates were harmful. Accordingly they are recommended.

Members of the group had seen examples of glucose concentration escape after reaching near-normal glucose levels, and felt that the evidence-based lesson of the Belfast paper (that these insulin-resistant patients require continued administration of higher rates of insulin than other patients on insulin infusions) was worth noting.[742]

## 12.5   Recommendations [2004]

102. **Professionals managing DKA in adults should be adequately trained, including regular updating, and be familiar with all aspects of its management which are associated with mortality and morbidity. These topics should include:**
   - **fluid balance**
   - **acidosis**
   - **cerebral oedema**
   - **electrolyte imbalance**
   - **disturbed interpretation of familiar diagnostic tests (white cell count, body temperature, ECG)**
   - **respiratory distress syndrome**
   - **cardiac abnormalities**
   - **precipitating causes**
   - **infection management, including opportunistic infections**
   - **gastroparesis**
   - **use of high dependency and intensive care units**
   - **recommendations 103 to 110 in this guideline.**

   **Management of DKA in adults should be in line with local clinical governance. [2004]**

103. **For primary fluid replacement in adults with DKA, use isotonic saline, not given too rapidly except in cases of circulatory collapse. [2004]**

104. **Do not generally use bicarbonate in the management of DKA in adults. [2004, amended 2015]**   Update 2015

105. **Give intravenous insulin by infusion to adults with DKA. [2004]**

106. **In the management of DKA in adults, once the plasma glucose concentration has fallen to 10–15 mmol/litre, give glucose-containing fluids (not more than 2 litres in 24 hours) in order to allow continued infusion of insulin at a sufficient rate to clear ketones (for example, 6 units/hour monitored for effect). [2004, amended 2015]**   Update 2015

107. **Begin potassium replacement early in DKA in adults, with frequent monitoring for the development of hypokalaemia. [2004]**

108. **Do not generally use phosphate replacement in the management of DKA in adults. [2004, amended 2015]**

109. **In adults with DKA whose conscious level is impaired, consideration should be given to inserting a nasogastric tube, monitoring urine production using a urinary catheter and giving heparin. [2004]**

110. **To reduce the risk of catastrophic outcomes in adults with DKA, ensure that monitoring is continuous and that review covers all aspects of clinical management at frequent intervals. [2004, amended 2015]**

Update 2015

# 13 Associated illness [2004]

## 13.1 Introduction

This chapter was a section of the 'Management of Late Complications' chapter in the 2004 guideline CG15. It has been moved to a separate chapter to separate associated illnesses from complications. The 2015 GDG did not update associated illness; 2004 evidence is reproduced verbatim in this chapter.

## 13.2 Rationale [2004]

Type 1 diabetes is an auto-immune disease associated with genes which modulate the immune response. Other auto-immune diseases are similarly associated, and manifestation of some of them can be sub-clinical while interacting with aspects of food absorption or metabolism. The evidence for routine screening for thyroid dysfunction was reviewed in 2015; recommendations concerning screening for other autoimmune conditions (Addison's disease, pernicious anaemia, premature ovarian failure) has not been reviewed or updated from 2004.

## 13.3 Evidence statements [2004]

**Latent pernicious anaemia**

Using a microbiological method to measure cobalamin concentration, one study from Australia found reduced cobalamin concentration in six out of 371 people with type 1 diabetes.[157,159] Four of the patients showed no clinical signs of pernicious anaemia, the fifth was mildly anaemic and the sixth patient was not available for further testing. This medium-sized study with methodological limitations gave a prevalence of latent pernicious anaemia of 11 per 1000 in people with type 1 diabetes (III).

**Prevalence of coeliac disease**

Using immunoglobulin A (IgA) class anti-endomysial antibodies (EmAb) detected by immunofluorescence (test) and histological confirmation of coeliac disease by small intestinal biopsy partial or total villous atrophy, a medium-sized study showed in an unselected sample at an outpatients clinic that the prevalence of coeliac disease in the sampled population was 6.4% and that EmA were highly predictive of the presence of coeliac disease on biopsy (DS).[677]

A larger study, but with potential methodological limitations, found that in a two-step screening process of anti-gliadin antibodies (GA) detected by enzyme-linked immunosorbent assay (ELISA) assay and IgA class EmAb detected by immunofluorescence, the predictive value of GA was moderate, with a high false-positive rate for IgA-GA.[656,657] Prevalence of coeliac disease in type 1 diabetes to be up to 2.6% and that after 30 years diabetes duration, the prevalence of coeliac disease was >6%. The study also found that EmAb were highly predictive of the presence of coeliac disease on biopsy (DS).

The frequency of coeliac disease-specific serologic markers and the prevalence of coeliac disease in families of patients with type 1 diabetes were evaluated in a medium-sized study using a two-step screening process.[463] The screening programme included circulating islet cell antibodies (ICA), anti-glutamic acid decarboxylase antibodies and GA, and then IgA class EmAb detected by immunofluorescence. This study found the prevalence of biopsy-proven coeliac disease to be 1.3% among patients with type 1 diabetes and zero among controls, or family. Of screening assays, only EmAb were highly predictive of the presence of coeliac disease (DS).

Another diagnostic study using IgA class EmAb compared people with type 1 diabetes with adults with coeliac disease as true positives (as determined by intestinal biopsy) and controls (healthy and diseased) as true negatives (as determined by intestinal biopsy).[621] The prevalence of biopsy-proven coeliac disease among adults with type 1 diabetes was 3.13%. This study showed IgA class EmAb had high specificity in detecting coeliac disease in people with type 1 diabetes (DS).

**Red cell distribution width**

Using red cell distribution width (RDW) as a screening test against EmAb and diagnostic duodenal biopsy as reference tests for coeliac disease one very small, methodologically-limited study demonstrated the poor specificity of RDW in predicting coeliac disease in people with type 1 diabetes.[354,355] Given the potential methodological limitations, this evidence was not used to support any recommendations in this area (DS).

## 13.4 Health economic evidence [2004]

The health economic searches found no relevant papers for the treatment of those with type 1 diabetes suffering from concurrent disease.

## 13.5 Considerations [2004]

While auto-immune conditions are probably more common in people with type 1 diabetes than in the general population, the group did not feel that this should lead to any formal system of surveillance for the development of such conditions.

## 13.6 Recommendations

111. **In adults with type 1 diabetes who have a low BMI or unexplained weight loss, assess markers of coeliac disease. [2004]**

112. **Be alert to the possibility of the development of other autoimmune disease in adults with type 1 diabetes (including Addison's disease and pernicious anaemia). For advice on monitoring for thyroid disease, see recommendation 150. [2004, amended 2015]**

Update 2015

# 14 Arterial risk control

The 2015 GDG updated the evidence for aspirin for the primary prevention of cardiovascular disease. All other aspects of this chapter are the work of the 2004 GDG and were not updated.

## 14.1 Aspirin for the primary prevention of cardiovascular disease [2015]

### 14.1.1 Introduction [2015]

Type 1 diabetes substantially increases the risk of a cardiovascular (CV) event. Although recent data show that absolute CV mortality rate has fallen in recent years, the age-adjusted incidence rate ratio remains elevated at 2.3 for men and 3.0 for women.[441] CV disease is the commonest cause of death in people with type 1 diabetes over the age of 40 years and regular assessment and active management of each individual's CV risk is essential.

Although good management of CV risk in type 1 diabetes is imperative, updating the 2004 sections of this chapter for the 2015 version was not prioritised (with one exception). This does not reflect the importance of the topic, rather the fact that several of the original questions have been updated by other pieces of NICE guidance. In the section "Interventions to reduce risk and to manage CVD", the evidence and recommendations on lipid-lowering measures have been reviewed and new guidance published as CG181 "Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease". Evidence pertinent to people with type 1 diabetes was considered separately by the GDG developing CG181, where available, and the relevant recommendations have therefore been taken to replace those from the 2004 type 1 diabetes guideline. Similarly, the evidence on blood pressure management has been updated for people with type 1 diabetes and renal impairment in CG182 "Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care", and the relevant recommendations replace those from 2004 for people with type 1 diabetes.

The only review question addressed by the 2015 type 1 diabetes GDG refers to the role of aspirin as a primary preventative agent. Low-dose aspirin (75-600 mg per day) has been shown to reduce the incidence of CV disease in people at high risk for other reasons, particularly if they have had a previous event.[39] However, its consumption is associated with an increased risk of haemorrhage and some of the data supporting its use come from the pre-statin era. In the non-diabetic population, the therapeutic ratio is such that aspirin is only recommended as secondary prevention. Because of the high risk of CV disease in the type 1 diabetes population, it is important to assess the potential benefit of aspirin for primary prevention in this population specifically, and to review the risk:benefit ratio.

**The updated review question in this chapter is:**

- In adults with type 1 diabetes, is aspirin an effective anti-platelet agent for the primary prevention of cardiovascular events?

The evidence and text from the previous guideline, CG15, that has been superseded by this update is in Appendix S.

### 14.1.2 Updated review question: In adults with type 1 diabetes, is aspirin an effective anti-platelet agent for the primary prevention of cardiovascular events?

For full details see review protocol in Appendix C.

**Table 152: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
|---|---|
| Intervention/s | Aspirin |
| Comparison/s | • Placebo<br>• Usual care/no intervention<br>• Low-dose versus high-dose |
| Outcomes | • Mortality – all-cause (dichotomous/time-to event)<br>• Mortality – CV (dichotomous/time-to event)<br>• MI – all-cause (dichotomous/time-to event)<br>• MI – fatal (dichotomous/time-to event)<br>• MI – non-fatal (dichotomous/time-to event)<br>• Stroke – all-cause (dichotomous/time-to event)<br>• Stroke – fatal (dichotomous/time-to event)<br>• Stroke – non-fatal (dichotomous/time-to event)<br>• Quality of life – measured by SF-36, DQoL, DSQoL (continuous)<br>• Adverse events – bleeding or gastrointestinal complications (dichotomous)<br>• HbA1c (continuous)<br>• Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported) |
| Study design | Randomised controlled trials (RCTs) |

### 14.1.2.1 Clinical evidence

We searched for randomised trials comparing the effectiveness of aspirin versus. placebo or usual care as a prophylactic treatment with the aim of preventing the development of CV events in adults with type 1 diabetes.

Two studies were included in the review (Hansen 2000[277] and ETDRS 1997[199]). Evidence from the included studies are summarised in the clinical GRADE evidence in Appendix I. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

Due to the scarcity of relevant studies found in the electronic literature search, a hand search of the literature was also conducted, based on references to studies, meta-analyses and guidelines that were referred to in the original NICE 2004 guideline (CG15)[506], and the SIGN diabetes guideline (2010)[639]. All studies referred to in these documents (apart from Hansen 2000[277] and ETDRS 1997[199]) were excluded from this review because they looked at the wrong populations – they were either type 2 diabetes, mixed population with no type 1 diabetes subgroup analysis, or did not have diabetes.

Because very few studies were found to answer this question, and our review sought to assess the impact of aspirin on the **primary** prevention of CV events in adults with type 1 diabetes, we decided to contact the authors of the large ETDRS study, in order to obtain specific data for type 1 diabetes adults who had no documented history of a CV event (that is, aspirin used for primary prevention of CV events). The original ETDRS study had looked at the efficacy of aspirin for both primary and secondary prevention, in a combined population of type 1 diabetes and type 2 diabetes. The authors supplied us with unpublished data[200] for the subpopulation of type 1 diabetes adults who had not previously had any CV events, and these data have been included in the review (for the outcomes they provided us– CV events, CV mortality, MI and stroke). However, for the outcomes of all-cause mortality and life-table 5-year results, we have used the data provided in the published paper (based on a mixed population of type 1 diabetes adults with and without a history of CV events – that is,

both primary and secondary prevention). This data has therefore been downgraded in GRADE for indirectness.

**Table 153: Summary of studies included in the review**

| Study | Intervention/ comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| ETDRS 1992[199,200] | Aspirin (650 mg) vs. placebo | n=1393 (unpublished data) or n=1130 (published data)[a] type 1 diabetes with diabetic retinopathy; 25% had proliferative retinopathy, 49% had a history of CV disease or previous CV event§ | 5 years follow-up (average) | • Mortality (all-cause)<br>• Mortality (CV)<br>• MI (fatal/non-fatal)<br>• Stroke (fatal/non-fatal) | HIGH-DOSE ASPIRIN |
| HANSEN 2000[277] | Aspirin (150 mg) vs. placebo | n=16 type 1 diabetes with persistent low-level (micro) albuminuria; 41% had proliferative retinopathy | 4 weeks treatment 6 months follow-up | • HbA1c<br>• Dyspepsia<br>• Adverse events | LOW-DOSE ASPIRIN |

(a) The ETDRS study population consisted of both type 1 diabetes and type 2 diabetes adults, who had previous CV events (that is, secondary prevention) or no previous CV event (that is, primary prevention). Data included for this review were taken from the published paper and some of the outcomes were provided to us by the study authors. The data from the study authors is specifically for the population relevant to this review (type 1 diabetes adults who did not have a previous CV event - that is, primary prevention).

(b) History of CV disease was defined as history of any of the following: coronary artery disease, congestive heart failure, MI or intermittent claudication. Patients reporting any of the following drug use were also considered to have CV disease history: long-term antianginal agents, beta-blockers, vasodilators, digitalis, antiarrhythmic agents, diuretics or other antihypertensive agents. Patients with a systolic blood pressure of more than or equal to 160 mmHg were also considered to have CV disease history.

**Outcomes**

In keeping with the small number of published studies included, no suitable conference abstracts were found.

There was no data reported in any of the studies for the following outcomes:

• quality of life
• hypoglycaemia

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**Table 154: Clinical evidence summary: Aspirin versus placebo (less than or equal to 6 months)**

| Outcomes | No. of studies | Imprecision | GRADE rating | Absolute difference<br><br>Aspirin | Control event rate (per 1000 patients)<br><br>Placebo |
|---|---|---|---|---|---|
| HbA1c | 1 study (n=17) | Very serious | VERY LOW | MD 0.1 lower (0.67 lower to 0.47 higher) | 8.5 final value in control group |
| Dyspepsia | 1 study (n=17) | Very serious | VERY LOW | 40 more per 1000 (from 230 fewer to 1000 more) | 333 |
| Adverse events | 1 study (n=17) | Very serious | VERY LOW | Not reported and not estimable – study indicates there was no difference between groups | |

**Table 155: Clinical evidence summary: Aspirin versus placebo (more than 6 months)**

| Outcomes | No. of studies | Imprecision | GRADE rating | Absolute difference<br><br>Aspirin | Control event rate (per 1000 patients)<br><br>Placebo |
|---|---|---|---|---|---|
| Mortality (all-cause) | 1 study (n=1130) | Serious | MODERATE | 16 fewer per 1000 (from 36 fewer to 14 more) | 68 |
| Mortality (CV) | 1 study (n=1393) | Very serious | LOW | 10 fewer per 1000 (from 26 fewer to 17 more) | 56 |
| CV events | 1 study (n=1393) | Very serious | LOW | 10 fewer per 1000 (from 33 fewer to 23 more) | 90 |
| MI (fatal and non-fatal) | 1 study (n=1393) | Serious | MODERATE | 14 fewer per 1000 (from 32 fewer to 14 more) | 68 |
| Stroke (fatal and non-fatal) | 1 study (n=1130) | Very serious | LOW | 7 more per 1000 (from 6 fewer to 33 more) | 18 |

### 14.1.2.2 Economic evidence [2015]

**Published literature**

No relevant economic evaluations comparing the relevant interventions were identified, either in this update or in the original guideline.

**Unit costs**

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

**Table 156: Unit costs**

| Drug | Dose | Cost | Pack size | Cost per tablet |
|---|---|---|---|---|
| Aspirin | 75 mg | 76p | 28 | 3p |
| Aspirin | 300 mg | 31p | 32 | 1p |

Source: BNF64[357]

**Table 157: Cost of cardiovascular-related complications**

| | At Time of Event | | Annual thereafter |
|---|---|---|---|
| Complication | Fatal | Non-Fatal | |
| Ischaemic heart disease | - | £3,337 | £1,103 |
| MI | £1,690 | £6,434 | £1,060 |
| Heart failure | £3,721 | £3,721 | £1,304 |
| Stroke | £4,963 | £3,936 | £744 |

Source:   Waugh N, Cummins E, Royle P, Clar C, Marien M, et al. *Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technol Assess 2010;14(36)*[730].

Note:     Updated to 2010/11 prices using PSSRU 2011[147]

**Table 6:     Pooled average cost of gastrointestinal bleeds**

| Group | Average cost | Lower quartile | Upper quartile |
|---|---|---|---|
| Elective | | | |
| Elective inpatient | £1,694 | £709 | £2,060 |
| Elective excess bed days | £243 | £170 | £301 |
| Non-elective | | | |
| Non-elective inpatient | £2,313 | £1,683 | £2,625 |
| Non-elective excess bed days (long stay) | £220 | £172 | £264 |
| Non-elective excess bed days (short stay) | £455 | £308 | £527 |

Source:   NHS Reference Costs[166]

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### 14.1.3    Evidence statements [2015]

**Clinical**

**Aspirin versus placebo (less than or equal to 6 months)**

Very low quality evidence from one study showed no clinical difference for:

- HbA1c (n=17)
- dyspepsia (n=17)

In the case of HbA1c, the direction of the estimate of effect favoured aspirin, whereas for dyspepsia, it favoured placebo.

Very low quality evidence from one study showed no difference[m] for:

- adverse events (n=17)

**Aspirin versus placebo (more than 6 months)**

Evidence from one study showed no clinical difference for:

- mortality – all-cause (Moderate quality evidence; n=1130)
- mortality - CV (Low quality evidence; n=1393)
- CV events (Low quality evidence, n=1393)
- MI – fatal and non-fatal (Moderate quality evidence; n=1393)
- stroke – fatal and non-fatal (Low quality evidence; n=1130)

In the cases of mortality (both all-cause and CV), CV events and MI, the direction of the estimate of effect favoured aspirin, whereas for stroke, it favoured placebo.

**Economic**

No relevant economic evaluations were identified.

### 14.1.4    Recommendations and link to evidence

| Recommendations | 113. Do not offer aspirin for the primary prevention of cardiovascular disease to adults with type 1 diabetes.[new 2015] |
|---|---|
| Relative values of different outcomes | The important (critical) outcomes are mortality and CV events. The GDG also felt that adverse events, particularly those affecting the gastrointestinal tract (for example, dyspepsia and bleeding), were important and had to be taken into consideration when balancing the benefits and harms of aspirin.<br><br>The outcomes of $HBA_{1c}$ and hypoglycaemia are less important for this question, although, it is appropriate to consider whether they are affected by aspirin. |
| Trade off between clinical benefits and harms | The GDG was interested in balancing the prevalence of dyspepsia and gastrointestinal bleeding against any reduction in CV events. There was a paucity of studies in people with type 1 diabetes. Within the data available, there was little |

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m  *Data required for calculating clinical difference or direction of effect was not reported, so this is based on statistical difference.*

| Recommendations | **113. Do not offer aspirin for the primary prevention of cardiovascular disease to adults with type 1 diabetes.[new 2015]** |
|---|---|
| | robust evidence from the type 1 diabetes population to suggest either benefit or harm from the therapy; all the 95% Confidence Intervals crossed the line of no difference, and when looking at the clinical importance of the effect sizes based on the absolute differences, none of the outcomes showed a clinically important effect.

In addition to looking at type 1 diabetes-specific evidence, the GDG considered the data from the general population because, although the risk of a CV event is much higher in a person with type 1 diabetes than in those without diabetes, there is no obvious reason why people with type 1 diabetes should respond differently to the beneficial or harmful effects of aspirin in primary prevention. The GDG noted that current guidance from the MHRA[479] suggests that the harms of aspirin for primary prevention outweigh the benefits.

It was also decided to contact authors of studies that had been initially excluded in the review because they were of a mixed type 1 diabetes and type 2 diabetes population, to request data for the type 1 diabetes subpopulation. None of these authors responded with any additional data. We also contacted the authors of the ETDRS study, because this study looked at the effects of aspirin for both primary and secondary prevention, and the authors provided some primary prevention-specific data which showed no clinical benefit of aspirin in reducing/preventing CV mortality, CV events or MI in adults with type 1 diabetes at an average of 5 years follow-up. |
| Economic considerations | No economic evidence was found. The GDG considered the low cost of aspirin and its potential side effects vs. the high cost of CV complications. Due to the low costs involved in treatment with aspirin, the clinically effective option is likely to be the cost effective one. Since the clinical data showed that there was no clinical benefit of aspirin for reducing/preventing CV mortality, CV events and MI in adults with type 1 diabetes at an average of 5 years follow-up, the GDG did not consider the use of aspirin to be cost-effective for primary prevention in adults with type 1 diabetes. |
| Quality of evidence | The evidence quality was considered as Very low for the ≤6 months data (based on the Hansen 2000 study) because there was very serious imprecision and the study design had a number of methodological flaws. The outcomes at >6 months were rated as Moderate to Low (based on the ETDRS study), because, although the study design was considered to be robust, the imprecision varied from serious to very serious. The main published ETDRS study also included a mixture of people who had previous CV events as well as those who had not, and so was considered both primary and secondary prevention. This was therefore downgraded for indirectness. However, for some of the outcomes in our review (CV events, CV mortality, MI and stroke), we were able to obtain unpublished data from the authors, which was for people with type 1 diabetes who had no previous history of CV disease (that is, the primary prevention data). This was therefore considered as more robust and relevant evidence, and was not downgraded for indirectness. |
| Other considerations | None. |

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### 14.1.5   Research recommendations

**30. In adults with type 1 diabetes, what is the clinical and cost effectiveness of aspirin and other anti-platelet agents who are at high risk for vascular disease (for example, smokers, those with renal disease, those with other evidence of vascular disease)?**

## 14.2   Identification of arterial risk [2004]

### 14.2.1   Rationale [2004]

People with type 1 diabetes are generally recognized to be at greatly increased risk of arterial disease (CVD) in middle age. While the literature on arterial risk factors and markers in the general population is large, it would not appear to follow that the findings can be simply carried over to people with type 1 diabetes. Similarly, the tools used to quantify arterial risk in the general population are known not to work well in people with type 2 diabetes, and seem even less likely to be valid in type 1 diabetes.

### 14.2.2   Evidence statements [2004]

**Arterial risk factors**

The Scottish Intercollegiate guidelines identify specific risk factors for CVD, such as cigarette smoking, dyslipidaemia, hypertension, hyperglycaemia, obesity and microalbuminuria (**IV**).[639]

The guideline reports on non-randomised studies showing that smoking is an independent arterial risk factor in people with diabetes.[639] Additional observational studies reported dyslipidaemia. An increased concentration of LDL cholesterol or total cholesterol has also been identified as an independent risk factor for arterial morbidity and mortality, and each 1.0 mmol/litre reduction of LDL cholesterol represents a 36% reduction in the risk of CVD (**IIa**).

Two controlled but not randomised studies reported within the guideline demonstrated the positive relationship between hypertension and risk of arterial death, with a progressive increase in risk with rising systolic pressure.[639] Each 10 mmHg reduction in systolic pressure is associated with a 15% (95% CI, 12 to 18) reduction in risk of arterial death over 10 years (**IIa**).

The link between glycaemia and arterial morbidity and mortality was also reported in two studies reviewed in the SIGN guideline 174. In one study, each 1.0% reduction in HbA1c was associated with a 21% (95% CI, 15 to 27) reduction in the risk of diabetes-related death and a 14% reduction for myocardial infarction (MI) over 10 years. (**IIa**)

Evidence for the other risk factors is sparse. In the SIGN guidelines, no studies were identified for linking obesity as an independent risk factor in established diabetes.[639] One observational study reported microalbuminuria as an independent marker associated with doubling in arterial risk, but, there is insufficient evidence to determine whether reducing albumin excretion rate specifically reduces arterial morbidity or mortality. (**IIa**)

A meta-analysis aimed at defining risk factors for CVD from studies in people with diabetes showed that, adjusted for age, both total mortality and death from all vascular causes increased significantly with total cholesterol level and systolic blood pressure, and decreased with the percentage of women.[363] Duration of diabetes and mean HbA1c were not considered to be associated with mortality. However, this meta-analysis did not contain a critical appraisal of included studies or details of approaches used to ensure study quality before inclusions and should, therefore, not be used as the basis for clinical recommendations. (**IIa**)

**Screening tests**

One systematic review examined 67 studies, addressing both screening for the primary detection of arterial risk factors and treatment of lipid abnormalities in asymptomatic people both with and without diabetes.[561] Reliability and effectiveness of each screening strategy for identifying lipid disorders was investigated, and showed that total cholesterol measurements generally have good reliability, with an analytic variability of less than or equal to 3% and a mean total biologic variability of the order of 6%. A total cholesterol level within 10% of the true value can be determined with two separate measurements, which do not differ significantly between fasting or non-fasting venous blood. (**III**)

Evidence within this systematic review 176 for HDL cholesterol showed a higher analytical (6%) and biological (7.5%) variation than total cholesterol, however, two or three values were required to estimate true HDL cholesterol levels to within 10% to 15%. Variations were also found between non-fasting and fasting blood samples as HDL cholesterol is 5% to 10% lower in the non-fasting state, suggesting that non-fasting measurements may slightly overestimate coronary heart disease risk, but not enough to make accuracy of screening unacceptable. (**III**)

Additional studies within this systematic review considered triglyceride screening. Values measured varied by 20 to 30% between fasting and non-fasting states.[561] LDL cholesterol is calculated from total and HDL cholesterol, as well as triglyceride measurements and application of the Friedewald equation. However, this equation has been found to be inaccurate at triglyceride levels greater than or equal to 4.5 mmol/litre when special techniques must be employed (for example, ultracentrifugation). (**III**)

Also considered in this systematic review was the comparable accuracy of total and HDL cholesterol from capillary blood samples.[561] These were found to be less reliable without proper attention to calibration and proper testing techniques. One study found that a Framingham-based coronary risk model was the best predictor of ischaemic heart disease mortality. Guidelines reported in the review concluded that the LDL:HDL cholesterol and the total:HDL cholesterol ratios performed equally well in determining arterial outcomes, and the least accurate screening test was that of measuring total cholesterol alone. (**III**)

Other studies included in this review assessing characteristics of the screening tests showed that the non-fasting total cholesterol alone is the easiest to perform for the patient and provider.[561] The total:HDL cholesterol ratio is easy for patients to obtain and for providers to interpret and performs equally accurately as the LDL:HDL cholesterol ratio strategy. However, one study in the review demonstrated that risk-based algorithms, which directly incorporate age, other risk factors and measures of total and HDL cholesterol, are the most accurate approach to screening. These processes are difficult to access and so supplemental tables, such as the Sheffield table, can improve the feasibility of a risk-based strategy. (**III**)

There was no evidence from this systematic review to inform the question of appropriate frequency of screening.[561] National guidelines recommend a 5-year interval for people with previous normal results and more frequent screening in those with borderline values. (**IV**)

**Prediction of arterial risk**

Six studies all published by the same group addressed the relative specificity and sensitivity of the different methods for predicting arterial risk (Sheffield, modified Sheffield, Joint British Guidelines, Canadian, Framingham categorical, New Zealand and Joint European guidelines, but not including the UKPDS risk engine).

One study comparing the Sheffield tables with the computer-calculated Framingham equation revealed a low sensitivity and specificity for the Sheffield tables (35% [95% CI, 28 to 42] and 98% [95% CI, 97 to 99], respectively).[59] The old tables only included patients with a systolic blood pressure of less than 160 mmHg, and a cholesterol greater than 5.5 mmol/litre. Adopting these exclusion criteria led to a substantial reduction in the number of patients eligible for screening without improving detection of risk assessment. (**DS**)

Another evaluation[235] studied all seven guidelines against the calculated Framingham equation in 906 people with diabetes, showing that Modified Sheffield tables have higher sensitivity (95% versus 37%) with a slight reduction in specificity (90% versus 97%) compared with the original tables, with a slightly better positive predictive value than the original version (80% versus 71%). The Joint British tables have good specificity (99%), but low sensitivity (77%). However, the tables perform well at the lower CHD risk of greater than or equal to 15% over 10 years (specificity, 92%; sensitivity, 96%). Canadian tables perform poorly at more than or equal to 30% risk, and only slightly better at the greater than or equal to 15% level of risk (specificity, 100%; sensitivity, 5%; and 85% and 98%, respectively). The Framingham categorical tables have a lower specificity (83%) for the identification of high-risk individuals (although risk is greater than or equal to 27%, not greater than or equal to 30%) and this deteriorates for identification of those at more than or equal to 15% risk (specificity, 77%). New Zealand tables had a sensitivity of 69% and specificity of 88% at a greater than or equal to 20% level of risk. At the more than or equal to 10% level of risk, specificity deteriorates to 58%. The Joint European tables have a sensitivity of 89% for risk levels greater than or equal to 20%, but specificity of only 71%. This means that 1 in 4 patients would be incorrectly identified as having a risk above the 20% threshold. (**DS**)

A further study from the same investigators assessed the PROCAM program against that of the Framingham equation.[236] Only 56% of the study population were eligible for evaluation with PROCAM. This evaluation also systematically underestimates risk in comparison with the Framingham equation at low levels of absolute risk, but overestimates at higher risk levels. (**DS**)

The sensitivity and specificity of various risk prediction tables and charts was also investigated in one comparative study.[359] Compared with the Framingham equation, the Sheffield tables had a low sensitivity (40% eligible for cholesterol-lowering treatment would be identified), but with high specificity and thus, low false-positive rates. The New Zealand tables had similar sensitivities and specificities to the Sheffield tables, but a 10% level of risk prediction of 5-year CVD risk threshold specificity is significantly lower than the Sheffield tables. The European tables have better sensitivity than the Sheffield and New Zealand tables, but specificity is significantly worse than other risk assessment levels leading to an equally low sensitivity. The joint British Societies table has significantly better specificities at greater than or equal to 15% and greater than or equal to 30% 10-year CHD risk than the modified Sheffield tables. Sensitivity is generally low, but high at the 15% 10-year CHD/10% five-year CVD risk level. Canadian tables are not reliable at greater than or equal to 30% risk, but are comparable with the modified Sheffield tables at 154% risk threshold. The Framingham equation had the best performance with sensitivity and specificity comparable to that of the modified Sheffield and joint British Society methods, respectively. (**DS**)

### 14.2.3   Consideration

The Group recognised the very considerable difficulties in reaching conclusions from the evidence in this area. Very little direct information pertaining to people with type 1 diabetes can be ascertained, whilst the importance of the issue is emphasized by the very high early CVD risk run by people with type 1 diabetes. Nevertheless, certain subgroups are known to be at particularly high risk (people with raised urinary albumin excretion), while others combine type 1 diabetes with combinations of classic risk factors typical of the metabolic syndrome and known to be predictors of high arterial risk in people with type 2 diabetes and indeed non-diabetic populations. A further group of people will

combine type 1 diabetes with a single arterial risk factor or risk marker, while others will have type 1 diabetes but appear low risk otherwise.

Accordingly, the important factors for surveillance are markers of urinary albumin excretion (most important), other classical risk factors, including full lipid profile, and risk markers, such as age, family history, and some ethnic groups. In accordance with the principle of unified organization of care, monitoring of these factors annually is to be recommended, but it was recognized that in low-risk individuals, technology might become capable of programming longer review intervals for serum lipids.

The group recognized that different ways of using information from a full lipid profile (calculated LDL and HDL separately, calculation of total cholesterol:HDL ratio and calculation of non-HDL cholesterol) are in use. While the group preferred the first of these, as not mixing lipid abnormalities of different pathogenesis and being a better route to using the treatments for different lipid disorders rationally, it was recognized that there was not good evidence to suggest supporting one approach over the others.

The group could find no confidence in any risk table, engine or equation when applied to people with type 1 diabetes.

### 14.2.4    Recommendations [2004]

114. **Assess arterial risk factors annually, including:**
- **albuminuria**
- **smoking**
- **blood glucose control**
- **blood pressure**
- **full lipid profile (including HDL and LDL cholesterol and triglycerides)**
- **age**
- **family history of arterial disease**
- **abdominal adiposity. [2004, amended 2015]**

115. **For guidance on tools for assessing risk of cardiovascular disease in adults with type 1 diabetes, see recommendation 1.1.9 in the NICE guideline on lipid modification. [new 2015]**

## 14.3    Interventions to reduce risk and to manage arterial disease [2004]

### 14.3.1    Rationale [2004]

Prevention of arterial risk in people with type 1 diabetes, through attention to blood glucose control (insulin therapy, patient education, nutrition and self-monitoring) is considered elsewhere in this guideline, and blood pressure management is considered in Section 14.4, below. However, in the general population (at much lower risk) and in people with type 2 diabetes, other therapies are known to reduce the risk of arterial events. Therefore, the current section deals with these approaches as applied to people with type 1 diabetes.

Update 2015

### 14.3.2 Evidence statements [2004]

**Lipid-lowering therapy**

The Scottish intercollegiate guidelines identify a role for lipid-lowering drugs in reducing ischaemic heart disease events, but not all-cause mortality in people with no known CVD, compared with placebo (Ia).[639]

SIGN guidelines on lipids and the prevention of ischaemic heart disease detail studies targeted at people with type 2 diabetes.[636] However, secondary prevention trials of lipids reported in the guideline have shown significant reduction in CVD in both type 1 and type 2 diabetes. These guidelines recommend the loss of weight, reduction of intake of saturated fat, increased consumption of fruit and vegetables, regular exercise and the introduction of a lipid-lowering drug treatment for primary prevention of arterial problems in high-risk people with diabetes. The guidelines also report a study raising concern about underestimating diabetic ischaemic heart disease risk, particularly in people with type 1 diabetes (Ia).

The SIGN guidelines report on a number of therapeutic studies.[639] The CARE study demonstrated a significant reduction in coronary events with pravastatin versus placebo, although, the magnitude of effect was lower than in the 4S study. The LIPID study also showed a trend to reduction in recurrent coronary events, but the numbers of people with diabetes in this study were too low to demonstrate statistical significance. The VA-HIT study showed significant secondary prevention of coronary events in men with diabetes aged less than 74 years, taking a fibrate (gemfibrozil) for a mean follow-up of 5.1 years (Ia).

Three RCTs reported on the positive effect of pravastatin on arterial outcomes in people with diabetes.[254,580,608] One study reported a significant change in total and LDL cholesterol, HDL cholesterol and triglycerides versus placebo.[608] After 24 weeks, the reduction in total cholesterol from baseline was 22%, LDL cholesterol 26%, and triglycerides decreased by 2%, accompanied by an increase in HDL cholesterol of 14%. Pravastatin was well tolerated throughout the study (Ib).

Similar results were seen in the further two trials. One study reported reductions in LDL cholesterol and VLDL cholesterol of 30% and 13%, respectively, with pravastatin compared with placebo, and significant increases in HDL cholesterol at 8 and 16 weeks.[580] The final study was in a majority of sulfonylurea-treated people with type 2 diabetes, and pravastatin reduced total and LDL cholesterol by 19% and 27%, respectively, in the diabetes group.[254] Compared with placebo, pravastatin caused a 13% decrease in triglycerides and a 4% increase in HDL cholesterol in people with diabetes. Results were similar to those in people without diabetes, and were unaffected by adjustment for age and gender (Ib).

The SIGN management of CVD in diabetes guidelines[639] cite results from the Scandinavian Simvastan study, which contained 204 people with diabetes (of a study population of 4444), and demonstrated that cholesterol-lowering therapy was highly effective compared with placebo in those undergoing revascularisation procedures, especially in those with diabetes (risk reduction 55% versus 32% in non-diabetes) (Ia).

Two RCTs reported the effect of simvastatin in people with diabetes. Total and LDL cholesterol levels and the ratio between LDL and HDL cholesterol were decreased following treatment in one study of 25 people with diabetes, whereas no difference was seen following placebo; no between group comparison was made.[620] The second study, containing 26 people with type 1 diabetes, also reported a significant reduction in the plasma concentrations of total cholesterol, LDL cholesterol and apolipoprotein B after 12 weeks of simvastatin treatment, whereas no changes were observed after placebo treatment (Ib).[326]

One study reported the effect of bezafibrate on arterial outcomes in 36 people with type 1 diabetes.[748] However, there are some potential methodological limitations in this study, which does not make this evidence a reliable basis for a clinical recommendation (Ib).

**Antiplatelet therapy as secondary prevention [2004]**

The North of England guidelines on aspirin for the secondary prophylaxis of vascular disease in primary care reported a pooled risk ratio by combining the meta-analysis of the Antiplatelet Collaborative Group with trials published after 1990 to establish the impact of antiplatelet therapy on subsequent MI, stroke and vascular death.[519] This provided strong evidence for a general protective effect of aspirin as antiplatelet therapy in patients at raised vascular risk. Few studies were found containing comparisons of aspirin and alternative antiplatelet agents to enable comparison of their relative effectiveness (Ia).

For evidence relating specifically to people with diabetes the North of England guidelines identified 8 trials contributing to an overall estimate of risk difference for arterial morbidity of 1.2% with aspirin compared with placebo or other antiplatelet agent.[519] These trials were homogeneous with a pooled incidence rate difference (by random effects model) of a 0.3% reduction in the risk of MI, stroke or vascular death from antiplatelet therapy for 1 year. This is not a statistically significant difference, and in summary, authors state that aspirin given to patients with diabetes appears to have a small and statistically uncertain effect upon the risk of experiencing a subsequent vascular event. They also suggest that the similar relative risk for MI, stroke and vascular death found in diabetes trials and other trials of patients at raised vascular risk, indicates that patients with diabetes alongside other indications of vascular risk are likely to benefit from routine aspirin therapy (Ia).

American Diabetes Association guidelines indicate that meta-analysis and large-scale collaborative trials in men and women with diabetes support the view that low-dose aspirin therapy should be prescribed as a secondary prevention strategy if no contraindications exist.[29] The guidelines also point to substantial evidence suggesting that low-dose aspirin therapy should be used as a primary prevention strategy in men and women with diabetes who are at a high risk for arterial events.

The meta-analysis of 145 prospective controlled trials of antiplatelet therapy by the Antiplatelet Trialists Group reported in the ADA guidelines showed a trend toward increased risk reductions with doses of aspirin of ≤325 mg per day, but the difference was not statistically significant.[29] An estimated 38±12 vascular events per 1000 patients with type 1 diabetes would have been prevented if they were treated with aspirin as a secondary prevention strategy (Ia).

The ADA guidelines also reported on the HOT study, which showed a reduction in arterial events following aspirin therapy compared with placebo of 15% and a 36% reduction in MI.[29] This study also showed that fatal bleeding, including intracerebral bleeding, were equal in the aspirin and control groups, whereas non-fatal minor bleeding episodes were more frequent in patients receiving aspirin. The US Physicians Health study reported in the same guideline compared aspirin (325 mg per day) with placebo in male physicians (without diabetes), resulting in a 44% risk reduction in MI among the treated group. In a subgroup of people with diabetes, there was a reduction in MI from 10% to 4%, yielding a relative risk of 0.39 for men with diabetes randomised to aspirin therapy (Ia).

The ADA guidelines also addressed the safety of aspirin use and reported several prospective randomised studies in which a trend for an increase in haemorrhagic stroke followed aspirin therapy, although, this has not reached statistical significance (Ia).[29]

Contraindications reported include allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding and clinically active hepatic disease (Ib).[29]

Relative risk of MI reported by the ETDRS group, in which roughly 48% of men and women with diabetes had a history of CVD, was lowered significantly in the first 5 years in those randomised to aspirin therapy (Ib).[199]

In the management of people with diabetes and new or established vascular disease, the SIGN guidelines refer to a meta-analysis of platelet inhibitor therapy demonstrating a 31% reduction in non-fatal reinfarction, a 42% reduction in non-fatal stroke and a 13% reduction in arterial mortality (Ia).[639]

One meta-analysis of 6 randomised, double-blind, placebo-controlled trials showed a significant pooled reduction in mortality following treatment with platelet glycoprotein inhibitors.[598] The most marked benefit was seen in patients undergoing percutaneous coronary intervention. A significant reduction in composite death or MI at 30 days was also seen following treatment in people with diabetes. However, potential methodological limitations of the trials included would not permit this analysis to be used as an evidence base to inform recommendations in this area (Ia).

Also reported in the SIGN guideline is a substudy analysis of a large RCT demonstrating that the addition of clopidogrel to aspirin over 3 to 12 months reduces the risk of fatal or non-fatal MI or stroke by 20% in patients with a past history of coronary heart disease presenting with acute coronary syndromes (without electrocardiographic ST elevation).[639]This risk reduction was however associated with an additional risk of bleeding (Ia).

The ADA guidelines also report from the CAPRIE study which showed that clopidogrel was slightly more effective than aspirin in reducing the combined risk of stroke, MI or vascular death in people with and without diabetes (effect sizes not stated) (Ia).[29]

**Management of arterial disease [2004]**

One RCT reviewed in the ADA guideline showed that thrombolytic therapy reduced mortality after acute MI in subjects with diabetes by ≤42% with no increase in risk of bleeding or stroke, and should not be withheld due to concern about retinal haemorrhage in patients with retinopathy.[29] This study also demonstrated that the indications and contraindications for thrombolysis in patients with diabetes are the same as those without (Ia).

The SIGN guideline reports on the results of the beta-blocker adrenergic pooling project study, which demonstrated that diabetes is not a contraindication to the use of beta-blockers, and that these reduce mortality, sudden cardiac death and reinfarction when given after acute MI[639] The guideline also cites the 1995 Collaborative Group on ACE inhibitor trials meta-analysis of nearly 100,000 patients which showed that receiving therapy with an ACE inhibitor within 36 hours of acute MI for ≥4 weeks, reduced mortality post MI. The majority of benefits occurred within the first few days when mortality was highest, benefiting patients at a higher risk to a greater absolute extent (Ia).

Three large trials (AIRE, SAVE and TRACE studies) also reviewed within the SIGN guideline have shown consistent reductions in mortality when ACE inhibitor therapy is given to people after acute MI with clinical evidence of heart failure or a reduced ejection fraction[639] A fourth study (SOLVD) demonstrated an absolute risk reduction for mortality of 4.5% in patients with diabetes and chronic heart failure given an ACE inhibitor compared with placebo over a mean follow-up of 4.5 years (Ia).

A predefined subgroup analysis of 3577 people over 55 years with diabetes (the majority of whom had type 2 diabetes) in the large multinational HOPE RCT 191 showed the effect of ramipril on arterial outcomes in people with diabetes. The rate of the combined primary outcome of MI, stroke or arterial death was significantly lower in the ramipril groups than in those receiving placebo; total mortality was reduced by 24%. Adjustment for changes in systolic and diastolic blood pressures did not change the magnitude of the effect (Ib).

Other results from the HOPE study in which patients aged over 55 years, with and without diabetes, who were randomised to receive 400 IU vitamin E for an average follow-up of 4.5 years, showed no effect of antioxidant over placebo.[761] Primary outcomes of MI, stroke or arterial death, or secondary outcomes of hospitalisations for angina or heart failure, were similar following treatment with vitamin E and placebo. No differences were observed in the frequency of outcomes in people with diabetes in the two treatment groups (Ib).

**Management of acute stroke [2004]**

SIGN guidelines state that the clinical presentation of stroke in people with diabetes is similar to that in people without diabetes.[639] There is little evidence specific to people with diabetes let alone specific to type 1 diabetes, suggesting that the management of stroke should be similar to that in people without diabetes.

### 14.3.3   Health economic evidence [2004]

Whilst economic analyses have been conducted on trials of lipid-lowering agents, no evaluation has specifically considered Type 1 diabetes. Three papers were identified within the health economic literature dealing with mixed diabetic populations.[267,268,360] An economic analysis of simvastatin using the 4S trial data suggests that it would provide cost-effective mortality reduction in the UK amongst a similar population.[360] A second cost-effectiveness paper351 also suggests that the simvastatin may be cost-effective in the UK for those aged 40 to 70 years with elevated cholesterol even if they have not been diagnosed with arterial disease. A third paper based outside the UK suggests that the benefits of simvastatin to diabetics with elevated lipid levels and arterial disease outweigh the benefit to those with elevated lipid levels and no prior arterial disease.[267]

As the GDG has no confidence in any existing risk table, engine or equation when applied to those with Type 1 diabetes, the degree to which models that make use of such equations can be relied upon is extremely limited.

### 14.3.4   Consideration [2004]

The data on arterial risk management in people with type 1 diabetes are few, though it is noted that studies in people with and without type 2 diabetes point to clinically effective interventions for those groups. In the absence of quantitative risk assessment and noting the economic evidence placed before the group it seemed clear that interventions in people with type 1 diabetes must be recommended considering their semi-quantitative CVD risk: high, moderate or no risk.

Given the high arterial risk of many people with type 1 diabetes, smoking was considered to be particularly disadvantageous.

### 14.3.5   Recommendations [2004]

These recommendations assume that arterial risk has been assessed according to the recommendations in section 14.1.5. Blood glucose control, blood pressure control and education programmes are considered elsewhere in this guideline (see sections 8, 14.4 and 7.2, respectively).

116. **For guidance on the primary prevention of cardiovascular disease in adults with type 1 diabetes, see recommendations 1.3.23 to 1.3.25 in the NICE guideline on lipid modification. [new 2015]**

117. **Give adults with type 1 diabetes who smoke advice on smoking cessation and use of smoking cessation services, including NICE guidance-recommended therapies. Reinforce these messages**

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annually for people who currently do not plan to stop smoking, and at all clinical contacts if there is a prospect of the person stopping. **[2004]**

118. **Advise young adult non-smokers never to start smoking. [2004]**

119. **Provide intensive management for adults who have had myocardial infarction or stroke, according to relevant non-diabetes guidelines. In the presence of angina or other ischaemic heart disease, beta-adrenergic blockers should be considered. (For use of insulin in these circumstances, see Section 15). For guidance on secondary prevention of myocardial infarction, see the NICE guideline on MI – secondary prevention. [2004, amended 2015]**

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## 14.4   Blood pressure [2004]

### 14.4.1    Rationale [2004]

Blood pressure is an accepted arterial risk factor. Some drugs used in blood pressure management have been suggested as having metabolic effects or interacting with insulin therapy. Accordingly, blood pressure management in people with type 1 diabetes might be different from people who do not have diabetes. However, those with developing diabetic kidney disease may have different needs again, and are considered separately.

### 14.4.2    Evidence statements [2004]

**Drug therapy**

A significant amount of research has been conducted into the treatment of hypertension in recent years. Primary endpoints for this research are the reduction of arterial and microvascular complications by the reduction of blood pressure to within target levels.

Three sets of national clinical guidelines have been published in the two years prior to 2004: Canadian,[466] American,[29] and Scottish[637] – presenting rigorous systematic reviews of evidence in this area to date.

The UKPDS RCT (in people with type 2 diabetes) showed that lowering blood pressure in people with diabetes reduces the risk of macrovascular and microvascular disease (Ib).[17]

British Hypertension Society guidelines recommend a threshold for initiating antihypertensive treatment in people with diabetes at less than 140/90 mmHg.[577] Target blood pressure for this group of people is advised at less than 140/80 mmHg unless nephropathy or proteinuria (more than 1 g per 24 hours) is present when this target is lowered to less than 130/80 mmHg and less than 127/75 mmHg, respectively. The guidelines also recommend that blood pressure reduction and ACE inhibitors can be employed to reduce the rate of decline in renal function in people with hypertension and diabetic nephropathy (IV).

British Hypertension Society guidelines suggest that treatment should essentially be the same in people with type 1 and type 2 diabetes.[577] Several studies are cited which provide evidence for the safety and efficacy of ACE inhibitors, dihydropyridine calcium channel blockers, low-dose thiazide diuretics and beta-adrenergic blockers in the treatment of hypertension in people with diabetes. The guidelines recommend that the choice among these drug classes should be determined using the criteria set out for people without diabetes (IV).

The large multicentre randomised ALLHAT trial showed no superiority of a calcium channel blocker (amlodipine) or an ACE inhibitor (lisinopril) over a thiazide diuretic (chlorthalidone) in preventing major coronary events or in increasing survival in older people both with and without type 2 diabetes.[7] This RCT of long duration found that lisinopril therapy had a 15% higher risk for stroke and a 10% higher risk of combined CVD compared with chlorthalidone in a mixed population with 36% of people with diabetes.[7] The 6-year absolute risk difference for combined CVD was 2.4%, which included a 19% higher risk of heart failure and 10% higher risk of hospitalised/fatal heart failure (not statistically significant), also a 11% higher risk for treated angina and 10% higher risk of coronary revascularisation were statistically significant outcomes. Patients assigned to amlodipine had a 38% higher risk of heart failure, a 6-year absolute risk difference of 2.5% and a 35% higher risk of fatal heart failure compared with those on chlorthalidone. Further long-term outcomes reported in this study showed that diuretic was superior to the calcium channel blocker in preventing major coronary events or increasing survival, although, their effect on overall CVD prevention was comparable. Diuretic treatment was superior to ACE inhibitor lowering of blood pressure and in preventing aggregate arterial events (mainly stroke, heart failure, angina and coronary revascularisation) in both people with and without type 2 diabetes (Ib).

Two meta-analyses of RCTs cited in the Scottish guidelines, demonstrated that thiazides, beta-blockers, ACE inhibitors and calcium channel blockers are all effective in lowering blood pressure and reducing the risk of arterial events (Ia).[637]

A large RCT of the use of an angiotensin II receptor antagonist compared with a beta-adrenergic blocker in people with diabetes (predominantly type 2 diabetes) found that the angiotensin II receptor antagonist significantly reduced the risk of arterial mortality or stroke, and MI over four or more years of follow-up (Ia).

RCTs reported within the SIGN guidelines state that combination therapy is often required to reach target blood pressure, either with the same class of drug, or in combination with another type of drug.[637] The superiority of one combination regimen over another has not been examined or documented in type 1 diabetes (Ia).

Several trials report the benefit of ACE inhibitors in producing highly significant and clinically important reductions in endpoints of MI, stroke and arterial death.

Multiple trials and systematic reviews have consistently demonstrated substantial benefits from ACE inhibitors in people with type 1 diabetes, with hypertension and diabetic nephropathy.[29,466,635,638] In diabetic nephropathy, these antihypertensives reduce progression from micro- to macroalbuminuria and to end-stage renal disease compared with placebo as reported in a well-developed systematic review (Ia).[466]

Two sets of SIGN guidelines recommend ACE inhibitors as first-line therapy in patients with microalbuminuria due to their additional benefit on renal function, based on a review of RCT-based evidence (Ia).[637,638]

Adverse effects of ACE inhibitors described in clinical trials and found to be problematic in clinical use include a persistent cough (IV).

The ADA technical review[29] and one RCT in the Canadian guidelines[466] suggest that if ACE inhibitors are prescribed, serum creatinine and potassium levels should be measured at baseline and 1 to 2 weeks after initiation (Ia).

The UKPDS showed apparent equivalence of beta-blockers (atenolol) with ACE inhibitors (captopril) to moderate blood pressure in people with diabetic nephropathy; this study was in people with type 2 diabetes and had insufficient power to show any change of clinical significance (Ia).[639]

Three randomised studies have shown similar reductions in proteinuria in diabetic antihypertensive patients with beta-blockers and ACE inhibitors as reported in a systematic review (Ia).[29]

Concern around the blunting of recovery from hypoglycaemia by beta-blockers was not confirmed in a large randomised study on people with type 2 diabetes, but caution is urged when prescribing to insulin-treated people with a history of severe hypoglycaemia (Ia).[29]

There is no robust evidence to recommend the use of alpha-blockers as first-line treatment in antihypertensive therapy. One ongoing multicentre trial is reported in a systematic review as having discontinued the alpha-blocker arm of the study due to increased incidence of arterial events in this treatment group (Ia).[29]

A recent meta-analysis suggests that dihydropyridine calcium channel blockers may be equivalent in protecting against stroke, but less effective in reducing MI and coronary events than ACE inhibitors, beta-blockers or diuretics (Ia).[29]

One randomised study found no difference between dihydropyridine calcium channel blockers and other antihypertensive drugs with respect to diabetic nephropathy.[212] In addition, the American guidelines urge caution as it is difficult to compare trials studying different calcium channel blockers due to their diverse pharmacological effects (Ia).[29]

Evidence for the use of thiazide diuretics is not as robust as for other antihypertensive therapies.[466] Treatment has been associated with hypokalaemia, hyponatraemia, volume depletion, hypercalcaemia and hyperuricaemia. Two retrospective studies reported in the American guidelines suggested increased arterial mortality, and other studies have shown that thiazides may not be as effective in subjects with significantly decreased renal function (IV).[29]

**Target blood pressure**

Two large multicentre trials included in a systematic review showed an improvement in arterial and microvascular outcome in patients randomised to lower target blood pressures compared with those with less intensive blood pressure lowering.[466] Evidence supports a treatment goal of a diastolic blood pressure of less than 80 mmHg (Ia).

No evidence exists on the appropriate target systolic blood pressure for people with type 1 diabetes. Consensus recommendations from the Canadian Hypertension Recommendations working group is that systolic blood pressure should be less than 130 mmHg (IV).[466]

The SIGN hypertension guidelines note that RCTs use target blood pressures of less than 130/80 mmHg in major outcome trials or 125/75 mmHg when proteinuria of more than 1 g per 24 hours is present (IV).[637]

**Behavioural therapy**

A rigorous systematic review performed in the production of the American Diabetes Association guidelines on the treatment of hypertension in diabetes reported one meta-analysis of RCTs showing that dietary management with moderate sodium restriction has been effective in reducing blood pressure in individuals with essential hypertension.[29] However, this has not been tested in a diabetic population. No evidence exists for the significant benefit of magnesium supplementation or calcium supplementation in people with diabetes (Ia).

Weight reduction has also been shown in a systematic review of non-RCTs to reduce blood pressure independently of sodium intake and to improve glucose and lipid levels (IIa).[29]

Smoking cessation, moderation of alcohol intake and mild physical activity have been recommended by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure to reduce blood pressure (IV).[29]

The American Diabetes Association guidelines recommend that patients with a systolic blood pressure of 130–139 mmHg or diastolic blood pressure of 80–89 mmHg should be given lifestyle or behavioural therapy as first-line treatment for a maximum of 3 months, based on evidence from large-scale RCTs (Ia).[29]

### 14.4.3   Health economic evidence [2004]

The health economic literature on type 1 diabetes does not assess the cost-effectiveness of ACE inhibitors in lowering blood pressure in isolation. The effect of ACE inhibitors in lowering blood pressure is linked in these studies to its effects in delaying kidney damage, and the GDG felt that no recommendations in regard of blood pressure lowering alone could be drawn from the existing evidence.

### 14.4.4   Consideration [2004]

The finding of raised blood pressure in people with diabetes is felt to be of different significance in the presence of nephropathy, if features of the metabolic syndrome are present, or in the absence of these findings. Other risk factors (age, ethnic group, family history and smoking) will be relevant in the last group, in whom it was felt management should echo that of non-diabetic people of the same age, but regarding the diabetes as a further substantial risk factor (formal risk calculation was considered above under CVD surveillance, and is not recommended). The combination of raised blood pressure and nephropathy, or features of the metabolic syndrome is, however, known to be very high risk indeed for premature CVD in early middle age. Accordingly, intervention levels and targets should be lower and more strictly applied than for the person with 'simple' hypertension. Very many suggestions for intervention levels based on evidence have been put forward by other groups, with (allowing for the gradual evolution of evidence) considerable coherence. The group assessed all the available recommendations in this area and reached a consensus based on small differences between these.

The problems of motivating professionals and people with diabetes to manage blood pressure appropriately, despite the clear arterial and macrovascular protection to be gained, were noted to be multifactorial. Accordingly, recommendations emphasising intervention levels, targeting, informed discussions and patient-held record cards were discussed. The problem of potential and minor side effects inhibiting the achievement of major clinical gains was felt to be worth mentioning. It was noted that lifestyle interventions have a role in blood pressure management (considered in more detail in other parts of this guideline).

### 14.4.5   Recommendations [2004]

120. **Intervention levels for recommending blood pressure management should be 135/85 mmHg unless the adult with type 1 diabetes has albuminuria or 2 or more features of the metabolic syndrome, in which case it should be 130/80 mmHg. See also recommendations 164-166 in Chapter 16.6. [2004]**

121. **To allow informed choice by the person with hypertension, discuss the following with them:**
   - **reasons for choice of intervention level**
   - **substantial potential gains from small improvements in blood pressure control**
   - **possible negative consequences of therapy.**

See also recommendations 164-165 in Section 16.5.36 [2004, amended 2015]

122. **Start a trial of a renin-angiotensin system blocking drug as first-line therapy for hypertension in adults with type 1 diabetes.** [2004, amended 2015]

123. Provide information to adults with type 1 diabetes on the potential for lifestyle changes to improve blood pressure control and associated outcomes, and offer assistance in achieving their aims in this area. [2004]

124. **Do not allow** concerns over potential side effects to inhibit advising and offering the necessary use of any class of drugs, unless the side effects become symptomatic or otherwise clinically significant. In particular:

   - **do not avoid** selective beta-adrenergic blockers **where indicated** in adults on insulin
   - low-dose thiazides may be combined with beta-blockers
   - when calcium channel antagonists are prescribed, use only long-acting preparations
   - use direct questioning to detect the potential side effects of erectile dysfunction, lethargy and orthostatic hypotension with different drug classes. [2004, amended 2015]

125. For guidance on blood pressure management in adults with type 1 diabetes and evidence of renal involvement, see recommendations 1.6.2-1.6.4 in the NICE guideline on **Chronic kidney disease** [new 2015]

# 15 Inpatient management

The 2015 GDG updated inpatient management in relation to insulin replacement (intravenous regimens and dose-adjustment devices). Other aspects of inpatient management were not updated and the content from CG15 is included.

## 15.1 Introduction [2015]

Diabetes control in hospital is complicated by the stress of the primary condition, the relative immobility of the bed-bound patient, and the change in usual food intake and daily routine. Usual insulin regimens are designed around mealtime insulin requirements, superimposed on a background insulin replacement to control endogenous glucose production – both these hyperglycaemic processes are altered during hospitalisation. The management of type 1 diabetes during hospitalisation aims to maintain near-normoglycaemia, despite these often unpredictable factors. Hyperglycaemia should be avoided, as it is associated with abnormalities of fluid and electrolyte balance, increased risk of infection and poorer outcomes. Hypoglycaemia should also be prevented as it can be associated with impaired brain function and cardiac arrhythmias. However the degree of glucose control associated with best outcome (that is, the target glucose ranges) and the regimens for achieving them remain controversial.

Protocol-driven management of glucose during hospitalisation is associated with better control and improved outcomes, such as shorter ICU stay[61], with evidence to support the ability of intravenous infusion regimens to improve glucose control and important outcomes after major surgery.[232] Some studies in critical care show better outcomes when blood glucose control is kept near-normal, between 4.4 and 6.1 mmol/litre with intravenous insulin regimens[238,711,726], but the benefits may be outweighed by a high risk of hypoglycaemia unless very well managed.[237,572]

The pharmacodynamics of intravenous insulin, with its rapid onset and offset of action, allows it to be adaptable to the changing physiology of the sick patient, titrated easily, and without a dosage threshold (8). Furthermore, insulin has minimal side effects except for hypoglycaemia.

Intravenous insulin regimens are reactive however (that is, the insulin infusion rate is adjusted after the glucose has moved away from target) and for all non-critically ill patients, who are eating, a basal/bolus insulin regimen is the preferred method of glycaemic control with appropriate corrective doses. Care must be taken to accommodate the unpredictable eating and diagnostic testing schedules that in-patients may face, which make the patient more susceptible to hypoglycaemia or hyperglycaemia.

An appropriate target range should be established for each patient group.

There are many protocols and guidelines governing in-patient insulin management, which include common themes such as the use of soluble insulin for continuous insulin infusion, titration of insulin dose against blood glucose and stepping down to normal therapy (for example, the NHS Diabetes and Joint British Diabetes Societies Inpatient Care Group guidance[170]).

Continuous infusion of soluble insulin is suggested for critically ill ICU patients, pre- and postoperative patients, peripartum women with hyperglycaemia, severe hyperglycaemia with metabolic decompensation (diabetic ketoacidosis and hyperosmolar non-ketotic states), and any patient in whom tight glycaemic control is clinically indicated. Paper-based and increasingly computer-based insulin infusion algorithms, some of which can be automated, are available to help clinicians achieve optimal glycaemic control.

Conversion from IV to SC insulin commonly occurs when the critical illness resolves and the patient is ready to begin eating or is in a stable condition with enteral nutrition.

Update 2015

**This chapter addresses this question:**

- In adults with type 1 diabetes who have been admitted to hospital (elective and emergency), what are the most effective intravenous insulin dose-adjustment devices and regimens for optimal diabetic control?

### 15.1.1 Review question: In adults with type 1 diabetes who have been admitted to hospital (elective and emergency), what are the most effective intravenous insulin dose-adjustment devices and regimens for optimal diabetic control?

For full details see review protocol in Appendix C.

**Table 158: PICO characteristics of review question**

| Population | Adults admitted to hospital with type 1 diabetes (this covers type 1a diabetes and type 1b diabetes) |
|---|---|
| | • Adult is defined as aged ≥18 years |
| | • Type 1 diabetes is defined (WHO definition and NICE 2004 GL) as: |
| Intervention/s | • IV insulin |
| | Note: only UK licensed interventions and doses will be considered |
| Comparison/s | • Subcutaneous insulin |
| | • Each other (different regimens) |
| | • Each other (different devices) |
| | • No comparison |
| | Note: only UK licensed interventions and doses will be considered |
| Outcomes | Outcomes |
| | • Achieving target BG levels (may be measured differently in studies) |
| | • Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported) |
| | • Time spent out of target glucose (Hypoglycaemia/Hyperglycaemia) |
| | • Duration of IV treatment |
| | • In-patient stay |
| | • In-patient mortality |
| | • Infection rate/wound healing |
| | • Quality of life – measured by SF-36, DQoL, DSQoL (continuous) |
| Study design | RCTs, observational studies |
| | • Unit of randomisation: individual patient |

### 15.1.2 Clinical evidence

Six studies were included in the review [120,134,336,469,568,727]. Evidence from these are summarised in Table 159 and Table 160, and in the clinical evidence profiles below in Table 161, Table 162 and Table 163. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix I and exclusion list in Appendix K.

Five studies reported data on IV insulin regimes during surgery. One study was an RCT comparing IV insulin versus SC insulin during surgery[120]. Data were reported for the following outcomes: achieving blood glucose targets; mild hypoglycaemia; duration of inpatient stay. One retrospective cohort study was identified comparing IV insulin, CSII continuation and CSII suspension during surgery[134]. Data were reported for the following outcomes: achieving blood glucose targets; severe

hypoglycaemia. The remaining three studies were case-series and the results are summarised in Table 159.

One study[727] reported data on IV insulin for inpatients with DKA, and this study was a case-series.

All the non-comparative observational studies (case-series), were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. Study details and the full results have been summarised narratively.

No data were reported on the following outcomes:

- Time spent out of target glucose (hypoglycaemia/hyperglycaemia)
- Duration of intravenous (IV) treatment
- In-patient mortality
- Quality of life

**Table 159: Summary of studies included in the review: Surgery**

| Study | Intervention | Comparison | Population | Outcomes |
|-------|-------------|------------|------------|----------|
| **RCTs** | | | | |
| CHRISTIANSEN 1988<br><br>RCT | IV infusion of glucose, insulin and potassium (GIK) for 24 hours | Pre-op SC insulin (Concomitant glucose infusion for 24 hours) | n=20<br>Adults<br>Insulin-dependent diabetics admitted for minor surgery<br><br>Follow-up = 3 days (op day and 2 days post-op) | IV GIK was better than SC insulin for:<br>Achieving target BG levels (5-10 mmol/litre) during 3 days (reported as % BG values within target range; 48% versus 26%, reported as p<0.01)<br>Achieving target BG levels (5-10 mmol/litre) during infusion period (reported as % BG values within target range; 67% versus 28%, reported as p<0.0001)<br>SC insulin was better than IV GIK for:<br>Hypoglycaemia, no. of patients with ≥1 BG level <5 mmol/litre (6/10 versus 4/10)<br><br>No difference between groups for:<br>Inpatient stay, median (range) 5(1-10) versus 5 (2-7) |
| **Observational Studies** | | | | |
| CORNEY 2012<br><br>Retrospective cohort | IV infusion n=20 (convert from SCII to IV infusion pre-op) | 1. CSII n=53 (continue CSII with supplemental SC or IV insulin if required)<br>2. Suspend CSII n=19 (with or without SC or IV insulin boluses) | n=99 cases (75 unique individuals<br>• Adults 85-90% type 1 diabetes<br>• Elective surgery CSII<br><br>Follow-up = inpatient | IV and CSII continuation was better than CSII suspension for:<br>% with intra-op target BG, % intra-op hypoglycaemia and % intra-op hyperglycaemia only reported graphically (no data). Comparison reported as P=0.034.<br><br>No difference between groups for:<br>Severe hypoglycaemia (intra-op BG <40 mg/dl or loss of consciousness): 0/20 versus 0/53 versus 0/19<br>QUALITY rating = LOW (see GRADE |

| Study | Intervention | Comparison | Population | Outcomes |
|---|---|---|---|---|
| | | | stay | tables in Appendix I) |
| HUSBAND 1986<br><br>Prospective case-series | IV infusion of GIK | None | n=128 (n=41 IDDM)<br>• Mainly adults<br>• Elective surgery<br><br>Follow-up = 3 days (op day and 2 days post-op) | Achieving target blood glucose levels (pre-op: 5-10 mmol/litre): 26/41<br>Achieving target blood glucose levels (op day: 5-12 mmol/litre with no hypoglycaemia <3 mmol/litre): 31/41<br>Mean BG values, mmol/litre: Pre-op: 8.2 (3.0); Post-op: 9.6 (3.4); op day: 8.9 (2.3); post-op day 1: 9.4 (1.9); post-op day 2: 10.2 (2.8)<br>Hypoglycaemia on op-day, no. of patients with BG level <5 mmol/litre: 4/41<br>Hyperglycaemia on op-day, no. of patients with BG level >12 mmol/litre: 6/41<br><br>VERY LOW QUALITY[a] |
| MCCAVERT 2010<br><br>Prospective case-series | IV infusion of GIK | None | n=69 (n=35 type 1 diabetes)<br>• Elective (n=21) or emergency (n=14) surgery<br><br>Follow-up = 3 days (op day and 2 days post-op) | Achieving target blood glucose levels (6.1-10 mmol/litre), mean % of patients over 3 days: elective 25.9%; emergency 22.7%<br>No hypoglycaemic episodes were reported<br>Wound infection: elective 2/21; emergency 1/14<br>Peritonitis: elective 1/21; emergency 0/14<br>Septicaemia: elective 0/21; emergency 2/14<br><br>VERY LOW QUALITY[a] |
| POPPE 2004<br><br>Retrospective case-series | Perioperative IV insulin protocol | None | n=50 type 1 diabetes (n=12, subgroup data only for the following outcomes)<br>• Surgical procedure as inpatient<br><br>Follow-up = first 24 hours of infusion | % of levels in the hyperglycaemic range (>12mmol/litre): 49.7%<br>Mean BG level: 12.1 (1.1) mmol/litre<br><br>VERY LOW QUALITY[a] |

(a) Data is from case-series, mostly of retrospective design. The quality has been rated as Very low because these study designs are associated with a high risk of bias.

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**Table 160: Summary of studies included in the review: Inpatients with DKA**

| Study | Intervention | Comparison | Population | Outcomes |
|---|---|---|---|---|
| WAGNER 1999<br><br>Prospective case-series | IV insulin infusion 'Very low-dose insulin application' | None | n=65<br>Adults and young people with type 1 diabetes<br>Severe ketoacidosis, admitted to ICU | Achieving target blood glucose levels - reported as mean (range) BG mg/dl at each time point:<br>admission 606(86-1191); after 1 hour 468(96-1075); after 4hr 376(66-1003); after 8 hours 283(107-738); after 12 hours 251(89-614)<br><br>VERY LOW QUALITY[a] |

(a) Data is from case-series. The quality has been rated as Very low because this study design is associated with a high risk of bias.

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**Table 161: Clinical evidence summary: IV insulin versus SC insulin during surgery**

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate ( per 1000) | Control event rate for continuous outcomes |
|---------|-------------------|-------------|--------------|---------------------|--------------------------------|-------------------------------------------|
| Mild hypoglycaemia | 1 (n=20) | Very serious | VERY LOW | 200 more per 1000 (from 160 fewer to 1000 more) | 400 per 1000 | n/a |
| Duration of inpatient stay | 1 (n=20) | Very serious | VERY LOW | Median 0 higher | n/a | Median 5 days |

**Table 162: Clinical evidence summary: IV insulin versus continuation of CSII (with supplemental SC or IV insulin if required) during surgery**

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate ( per 1000) | Control event rate for continuous outcomes |
|---------|-------------------|-------------|--------------|---------------------|--------------------------------|-------------------------------------------|
| Severe intra-op hypoglycaemia | 1 (n=73) | none | LOW | 0 more per 1000 | 0 per 1000 | n/a |

**Table 163: Clinical evidence summary: IV insulin versus suspension of CSII (with or without IV or SC insulin bolus) during surgery**

| Outcome | Number of studies | Imprecision | GRADE rating | Absolute difference | Control event rate ( per 1000) | Control event rate for continuous outcomes |
|---------|-------------------|-------------|--------------|---------------------|--------------------------------|-------------------------------------------|
| Severe intra-op hypoglycaemia | 1 (39) | none | LOW | 0 more per 1000 | 0 per 1000 | n/a |

### 15.1.3 Economic evidence [2015]

**Published literature**

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix E.

**Unit costs**

Unit costs of different insulin preparations that can be delivered intravenously or subcutaneously are reported in Appendix Q to aid consideration of cost-effectiveness.

### 15.1.4 Evidence statements [2015]

**Clinical**

**IV insulin versus SC insulin during surgery**

Very low quality evidence from one RCT (n=20) showed no clinical benefit of iv insulin for:

- Mild hypoglycaemia
- Duration of inpatient stay

In the case of mild hypoglycaemia, the direction of the estimate of effect favoured SC insulin, and for inpatient stay, both groups had the same median duration.

Very low quality evidence from one RCT (n=20) showed benefit[n] of iv insulin for:

- percentage of BG values within target range during all 3 days and during infusion period.

**IV insulin during surgery versus continuation of CSII (with supplemental SC or IV insulin if required) during surgery**

Low quality evidence from one cohort study (n=73) showed no clinical difference between IV insulin for:

- Severe intra-operative hypoglycaemia

The direction of the estimate of effect did not favour either group as there were zero events in each arm.

Low quality evidence from one cohort study (n=73) showed no difference[n] between IV insulin and CSII for:

- Percentage of patients achieving the intra-operative target BG
- Percentage of patients with intra-operative hypoglycaemia
- Percentage of patients with intra-operative hyperglycaemia

**IV insulin versus suspension of CSII (with or without IV or SC insulin bolus) during surgery**

Low quality evidence from one cohort study (n=39) showed no clinical difference between IV insulin for:

- Severe intra-operative hypoglycaemia

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n   Data required for calculating clinical difference or direction of effect was not reported, so this is based on statistical difference.

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The direction of the estimate of effect did not favour either group as there were zero events in each arm.

**IV infusion**

Low quality evidence from three case series' showed that for IV infusion:

- Most patients (more than 60%) achieved target blood glucose levels preoperatively and on operation day (one study, n=128).
- Approximately 20% of patients achieved target blood glucose levels over 3 days (one study, n=69)
- Very few (approximately 10%) patients had hypoglycaemia on operation day (one study, n=128).
- Very few (approximately 15%) patients had hypoglycaemia on operation day (one study, n=128).
- There were no hypoglycaemic events (one study, n=69)
- There was a low incidence of infection (one study, n=69)
- Most patients (approximately 50%) had blood glucose levels within the hyperglycaemic range (one study, n=50).

**Inpatients with DKA**

Very low quality evidence from one study (n=65) showed that mean blood glucose levels decreased over time with IV insulin infusion.

**Economic**

No relevant economic evaluations were identified.

### 15.1.5    Recommendations and link to evidence

| Recommendations | 126. Aim for a target plasma glucose level of 5-8 mmol/litre for adults with type 1 diabetes during surgery or acute illness. [new 2015]<br><br>127. Establish a local protocol for controlling blood glucose levels in adults with type 1 diabetes during surgery or acute illness to achieve the target level. [new 2015]<br><br>128. Use intravenous in preference to subcutaneous insulin regimens for adults with type 1 diabetes:<br><br>    • if the person is unable to eat or is predicted to miss more than 1 meal or<br><br>    • if an acute situation is expected to result in unpredictable blood glucose levels - for example, major surgery, high-dose steroid treatment, inotrope treatment or sepsis or<br><br>    • if insulin absorption is expected to be unpredictable, for example because of circulatory compromise. [new 2015]<br><br>129. Consider continuing the person's existing basal insulin regimen (including basal rate if they are using continuous subcutaneous insulin infusion [CSII or insulin pump] therapy) together with protocol-driven insulin delivery for controlling blood glucose levels in adults with type 1 |
|---|---|

*Update 2015*

**diabetes during surgery or acute illness. [new 2015]**

130. **Use subcutaneous insulin regimens (including rapid-acting insulin before meals) if an adult with type 1 diabetes and acute illness is eating. [new 2015]**

131. **Enable adults with type 1 diabetes who are hospital inpatients to self-administer subcutaneous insulin if they are willing and able and it is safe to do so. [new 2015]**

| | |
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| Relative values of different outcomes | In order to establish the best means of treating a person with type 1 diabetes when admitted to hospital with a medical or surgical emergency, or for a non-urgent surgical procedure, the GDG sought evidence with the following critical outcomes:<br><br>• Maintenance of stable plasma glucose levels within an acceptable range. Closely linked to this is the question of what is the best blood glucose target range. There is evidence from a number of emergency situations, including common conditions such as acute coronary syndromes and COPD exacerbations, that those with elevated blood glucose have worse clinical outcomes<br>• Mortality. No papers covering this important outcome were found<br>• Hypoglycaemia and severe hypoglycaemia (requiring help from 3rd party for correction)<br><br>In addition the GDG agreed to look at data on:<br>• Quality of life<br>• Infection rates<br>• Duration of intravenous treatment (IV lines are a risk factor for hospital-acquired infection)<br>• Length of hospital stay |
| Trade-off between clinical benefits and harms | There are essentially three ways of controlling plasma glucose levels when a person is too unwell to manage this with their usual regimen. The first is to administer short-acting subcutaneous (s/c) insulin in variable amounts, depending on the current plasma glucose concentration. Basal insulin may be continued. Any necessary intravenous fluids are given separately. The second and third are to use intravenous insulin infusion either as:<br><br>• A variable rate intravenous insulin infusion (VRIII), commonly referred to as a "sliding scale", in which an insulin infusion is adjusted regularly on the basis of frequent bedside plasma glucose measurements with intravenous glucose, potassium and other fluids given separately,<br>• Addition of short-acting insulin to a bag of glucose solution administered intravenously at a constant rate. Potassium is usually also added, and the amount of both this and the insulin in any bag can be varied, the latter according to frequent bedside plasma glucose measurements. This is often referred to as a GKI infusion. Both intravenous methods are in use around the UK.<br><br>Only one RCT comparing these two methods was found (Christiansen et al.). This showed better control of blood glucose levels using GKI. There was no difference in the hypoglycaemia incidence, or in length of stay in hospital.<br><br>The 5 other papers considered were case-series, but only 3 of these allowed comparison of sliding scales with GKI. There were no significant differences between the 2 methods in either blood glucose control or hypoglycaemia. One study reported |

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| | infection rates, but in this study some of the patients received VRIII in error, and the GDG did not feel that any value could be placed on the reported difference in infection.<br><br>Rather than always using VRIII or GKI, some anaesthetists do not give any insulin at onset of surgery but monitor blood glucose and start treatment if this rises. One study (Corney et al.) included an arm in which this approach was evaluated. Blood glucose control in this arm of the study was poorer than with either VRIII or GKI. |
| Economic considerations | No health economic evaluations were identified and therefore unit costs were considered.<br><br>The GDG also considered whether there were any differences in cost related to the need for monitoring blood glucose with the two regimens. However, this consideration would not affect many of these patients since those requiring major surgery, and some of the medical emergencies, would require HDU or ICU monitoring anyway. The GDG concluded that the cost effectiveness of different strategies was driven by other considerations such as convenience and safety. |
| Quality of evidence | Overall the quality of evidence was considered Very low. The only RCT was small, and the GDG felt that the dose of insulin used in the VRIII arm of the study was too low.<br>The case series were also relatively small, with low event rates. In addition, one of those which allowed comparison between the 2 regimens was a retrospective series (Poppe 2004).<br><br>There is also an issue with the age of some of the studies since the insulins used in these have been superseded, and the results may not be applicable to present-day practice.<br><br>No studies were found covering acute medical emergencies, and any conclusions for that situation were necessarily based on extrapolation from the studies of elective surgery, plus GDG experience and consensus. |
| Other considerations | The GDG were concerned about the lack of data and considered whether there was any useful information to be obtained from papers in mixed population of type 1 and type 2 diabetes, many of which are in the list of excluded studies. Clearly less importance could be attached to these but the GDG noted:<br>• Abelev 2011 showed shorter length of hospital stay with GKI versus subcutaneous insulin<br>• Furnary 2006 in the USA looked at mortality rates for cardiac surgery when a switch from s/c insulin to intravenous was made, and showed a marked decrease.<br>• However, the GDG were unsure how well intravenous regimens had been used in the Furnary study, and noted the paper by Golightly (2006) which demonstrated how poorly these were implemented in many instances<br>• Gan (2009) also considered patients undergoing cardiac surgery and showed that arrhythmia incidence increased once the blood glucose level was >8 mmol/litre.<br>• Simmons (1994) showed higher rates of adverse events with GKI than s/c insulin<br><br>Some GDG members reported that use of GKI was not permitted in their hospital because of safety concerns around injecting insulin into bags of fluid. |

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The GDG also noted the NICE clinical guideline 130[511] which considered the management of hyperglycaemia in the context of acute coronary syndromes. The TA concluded that the blood glucose should be maintained below 11 mmol/litre during the acute illness. Of note, the TA was not confined to type 1 diabetes, but rather looked at management of all people with an elevated blood glucose irrespective of any diagnosis of diabetes.

The GDG were in agreement that if people with diabetes are eating reasonably normally then their usual insulin regimen is the best way of controlling diabetes during an admission, and this should be possible for lesser surgical procedures or less severe medical emergencies. They also agreed that if a person is able to administer their own usual insulin, and are willing to do this, then this is the safest way of managing insulin during an admission. In more severe circumstances the GDG did not feel that there was sufficient evidence to recommend GKI over the VRIII, or vice-versa. They concluded that it was more important that hospitals have a clear protocol in place, using one or the other of these methods, but that stopping insulin in type 1 diabetes and waiting to see if the plasma glucose rises is not acceptable. They also agreed that there were some circumstances in which intravenous insulin would be preferred to the s/c route.

Regarding optimal plasma glucose levels, the GDG could not find any reason why control should be less tight during an intercurrent illness or surgical procedure than at other times. They also noted the (extrapolated) evidence from cardiac surgery regarding adverse effects of a plasma glucose >8 mmol/litre. They therefore agree to recommend a target range of 5-8 mmol/litre.

The GDG were aware of a National Patient Safety Agency alert [514] encouraging empowerment of patients to self-administer insulin if willing and able to, and this informed recommendation 126.

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### 15.1.6   Research recommendations

**31. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of optimal blood glucose control, patient-reported outcomes and experience, length of stay, and short-term complications) of closed loop insulin delivery systems and automated insulin dose advisors during in-hospital care, and could the development of new systems and technologies improve on current clinical outcomes?**

## 15.2   Inpatient management [2004]

### 15.2.1   Rationale [2004]

People with Type 1 diabetes often find that time in hospital, or other institutional care, is stressful. The delicate equilibrium they may have established with their insulin therapy can be destroyed by the change in routine, change in nutrition and the effects of illness and procedures. They find too often that the expertise they bring to their diabetes management is underused by staff with less knowledge of the condition than themselves. Special insulin regimens may be needed to cope with procedures which interfere with eating patterns, or which cause enough metabolic stress to otherwise disturb control of diabetes. In some acute situations there is evidence that special insulin management may improve the outcomes of other medical conditions.

[511]The overwhelming majority of admissions of people with diabetes are for non-diabetes related medical and surgical conditions. Indeed the problems discussed above are likely to be greater when care is outside the responsibility of the multidisciplinary diabetes team. Accordingly the evidence search and recommendations are intended to cover hospital and other institutional care across all specialties. However, some aspects of continuing self-care will self-evidently not be relevant during extreme critical illness.

The principles espoused are seen as applying, in general, to other institutional care (prisons, residential and nursing homes) as well as hospital care.

### 15.2.2    Evidence statements [2004]

**Multidisciplinary team care**

One study showed a significant reduction in length of stay in hospital following supervision by a diabetes specialist nurse.[156] Significant differences were also seen in patient satisfaction and diabetes knowledge, although not for readmission frequency, referral rates or quality of life (Ib).

A cohort study showed a significant reduction in length of stay in medical and surgery wards in patients with diabetes following the introduction of a diabetes nurse advisor (IIa).[107]

A prospective randomised study examining the impact of a specialist diabetes team on inpatient management demonstrated a significant increase in documentation of instructions for blood glucose monitoring, insulin administration, received education and nutritional consultation.[391] Patients were significantly less likely to be readmitted within three months following supervision by a specialist diabetes team (Ia).

### 15.2.3    Health economic evidence [2004]

One UK-based study suggested that the provision of a hospital-based diabetes specialist nurse lowered the cost per patient admission without producing a significant difference in readmission, quality of life or patient satisfaction.[156]

### 15.2.4    Consideration [2004]

The evidence supporting the benefit of specialist multidisciplinary team advice in giving healthcare and cost gains to inpatients outside specialist diabetes wards was felt to be conclusive. Professional and patient members of the group were sadly familiar with the failure of some wards to use the expertise of people with diabetes, and the distress this can cause when care becomes suboptimal as a result. This was noted to be particularly the case in relation to nutritional intake and insulin therapy.

### 15.2.5    Recommendations [2004]

132. **From the time of admission, the adult with type 1 diabetes and the team caring for him or her should receive, on a continuing basis, advice from a trained multidisciplinary team with expertise in diabetes. [2004]**

133. **Throughout the course of an inpatient admission, respect the personal expertise of adults with type 1 diabetes (in managing their own diabetes) and routinely integrate this into ward-based blood glucose monitoring and insulin delivery. [2004, amended 2015]**

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134. **Throughout the course of an inpatient admission, the personal knowledge and needs of adults with type 1 diabetes regarding their dietary requirements should be a major determinant of the food choices offered to them, except when illness or medical or surgical intervention significantly disturbs those requirements. [2004]**

135. **Members of care teams caring for adults with type 1 diabetes in institutions, such as nursing homes, residential homes and prisons, should follow the recommendations in this section. [2004]**

**Management during acute arterial events**

136. **Provide optimal insulin therapy, which can be achieved by the use of intravenous insulin and glucose, to all adults with type 1 diabetes with threatened or actual stroke. Critical care and emergency departments should have a protocol for such management. [2004, amended 2015]**

# 16  Management of complications

The 2015 GDG updated treatment of gastroparesis, insulin-induced neuropathy and monitoring for thyroid disease. The evidence and text from the previous guideline, CG15, that has been superseded by these updated sections is in Appendix S. Other complications were not updated; the original content from 2004 has been presented.

## 16.1  Gastroparesis [2015]

### 16.1.1  Introduction

Gastroparesis is the term used to describe delayed gastric emptying in the absence of mechanical obstruction.[554] It may occur as part of the manifestation of autonomic neuropathy in people with diabetes: dysfunction of the vagus nerve and intrinsic enteric autonomic nerves are involved in its pathogenesis. Patients can present with bloating and early satiety and, in more advanced disease, post-prandial vomiting, inability to eat, weight loss and malnutrition may occur (2). Diagnosis is usually made by studying gastric emptying for solids and liquids with scintigraphy studies, although improvements in emptying may not correlate directly with symptoms (3). Symptoms of gastroparesis may, however, be exacerbated by high blood glucose concentrations at the time of eating, as hyperglycaemia causes a physiological delay in gastric emptying even in health (4). Gaining control of the blood glucose during the investigation and treatment of autonomic neuropathic gastroparesis is therefore important, in addition to other treatments aimed at improving gastric emptying (5).

Impaired extrinsic and intrinsic innervation may occur elsewhere in the gastrointestinal tract in association with gastroparesis. Constipation is common but profuse and watery diarrhoea, typically occurring at night, and alternating with constipation, has also been described.[523]

Management of gastroparesis should include nutritional assessment and support, and attempts at symptomatic relief and optimisation of glycaemic control (6). In severe cases, the stomach may need to be bypassed with feeding via jejunostomy. Therapies to enhance gastric emptying include medications, electrical stimulation and surgery

**The GDG asked this question:**

- In adults with type 1 diabetes, what is the most effective treatment for gastroparesis?

### 16.1.2  Review question: In adults with type 1 diabetes, what is the most effective treatment for gastroparesis?

For full details see review protocol in Appendix C.

**Table 164: PICO characteristics of review question**

| Population | • Adults with type 1 diabetes and Gastroparesis |
| --- | --- |
| | • Adults with type 1 diabetes or type 2 diabetes (in the same study) and gastroparesis |
| Intervention/s | • Prokinetic agents/gastroprokinetic agents (for example, erythromycin) |
| | • 5-Hydoxytryptamine antagonists (for example, ondansetron) |
| | • Anti-emetics |
| | • Botulinum toxin |
| | • Electrical stimulation interventions |
| | • Intensive insulin treatment/glucose control |
| | • Dietary changes |
| | • Enteral feeding |

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| | • Acupuncture |
| | • Aldose reductase inhibitors (including epalrestat) |
| | • Histamine-2 receptor antagonists |
| | • Centrally acting antidepressants |
| | • Surgical interventions (including gastrectomy) |
| **Comparison/s** | • Placebo |
| | • Standard care |
| | • Each other (within class and between-class comparisons) |
| | • Continuous agent versus other agents |
| | • Rotation of medications |
| **Outcomes** | • Hospital admissions |
| | • Severe hypoglycaemia |
| | • Vomiting - including frequency |
| | • Weight loss |
| | • Quality of Life:SF-36 |
| | • HbA1c |
| | • Symptom control - as defined by the study |
| **Study design** | RCTs, prospective observational studies |

### 16.1.3    Clinical evidence

We searched for RCTs and prospective observational studies assessing the most effective treatment for Gastroparesis in adults with type 1 diabetes. Due to lack of data specifically in a type 1 diabetes population, and because gastroparesis and its treatment is not dependent upon/not affected by the type of diabetes, we extended the inclusion criteria to include studies that involved a mixed population of type 1 diabetes and type 1 diabetes, regardless of the percentage of type 1 diabetes that was present.

We also included two of the three relevant studies from the old 2004 NICE guideline on type 1 diabetes in adults, that met our inclusion criteria.[347,617]. The third study[169] was excluded as it did not report our pre-specified outcomes and had only a 3hr treatment time.

Overall, eighteen studies have been included in this review.[13,14,86,225,228,329,347,406,467,467,468,531,532,550,592,592,617,647,655,661,661,695,696,712] Evidence from these are summarised in the GRADE tables and narrative evidence statements. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

The 18 included studies consisted of fourteen RCTs[13,14,86,225,228,347,467,467,468,531,532,550,592,592,617,655,661,661] and five observational studies[329,406,647,695,696,712]. Four of the RCTs [13,86,347,468] also included observational data (the follow-up period consisted of all participants being put on the treatment arm for a period of time). One of the RCTs (Janssens 1990)[347] was only used for observational data, as the RCT part of the study consisted of only 1 day of treatment, and thus did not meet our inclusion criteria.

All non-comparative observational studies were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. Where data was not suitable for GRADE, a narrative report is given (see 16.5.1.1 and 16.5.1.2).

Outcomes reported include:

- Quality of Life
- Vomiting

- Adverse events
- Scores for upper GI symptoms
- HbA1c (%)
- Weight change

Included studies did not report on the following outcomes:

- Severe hypoglycaemia

There is National Institute for Health and Care Excellence (NICE) interventional procedure guidance (IPG103; issue date December 2004) on gastroelectrical stimulation for the treatment of gastroparesis Gastric Electrical Stimulation for Gastroparesis. This guidance was not specific to diabetic gastroparesis, and so we have only incorporated into our review any relevant references from the IPG that specifically looked at electrical stimulation in diabetic gastroparesis populations.

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**Table 165: Summary of studies included in the review**

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| **RCTs** | | | | | |
| Gastric electrical stimulation | | | | | |
| ABELL 2003[13] | GES system (implanted) System on vs. off | n=33 gastroparesis n=17 diabetes Cross-over RCT | 1 month treatment (each cross-over period) | Total symptom score Vomiting frequency | Data reported for the diabetic subgroup |
| ABELL 2011[13,14] | GES system (implanted) System on vs. off | n=58 gastroparesis n=13 diabetes Cross-over RCT | 72 hours treatment (each cross-over period) | Vomiting score | Data reported for the diabetic subgroup |
| FROKJAER 2008[228] | GES system (implanted) System on vs. off | n=7 diabetes with gastroparesis n=6 type 1 diabetes Cross-over RCT | 1 month treatment (each cross-over period) | Vomiting episodes | |
| MCCALLUM 2010B[467,468] | GES system (implanted) System on vs. off | n=45 diabetes with gastroparesis Cross-over RCT | 3 months treatment (each cross-over period) | Vomiting episodes | |
| Botox (BoNT/A) | | | | | |
| FRIEDENBERG 2008[225] | BOTOX (BoNT/A) 200U BoNT/A (5 ml volume) injection vs. placebo saline injection | n=32 gastroparesis n=18 diabetes RCT | 1 injection; 1 month follow-up. | Symptom severity score (GCSI) | Data reported for the diabetic subgroup |
| Erythromycin | | | | | |
| SAMSOM 1997[617,618] | Erythromycin (250 g orally, 3 times a day, 30 minutes pre-meal) vs. placebo tablet | n=12 with type 1 diabetes Cross-over RCT | 2 weeks treatment (each cross-over period) | Symptom severity score | |
| Metoclopramide | | | | | |
| MCCALLUM 1983[467] | Metoclopramide (10 mg tablets) four times daily vs. placebo | n=44 with diabetes (95% type 1 | 3 weeks treatment | Vomiting severity score | |

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| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | | diabetes) | | Adverse events | |
| | | RCT | | | |
| RICCI 1985[592] | Metoclopramide (10 mg tablets) four times daily vs. placebo | n=13 with type 1 diabetes<br>Cross-over RCT | 3 weeks treatment (each cross-over period) | Symptom score – frequency<br>Adverse events | |
| | | | | | |
| **Domperidone, and domperidone vs. metoclopramide** | | | | | |
| BRAUN 1989[86] | Domperidone (10 or 20-mg tablets) four times daily vs. placebo | n=13 diabetes (95% type 1 diabetes)<br>Cross-over RCT | 1 month RCT treatment (each cross-over period) | Symptom frequency score<br>Symptom intensity score<br>Vomiting | Run-in phase – all given domperidone treatment<br>Only patients who improved n domperidone in the run-in phase entered the subsequent RCT phase of the study.<br>RCT followed by observational period – all given domperidone for up to 2 years (mean 467 days) |
| PATTERSON 1999 [549,550] | Domperidone (two 10 mg tablets) four times daily vs. metoclopramide + placebo tablet (one 10 mg tablet + one placebo tablet) four times daily | n=95 with type 1 diabetes<br>RCT | 4 weeks treatment | Vomiting<br>Symptom severity score | |
| SILVERS 1998[655] | Domperidone (two 10-mg tablets) four times daily vs. placebo (two identical dummy tablets) four times daily | n=208 with type 1 diabetes<br>n=105 Domperidone;<br>n=103 placebo<br>RCT | 4 weeks | QoL (physical and mental component)<br>Vomiting<br>Adverse events | Patients receiving cisapride or metoclopramide were required to undergo a washout period of 1 week before enrolment. |
| **Small particle diet** | | | | | |
| OLAUSSEN 2014[531,532] | Small particle diet (foods of small particle size or able to process to | n=56 with type 1 diabetes | 20 weeks | HbA1c<br>QoL (physical and | |

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| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | small size) vs. normal diabetes diet (foods recommended for people with diabetes, any particle size, low GI) | n=28 small particle size; n=28 usual diet RCT | | mental component) Vomiting severity Weight change | |
| **Observational studies** | | | | | |
| Gastric electrical stimulation | | | | | |
| ABELL 2003[13] | GES system (implanted) System on vs. off | n=33 gastroparesis n=17 diabetes Observational data within an RCT | 6 months follow-up (all had GES turned ON) | Total symptom score Vomiting frequency SF-36. | Cross-over RCT but gives observational data at 6 and 12 months – all had GES system turned ON |
| MCCALLUM 2010B[467,468] | GES system (implanted) System on vs. off | n=45 diabetes with gastroparesis Observational data within an RCT | 12 months follow-up (all had GES turned ON) | Vomiting episodes Symptom severity score | Cross-over RCT but gives observational data at 12 months – all had GES system turned ON |
| TIMRATANA 2013[695,696] | GES system (implanted; laparoscopic) | n=110 gastroparesis n=55 diabetes Prospective case-series | 27 months follow-up (mean) | HbA1c Nausea Vomiting Bloating Pain Adverse events | |
| VANDERVOORT 2005[712] | Electrical stimulation Stimulator (Itrel 3, Model 7425, Medtronic Kerkrade, the Netherlands)and two unipolar intramuscular electrodes | n=17 with type 1 diabetes with Gastroparesis refractory to conventional medical therapy. Prospective case-series | 12 months | Weekly vomiting frequency Weekly nausea frequency HbA1c (%) | Prior to entry, upper GI ENDOSCOPY was performed to exclude mechanical causes of gastric outlet obstruction. |
| Domperidone | | | | | |

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| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| BRAUN 1989[86] | Domperidone (10 or 20 mg tablets) four times daily | n=13 diabetes (95% type 1 diabetes) Observational data within an RCT | 12 weeks and median 467 days treatment | Symptom frequency score Symptom intensity score | Cross-over RCT but gives observational data after run-in (12 weeks all had domperidone treatment) Also gives observational data after the RCT (extension of median 467 days, all had domperidone treatment). |
| HOROWITZ 1985[329] | Domperidone (two 10 mg tablets) three times daily | n=12 with type 1 diabetes and autonomic neuropathy Prospective case-series | Median 38 days | Hypoglycaemia episodes HbA1c Vomiting Symptom severity score | Patients had autonomic neuropathy and other complications of diabetes. |
| Other interventions | | | | | |
| JANSSENS 1990[347] | Erythromycin (200 mg IV infusion for 15 minutes post-meal) vs. placebo infusion | n=10 with type 1 diabetes Observational data within an RCT | 4 weeks follow-up (all on erythromycin treatment) | HbA1c | Cross-over RCT but gives observational data at 4 weeks – all had erythromycin treatment |
| LACY 2004[406] | Botulinum toxin A Injection of the pylorus with 200 units during upper endoscopy. Patient was observed for 1-2 h in the recovery area and then discharged home. | n=8 with type 1 diabetes Control group consisted of age and sex-matched control subjects without diabetes and without any complaints. Observational study (case-control) | 12 weeks | Mean symptom score SF-36 questionnaire scores HbA1c (%) | Patients underwent esophagogastroduodenoscopy (before intervention) to rule out mechanical obstruction. |
| SHARMA 2011[647] | CSII pump therapy (previously on MDI) | n=26 type 1 diabetes with | 1 year | HbA1c (%) Weight change | |

| Study | Intervention/comparison | Population | Follow-up | Outcomes | Comments |
|---|---|---|---|---|---|
| | | gastroparesis Prospective case-series | | Hospital admissions | |

**Table 166: Clinical evidence summary table: Metoclopramide versus placebo (less than 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference Metoclopramide | Control event rate (per 1000 patients) Placebo |
|---|---|---|---|---|---|
| Symptom score (max 100 = worse) | 1 study (n=13) | Serious imprecision | LOW | MD 18.8 lower (46.18 lower to 8.58 higher) | 45.3 final value in control group |
| Symptoms - felt better, no. of patients | 1 study (n=10) | Serious imprecision | VERY LOW | RR 15.0 (0.97 – 231.8) | 0 |
| No vomiting, no. of patients | 1 study (n=10) | Serious imprecision | VERY LOW | RR 13.0 (0.83 – 203.8) | 0 |
| Vomiting, no. of patients improving by score ≥2 | 1 study (n=44) | Very serious imprecision | VERY LOW | 100 more per 1000 (from 245 fewer to 915 more) | 500 |
| Weight loss, no. of patients | 1 study (n=10) | Very serious imprecision | VERY LOW | 300 fewer per 1000 (from 498 fewer to 276 more) | 600 |
| Adverse events, no. of patients | 2 studies (n=60) | Serious imprecision | LOW | 295 fewer per 1000 (from 79 fewer to 738 fewer) | 719 |

**Table 167: Clinical evidence summary table: Domperidone versus placebo (less than 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference Domperidone | Control event rate (per 1000 patients) Placebo |
|---|---|---|---|---|---|
| Quality of Life (QoL) SF36 (36 items across 8 domains that can be reduced to 2 indexes) – Physical component | 1 study (n=203) | No serious imprecision | MODERATE | MD 2.42 higher (2.21 to 2.63 higher) | -1.77 final value in control group |
| Quality of Life (QoL) SF36 (36 items across 8 domains that can be reduced | 1 study (n=203) | No serious imprecision | MODERATE | MD 0.12 lower (0.40 lower to 0.16 higher) | -0.96 final value in control group |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br>Domperidone | Control event rate (per 1000 patients)<br>Placebo |
|---|---|---|---|---|---|
| to 2 indexes) – Mental component | | | | | |
| Vomiting | 1 study (n=208) | Very serious | VERY LOW | 44 fewer per 1000 (from 49 fewer to 29 more) | 49 |
| Adverse events | 1 study (n=208) | No serious imprecision | Moderate | 574 fewer per 1000 (from 631 fewer to 372 more) | 631 |

**Table 168: Clinical evidence summary table: Domperidone versus metoclopramide (less than 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br>Domperidone | Control event rate (per 1000 patients)<br>Metoclopramide |
|---|---|---|---|---|---|
| Symptom severity score (TSS) – max score 12 | 1 study (n=93) | No serious imprecision | MODERATE | MD 0.38 lower (0.58 to 0.18 lower) | 5.09 final value in control group |

**Table 169: Clinical evidence summary table: Erythromycin versus placebo (less than 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br>ERYTHROMYCIN | Control event rate (per 1000 patients)<br>PLACEBO |
|---|---|---|---|---|---|
| Symptom severity score (max. 3.0) | 1 study (n=12) | Serious | LOW | MD 0.28 lower (0.9 lower to 0.34 higher) | 1.81 final value in control group |
| Individual symptoms severity scores (max. 3.0) | 1 study (n=12) | Serious | LOW | NS improvement in any individual symptom score. | - |

**Table 170: Clinical evidence summary table: Botox versus placebo (less than 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br>Botox | Control event rate (per 1000 patients)<br>Placebo |
|---|---|---|---|---|---|
| GCSI score reduction (maximum 45) | 1 study (n=32) | Very serious | VERY LOW | MD 2.3 lower (11.62 lower to 7.02 higher) | 13.7 |

**Table 171: Clinical evidence summary table: Electrical stimulation: ON versus OFF (less than 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>ON | Control event rate (per 1000 patients)<br><br>OFF |
|---|---|---|---|---|---|
| Total symptom severity score (TSS) - 6 symptoms (Max 24) | 1 study (n=17) | Not serious | LOW | MD 1.9 lower (2.98 to 0.82 lower) | 13.2 final value in control group |
| Total symptom severity score (TSS) - 7 symptoms (Max 28) | 1 study (n=45) | Serious | LOW | MD 1.08 higher (1.65 lower to 3.81 higher) | 9.81 final value in control group |
| Total symptom frequency score (TSS) - 7 symptoms (Max 28) | 1 study (n=45) | No serious | MODERATE | MD 0.61 higher (2.4 lower to 3.62 higher) | 11.89 final value in control group |
| Vomiting severity score (Max 4) | 1 study (n=45) | Serious | LOW | MD 0.42 higher (0.1 lower to 0.94 higher) | 1.64 final value in control group |
| Vomiting frequency (episodes/day) | 1 study (n=7) | Very serious | VERY LOW | MD 0.8 higher (0.21 lower to 1.81 higher) | 0.33 final value in control group |
| Vomiting frequency score (Max 4) | 1 study (n=45) | No serious | MODERATE | MD 0.28 higher (0.32 lower to 0.88 higher) | 2.03 final value in control group |
| Weekly vomiting frequency; episodes/week | 1 study (n=17) | Serious | VERY LOW | Median 6.0 (IQR 3.0-14.8) | Median 12.8 (5.5-24.2) |
| Weekly vomiting frequency; episodes/week | 1 study (n=45) | Serious | LOW | Median 3.8 (IQR 0.75-14.0) | Median 4.3 (0.4-15.1) |
| Vomiting score | 1 study (n=17) | No serious | LOW | -0.31 units/day (-0.64, 0.02) with stimulation (p=0.069) | |

**Table 172: Clinical evidence summary table: Small particle size diet versus usual diabetic diet (less than 6 months)**

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br><br>Small particle diet | Control event rate (per 1000 patients)<br><br>Placebo |
|---|---|---|---|---|---|
| HbA1c, % | 1 study (n=56) | Serious | VERY LOW | MD 0.4 lower (0.9 lower to 0.1 higher) | 7.8% |
| SF-36 – PCS | 1 study (n=56) | Serious | VERY LOW | MD 4.70 higher (1.53 lower to 10.93 higher) | 35.5 |
| SF-36 - MCS | 1 study (n=56) | Serious | VERY LOW | MD 2.30 higher (5.56 lower to 10.16 higher) | 41.5 |
| Vomiting severity | 1 study | Serious | VERY LOW | MD 0.56 lower (1.01 to 0.11 lower) | Not reported |

| Outcomes | Number of studies | Imprecision | GRADE rating | Absolute difference<br>Small particle diet | Control event rate (per 1000 patients)<br>Placebo |
|---|---|---|---|---|---|
| | (n=56) | | | | |
| Weight change, kg | 1 study (n=56) | No serious | LOW | MD 0.012 lower (1.6 lower to 1.6 higher) | 78.5 |

### 16.1.4    Economic evidence

**Published literature**

No relevant economic evaluations were identified.

One economic evaluation relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[276] This is summarised in Appendix L, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

**Unit costs**

Relevant unit costs are provided below to aid consideration of cost effectiveness.

**Table 173: Staff costs**

| Group | Cost |
|---|---|
| Dietitian (band 5) | £34 |
| GP appointment | £43 |
| Consultant: medical | £157 |

*Source:    PSSRU 2012[148]*

**Table 174: Pharmacological treatments**

| Dose | Administration | Unit cost (per individual dose) | Annual cost |
|---|---|---|---|
| Metoclopramide[a] | | | |
| 10 mg 3 times a day | Tablet (10 mg) | £0.03 | £36 |
| 10 mg 3 times a day. | Oral solution (150 ml, 5 mg/5 ml) | £1.52 | £1,662 |
| 10 mg 3 times a day | Injection (2 ml amp, 5 mg/ml) | £0.26 | £285 |
| Erythomycin[b] | | | |
| 250 mg 3 times a day | Tablet (250 mg) | £0.07 | £72 |
| 250 mg 3 times a day | Capsules (250 mg) | £0.84 | £916 |
| 250 mg 3 times a day | Oral solution (100 ml, 250 mg/5 ml) | £0.20 | £215 |
| Domperidone | | | |
| 10 mg 3 times a day | Tablet (10 mg) | £0.04 | £42 |
| 20 mg 4 times a day | Tablet (10 mg) | £0.04 | £113 |
| 10 mg 3 times a day | Oral solution (200 ml, 1 mg/ml) | £0.63 | £686 |
| 20 mg 4 times a day | Oral solution (200 ml, 1 mg/ml) | £0.63 | £1,829 |

*Source: All doses and costs from MIMS Dec 2013 [10]*
*(a) MHRA warning*
*(b) Off license use*

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**Table 175: Cost of hospital stay**

| HRG[a] | HRG codes[b,c] | National Average Unit Cost | Lower Quartile Unit Cost | Upper Quartile Unit Cost |
|---|---|---|---|---|
| Non-malignant stomach or duodenum disorders (elective inpatient) | FZ43A, FZ43B, FZ43C[d] | £1,872 | £1,024 | £2,201 |
| Non-malignant stomach or duodenum disorders (non- elective inpatient) | FZ43A, FZ43B, FZ43C[e] | £1,023 | £782 | £1,169 |

(a) *Gastroparesis is coded under this HRG but unable to work out the percentage of these finished consultant episodes which are accredited to gastroparesis.*
(b) *NHS Reference Costs[166]*
(c) *HRG codes for all levels of complications have been included and a weighted average calculated*
(d) *Total activity – 2,021 finished consultant episodes*
(e) *Total activity – 31,762 FCE's*

**Table 176: Cost of enteral tube feeding and parenteral nutrition**

| Feeding Method | Total Cost | Eligible patients | Annual cost per patient |
|---|---|---|---|
| Enteral tube | £112,396,000 | 93,186 | £1,206 |
| Parenteral nutrition | £25,719,000 | 18,100 | £1,421 |

(a) *NICE CG32: Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition- Costing Report[507]*

**Table 177: Cost of electrical stimulation – Medtronic Enterra System**

| Component | Ex. VAT | Inc. VAT |
|---|---|---|
| Neurostimulator[a] | £4,700[a] | £5,640 |
| Electrode leads (x2)[a] | £2,600[a] | £3,120 |
| Laparoscopic surgery[b] | - | £5,000[b] |
| Total cost[c] | - | £13,760[c,d] |

(a) *Personal communication with Medtronic*
(b) *Estimated cost[330]*
(c) *Likely to underestimate the total cost as this does not include follow-up cost, device replacement or any adverse events.*
(d) *The device has a limited lifespan dictated principally by battery life, officially estimated at 5 to 10 years, although in practice 7 to 12 years is the norm. When the device has expired it will require surgery to be removed or replaced.*

## 16.1.5 Evidence statements

**Clinical**

**Evidence from RCT data**

**Metoclopramide versus placebo**

Low and Very low quality evidence from small studies showed a clinical benefit of metoclopramide over placebo at less than 6 months for symptom score, the number of patients who felt better, the number who had no vomiting, the number who lost weight, and the number who experienced adverse events. However, there was no clinical difference between metoclopramide and placebo for the number of patients improving vomiting by a score more than or equal to 2.

**Domperidone versus placebo**

Moderate and Very low quality evidence from a single study showed a clinical benefit of domperidone over placebo at less than 6 months (4 weeks) for the physical component of the SF-36 QoL measure, reduction in vomiting, and reduction in adverse events. However there was no clinical

difference between domperidone and placebo at less than 6 months (4 weeks) for the mental component of the SF-36 questionnaire scores.

**Domperidone versus metoclopramide**

Moderate quality evidence from a single study showed no clinically significant benefit of domperidone and metoclopramide at less than 6 months (4 weeks) for total symptom severity score.

**Erythromycin versus placebo**

Low quality evidence from a small single study showed no clinical difference between erythromycin and placebo at less than 6 months (2 weeks) for both individual and total symptom severity scores.

**Botox versus placebo**

Very low quality evidence from a small single study showed no clinical difference between Botox and placebo at less than 6 months (1 month) for reduction in GCSI score.

**Electrical stimulation ON versus OFF**

Moderate, Low, and Very low quality evidence from small studies showed a clinical benefit of electrical stimulation compared with no stimulation at less than 6 months for weekly vomiting frequency (episodes/week). However the evidence also showed clinical harm of electrical stimulation in terms of vomiting severity score, and vomiting frequency (episodes/day). There was no clinical difference for total symptom severity scores, vomiting frequency score, vomiting score, or for weekly vomiting frequency (episodes/week – a different study to the one that showed clinical benefit).

**Small particle diet versus normal diabetic diet**

Low and Very low quality evidence from a single study showed a clinical benefit of small particle diet compared with usual diabetic diet at less than 6 months (20 weeks) for HbA1c, vomiting severity, and for QoL (SF-36 physical component). There was no clinical difference for QoL (SF-36 mental component), and for weight change.

**Evidence from observational data - narrative summary**

The following studies have been summarised as a narrative because they were not suitable study designs for meta-analysis or GRADE. All observational study data is graded as Low quality.

**Botulinum toxin A during upper endoscopy**

One case-control study (n=8; n=16, including controls) LACY 2004[406] found that compared with baseline, there was a reduction in symptom score at 12 weeks, but there were no differences in HbA1c or SF-36.

**Electrical stimulation**

One study (n=17), reporting observational follow-up data from an RCT (ABELL 2003)[13] found that compared with baseline, after treatment with electrical stimulation there were improvements in weekly vomiting frequency, total symptom severity score, and SF-36 physical function at both 6 months and 12 months. However, SF-36 mental component was worse.

One study (n=45), reporting observational follow-up data from an RCT (MCCALLUM 2010B)[467,468] found that compared with baseline, after treatment with electrical stimulation there were

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improvements in symptom scores (both frequency and severity), SF-36, and in-hospital days at 4.5 months. However, there was no impact on HbA1c, weekly hypoglycaemic episodes or BMI.

One study, a case-series (n=17), (VANDERVOORT 2005)[712] found that compared with baseline, after treatment with electrical stimulation there were improvements in HbA1c, and weekly nausea and vomiting at 6 months and 12 months.

One study, a case-series (n=55), TIMRATANA 2013 [695,696] found that compared with baseline, after a mean of 27 months treatment with laparoscopic electrical stimulation there were improvements in nausea, vomiting, and pain. However there was no difference for bloating, and there were 5 adverse events (post-surgical complications).

### Erythromycin

One study (n=10), found accelerated gastric emptying after a single intravenous administration of erythromycin given in an RCT design, each subject receiving active or placebo in random order, and also reported observational follow-up data with all subjects continuing on oral erythromycin (JANSSENS 1990)[347] which had intermediate effect on gastric emptying, anecdotal evidence of subjective improvement and an HbA1c at 4 weeks of 7.6 (5.1-10.0%) versus baseline 8.5 (5.3-11.6)% (non-diabetic range 3.6-6.4%), for which there was no statistical analysis. .

### CSII pump therapy

One study (n=26), a case-series (SHARMA 2011)[647], found that compared with baseline, after treatment with CSII pump therapy there were improvements in BMI (which was increased at 6 months) and HbA1c and frequency of hospital admissions due to gastroparesis measured one year into therapy.

### Domperidone

One study (n=13), reporting observational follow-up data from an RCT (n=1989)[86] found that compared with baseline, after treatment with domperidone, there were improvements in the intensity and severity of all individual symptoms at 12 weeks, as well as the total symptom scores (TSS) at 12 weeks and median of 467 days.

One study (n=12), a case-series (HOROWITZ 1985)[329], found that compared with baseline, after treatment with domperidone, there were improvements in the severity of symptoms at median 38 days.

### Economic

No relevant economic evaluations were identified.

### 16.1.6    Recommendations and link to evidence

| Recommendations | 137. Consider domperidone[o] (in preference to metoclopramide) for treating gastroparesis[p] in adults with type 1 diabetes. [new 2015]<br><br>138. Consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes who have gastroparesis. [new 2015]<br><br>139. Advise a small-particle-size diet (mashed or pureed food) for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis. [new 2015]<br><br>140. Refer adults with type 1 diabetes who have gastroparesis for specialist advice if the interventions in recommendations 138 and 139 are not beneficial or not appropriate. [new 2015] |
|---|---|
| Research recommendation | Further research and RCTs are required for further assessment of interventions for gastroparesis, including the use of dopamine antagonists and patient selection, and clinical and cost effectiveness of gastric electrical stimulation interventions. |
| Relative values of different outcomes | The available RCT evidence and evidence from prospective observational studies was sought for the following interventions used in the management of gastroparesis:<br><br>• Dopamine antagonists (for example, metoclopramide, domperidone)<br>• Prokinetic agents/gastroprokinetic agents (for example, erythromycin)<br>• 5-Hydoxytryptamine antagonists (for example, ondansetron)<br>• Anti-emetics<br>• Botulinum toxin<br>• Electrical stimulation interventions<br>• Intensive insulin treatment/glucose control<br>• Dietary changes<br>• Enteral feeding<br>• Acupuncture<br>• Aldose reductase inhibitors (including epalrestat)<br>• Histamine-2 receptor antagonists<br>• Centrally acting antidepressants<br>• Surgical interventions (including gastrectomy)<br><br>The evidence was reviewed to look at the impact of each intervention on the symptoms and clinical outcomes experienced by individuals with gastroparesis, including:<br><br>• Nausea and Vomiting – the most common symptoms reported by individuals with gastroparesis as a consequence of gastric stasis, and the greatest contributor to reduced quality of life.<br>• Quality of life – this has been reported to be significantly reduced in individuals with gastroparesis |

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o   Although this use is common in UK clinical practice, at the time of consultation (December 2014), domperidone did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.

p   Diagnosis of gastroparesis needing specific therapy can only be made in the absence of hyperglycaemia at the time of testing, because hyperglycaemia induces a physiological delay in gastric emptying.

| Recommendations | 137. Consider domperidone$^o$ (in preference to metoclopramide) for treating gastroparesis$^p$ in adults with type 1 diabetes. [new 2015]<br><br>138. Consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes who have gastroparesis. [new 2015]<br><br>139. Advise a small-particle-size diet (mashed or pureed food) for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis. [new 2015]<br><br>140. Refer adults with type 1 diabetes who have gastroparesis for specialist advice if the interventions in recommendations 138 and 139 are not beneficial or not appropriate. [new 2015] |
|---|---|
| | • Hypoglycaemia - Hypoglycaemia is a regular occurrence in many people with type 1 diabetes and gastroparesis. The action of administered insulin at mealtimes can be faster than the rate of absorption of carbohydrate from the digestive tract due to reduced gastric motility. Particular focus was given to the incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a 3rd party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes.<br>• Glycaemic control -. Increased lability of blood glucose levels has been described in individuals with gastroparesis, as both postprandial hypo- and hyper-glycaemia can occur as insulin absorption fails to match glucose absorption from the meal. This can be a disincentive for people to take insulin.<br>• Weight loss – this can occur in patients with gastroparesis as a consequence of early satiety and vomiting and subsequent food avoidance. Furthermore, absorption of nutrients from the digestive tract might be less when gut motility is reduced.<br>• Hospital admissions – gastroparesis is associated with increased risk of hypoglycaemia and episodes of intractable vomiting, which may increase the risk of ketoacidosis, all of which can result in admission to hospital.<br>• Adverse events – if any treatment causes adverse events, its benefits must be weighed against the frequency and severity of such adverse events. |
| Trade-off between clinical benefits and harms | **Dopamine antagonists**<br>Three very old and very small RCTs, each reporting different outcomes, about the use of metoclopramide in the management of gastroparesis (McCallum 1983, Ricci 1985, Snape 1982) showed that it reduced physical symptoms and vomiting, and more patients experienced weight gain. The number of patients with adverse events was also lower with metoclopramide.<br><br>One RCT using domperidone in the management of gastroparesis (Silvers 1998) showed that it reduced physical symptoms and vomiting, but had no effect on the mental symptoms associated with gastroparesis. No adverse events were reported in this trial.<br><br>A randomised controlled trial comparing domperidone use to metoclopramide showed that metoclopramide was more likely to induce central nervous system side-effects. [549,550]<br><br>**Promotility agents** |

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| Recommendations | 137. **Consider domperidone[o] (in preference to metoclopramide) for treating gastroparesis[p] in adults with type 1 diabetes. [new 2015]**<br><br>138. **Consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes who have gastroparesis. [new 2015]**<br><br>139. **Advise a small-particle-size diet (mashed or pureed food) for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis. [new 2015]**<br><br>140. **Refer adults with type 1 diabetes who have gastroparesis for specialist advice if the interventions in recommendations 138 and 139 are not beneficial or not appropriate. [new 2015]** |
|---|---|
| | Erythromycin increases gastric motility but a significant reduction in symptom severity scores was not achieved in trials (Samsom 1997). An observational study reported an improvement in glycaemic control following a single intravenous infusion of erythromycin use (HbA1c 8.0% at baseline reducing to 7.6% at four weeks) (Janssens 1990). The GDG did not consider the association between the treatment and the improvement to be necessarily causal<br><br>**Botulinum toxins**<br>An observational study reported that Botox significantly reduced gastroparesis symptoms (Lacy 2004) but this study was in only eight patients. No significant impact on quality of life was achieved and glycaemic control was not significantly different from baseline. A subsequent RCT showed that Botox treatment was less effective than placebo in reducing gastroparesis cardinal symptom index (GCSI) scores (Friedenberg 2008).<br><br>**Gastric electrical stimulation interventions**<br>Four observational studies [712]/[13,695,713]) reported a favourable outcome for electrical stimulation interventions for gastroparesis (reduction in weekly vomiting frequency and reduction in symptom severity scores), with one of the trials also reporting a significant improvement in glycaemic control. [712]<br><br>However, subsequent RCTs investigating electrical stimulation interventions randomised to 'on' or 'off' reported variable outcomes: symptom severity scores improved in one study [13,14] but other studies reported no benefit ([228,468]) and suggested it could cause a harmful increase in the frequency of vomiting.<br><br>**Small particle diet**<br>One RCT comparing the effect of a small particle diet vs. a normal diabetic diet (any particle size) in the management of gastroparesis (Olaussen 2014) showed that it reduced HbA1c and vomiting severity, and improved the physical component of SF-36. However, there was no difference on the mental component of Sf-36 or on weight loss.<br><br>**Intensive insulin treatment with CSII**<br>An observational study for the use of continuous subcutaneous insulin infusions (CSII) in individuals with gastroparesis showed that extended insulin bolus regimens could be used with meals to improve clinical outcomes (Sharma 2011). The study |

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| | |
|---|---|
| **Recommendations** | **137. Consider domperidone[o] (in preference to metoclopramide) for treating gastroparesis[p] in adults with type 1 diabetes. [new 2015]**<br><br>**138. Consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes who have gastroparesis. [new 2015]**<br><br>**139. Advise a small-particle-size diet (mashed or pureed food) for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis. [new 2015]**<br><br>**140. Refer adults with type 1 diabetes who have gastroparesis for specialist advice if the interventions in recommendations 138 and 139 are not beneficial or not appropriate. [new 2015]** |
| | reported that glycaemic control improved significantly (HbA1c 9.8% at baseline versus 8.0% at one year), a weight gain of 2.9 kg was achieved at 6 months, and hospital admission frequency for management of gastroparesis was reduced from 8.5 median inpatient bed days/patient/year down to 0 days at one year follow-up.<br><br>No RCT evidence or evidence from prospective observational studies was found for other interventions used in the management of gastroparesis by the GDG, including enteral/parenteral feeding and gastrectomy. |
| Economic considerations | The primary treatment goals for gastroparesis related to diabetes are to improve gastric emptying, improve quality of life and to regain control of blood glucose levels. No cost effectiveness analysis was available about the impact of interventions on these outcomes for the management of gastroparesis in adults with type 1 diabetes.<br><br>The annual unit costs of some of the interventions were presented to the GDG for consideration when making recommendations.<br><br>Given the relatively low cost and the availability of dopamine antagonists (metoclopramide £36 per year for 10 mg three times a day; domperidone £42 per year for 10 mg three times a day), these medications were considered to be a cost-effective treatment for the management of gastroparesis symptoms, especially if their use might reduce the frequency of non-elective inpatient hospital stays for treatment of gastroparesis (national average £1,023 per stay).<br><br>Electrical stimulation interventions were costed at £13,760 per system implant. The evidence of clinical benefit was not consistent across studies, and the intervention was considered unlikely to be cost-effective. |
| Quality of evidence | As the number and size of the trials investigating interventions for gastroparesis in adults with type 1 diabetes are small, the GDG reviewed additional evidence from trials that were undertaken in mixed populations of type 1 and type 2 diabetes patients, although the GDG did not consider evidence taken from studies looking at populations only with type 2 diabetes.<br><br>The available RCT evidence was GRADE assessed for quality:<br><br>• The GRADE quality of the evidence for metoclopramide versus placebo ranged from Low to Very low, with a serious/very serious risk of bias.<br><br>• The GRADE quality of the evidence for domperidone versus metoclopramide was Moderate, with a serious risk of bias.<br><br>• The GRADE quality of the evidence for domperidone versus placebo ranged from Moderate to Very low, with a serious risk of bias.<br><br>• The GRADE quality of the evidence for erythromycin versus placebo was low, with |

| Recommendations | 137. Consider domperidone<sup>o</sup> (in preference to metoclopramide) for treating gastroparesis<sup>p</sup> in adults with type 1 diabetes. [new 2015]<br><br>138. Consider continuous subcutaneous insulin infusion (CSII or insulin pump) therapy for adults with type 1 diabetes who have gastroparesis. [new 2015]<br><br>139. Advise a small-particle-size diet (mashed or pureed food) for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis. [new 2015]<br><br>140. Refer adults with type 1 diabetes who have gastroparesis for specialist advice if the interventions in recommendations 138 and 139 are not beneficial or not appropriate. [new 2015] |
|---|---|
| | a serious risk of bias.<br>• The clinical evidence profile for the botulinum toxins was of Very low quality but with no serious risk of bias.<br>• The quality of evidence from electrical stimulation studies ranged from High to Very low but there was a serious risk of bias for many of the measured outcomes. |
| Other considerations | The European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) guidance has suggested that domperidone, metoclopramide and ondansetron should not be used for more than 5 days due to an increased risk of cardiovascular disease and the risk of developing tardive dyskinesia, outweighing the benefits of symptom relief. The exception to this in the UK is their use following radiotherapy and chemotherapy. These recommendations are not based on clinical study data but made following a review of completed adverse drug event reports, and the GDG considered that they were not primarily intended for complex, chronic causes of vomiting such as diabetic gastroparesis<br>The GDG noted that all the RCTs for metoclopramide were small n=10 to n=44 patients). The single RCT on domperidone was larger and no adverse events were reported in this study in individuals with gastroparesis (Silvers 1998). The GDG also noted that in a randomised controlled trial comparing domperidone use to metoclopramide (Patterson 1999), domperidone was less likely to induce central nervous system side-effects. The GDG therefore concluded that domperidone should be preferred to metoclopramide for the management of gastroparesis symptoms. |

### 16.1.7 Research recommendations

**32. In adults with type 1 diabetes, clinical and cost effective treatments for diabetic gastroparesis are needed, together with further evidence for the clinical and cost effectiveness of existing treatments such as dopamine antagonists, insulin pump therapy, and gastric electrical stimulation.**

## 16.2 Erectile dysfunction [2015]

### 16.2.1 Introduction [2015]

Erectile dysfunction in men with diabetes is common, and to a greater extent than in the matched general population. While psycho-sexual causes are no less common in men with type 1 diabetes

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than men without, the man with diabetes may also experience impaired sexual function as a result of diabetic autonomic neuropathy and/or vascular disease, either of which can impair the ability to achieve an erection. It is therefore appropriate to include an assessment of erectile function in reviewing the man with type 1 diabetes. There are treatments now available to help men with erectile dysfunction achieve erection sufficient to allow intercourse.

The assessment of fertility and hypogonadism in men is beyond the scope of the present review.

**The GDG addressed only this question:**

- What pharmacological treatment should be used to manage erectile dysfunction in men with type 1 diabetes?

### 16.2.2 New review question [2015]: What pharmacological treatment should be used to manage erectile dysfunction in men with type 1 diabetes?

### 16.2.3 Clinical evidence [2015]

The pharmacological management of erectile dysfunction was originally covered as part of the 2004 guidance. Updated searches were carried out by the NICE 2015 GDG, developing guidance for type 2 diabetes, who looked at both type 1 diabetes and type 2 diabetes populations as part of their review. The evidence that was found assessed the impact of treatments in mixed populations of people with type 1 diabetes or type 2 diabetes; two of the assessed studies reported outcomes exclusively in adults with type 1 diabetes type 1 diabetes (Stuckey 2003, Ziegler 2006). The type 1 diabetes GDG subsequently interpreted the evidence independently and produced their own recommendations for the management of erectile dysfunction in adults with type 1 diabetes.

Details of the evidence used for this review can be found in the NICE 2015 clinical guideline for type 2 diabetes (due for publication August 2015 However, forest plots pertaining to the two studies that performed a subgroup analysis in people with type 1 diabetes, can be found in Appendix J.

### 16.2.4 Economic evidence [2015]:

The economic literature review for this question was also conducted by the type 2 diabetes guideline GDG (as per clinical evidence) on behalf of type 1 diabetes in adults.

### 16.2.5 Evidence statements [2015]

Please see the 2015 NICE type 2 diabetes guideline (add hyperlink when published)

### 16.2.6 Recommendations and links to evidence [2015]

| Recommendations | |
|---|---|
| | 141. **Offer men with type 1 diabetes the opportunity to discuss erectile dysfunction as part of regular review. [2015]** |
| | 142. **Offer a phosphodiesterase-5 inhibitor to men with type 1 diabetes with isolated erectile dysfunction unless contraindicated. Choose the phosphodiesterase-5 inhibitor with the lowest acquisition cost. [new 2015]** |
| | 143. **Consider referring men to a service offering further assessment and other medical, surgical or psychological management of erectile dysfunction if phosphodiesterase-5 inhibitor treatment is unsuccessful** |

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| | **or contraindicated. [2015]** |
|---|---|
| Relative values of different outcomes | The review question addressed whether pharmacological treatment should be used in the management of erectile dysfunction in adults with type 1 diabetes. A literature review was undertaken to assess the evidence for the following pharmacological interventions<br><br>• Phosphodiesterase-5 inhibitors (PDEIs)<br>• Testosterone therapy<br>• Alprostadil<br><br>The main outcomes for this review question were erectile function, quality of life and adverse events.<br>Erectile function was assessed using four main measures:<br>• Erectile function domain of the international index of erectile function (IIEF) questionnaire<br>• Question 2 from the sexual encounter profile (SEP-2) relating to success in penetration<br>• Question 3 from the sexual encounter profile (SEP-3) relating to success in intercourse<br>• Global efficacy question (GEQ) relating to whether treatment has improved erections<br>Adverse events assessed included headache, flushing, upper respiratory tract infection, dyspepsia, abnormal vision. |
| Trade off between clinical benefits and harms | Pair-wise comparisons showed that erectile function was significantly improved with use of PDEIs compared with placebo. Subsequent review of the available evidence comparing PDEIs showed no significant difference in outcome achieved for measures of erectile function using sildenafil, vardenafil or tadalafil.<br>One study (Boulton 2001) reported a significantly improved quality of life score with sildenafil use compared with placebo.<br>The use of PDEIs was associated with a significantly increased risk of developing adverse events when compared with placebo. Adverse events included headaches, flushing, upper respiratory tract infections, dyspepsia and abnormal vision. The GDG considered these to be relatively mild side-effects compared with the benefits in erectile function gained. The available evidence did not suggest that the use of a particular PDEI might have an improved side effect profile compared with other PDEIs. It is noted that all trials will have excluded men with known contraindications, listed by the British National Formulary as concomitant use of nitrates, where vasodilation or sexual activity is inadvisable, men with a history of non-arteritic anterior ischaemic optic neuropathy; to which manufacturers have added systolic blood pressure below 90 mmHg, recent stroke, unstable angina, and myocardial infarction.<br>One open-label trial of oral testosterone supplementation therapy (120 mg oral testosterone undecanoate per day) compared with no treatment (Boyanov 2003) reported significantly improved erectile function, blood glucose control and lower body weight. Subgroup analyses by baseline HbA1c levels for all assessed studies showed that there were no differences in erectile function between the different levels of baseline HbA1c. |
| Economic considerations | Literature searches were undertaken for cost utility analyses of the pharmacological management of erectile dysfunction in adults with diabetes.<br>No cost utility analyses about the use of testosterone therapies in individuals with diabetes were available for review. |

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| | |
|---|---|
| | Three cost utility analyses about the use of PDEIs were recognised as suitable for further assessment (Aspinall 2011, Smith 2000, Stolk 2000) but none of the studies were specific to diabetes populations. However, the GDG accepted that it was possible to extrapolate findings from these studies to populations with diabetes. One of the three studies stated that no difference in clinical effectiveness of treatment interventions by risk factor (including diabetes) had been identified in the cost utility analysis (Aspinall 2011). |
| | Of the three cost utility analyses, one compared sildenafil to no treatment (Smith 2000), one compared sildenafil to injection therapies (Stolk 2000) and the third study assessed the cost-effectiveness of varying doses of vardenafil (Aspinall 2011). |
| | All three studies reported that sildenafil (Smith 2000, Stolk 2000) and vardenafil (Aspinall 2011) were cost-effective in comparison to placebo or alternative treatments, with incremental cost-effectiveness ratios likely to remain below conventional thresholds in the majority of cases. Sildenafil treatment was cost-effective compared with no treatment at $50,000 per QALY threshold (Smith 2000); sildenafil was cost-effective compared with usual care at $20,000 per QALY threshold (Stolk 2000); and provision of extra doses of vardenafil was cost-effective compared with less monthly doses at $50,000 per QALY threshold. It was noted that all three cost utility analyses contained assumptions that were conservative or biased towards the alternative treatment but under sensitivity analysis, the treatment option remained likely to be cost-effective. |
| | The GDG recognised that individuals with diabetes might require higher doses of PDEIs but the available evidence reviewed indicated that available treatments were still likely to increase utility by an extent that would offset reasonable costs. Sildenafil is now off patent, and the estimated annual cost of treatment is £75/year. By comparison, tadalafil currently has an estimated annual cost of treatment of £715/year. The reviewed evidence did not indicate a significant difference in adverse event profiles for different PDEIs, and therefore the GDG recommended that the PDEI with the lowest acquisition cost be selected by prescribers for the management of erectile dysfunction in adults with type 1 diabetes. |
| Quality of evidence | Only randomised controlled trials (RCTs) were included for the evidence review. Nine RCTs originally included in the literature review for the development of CG 66 (Boulton 2001, Buvat 2006, Goldstein 2003, Ishii 2006, Rendell 1999, Saenz de Tejada 2002, Safarinejad 2004, Stuckey 2003, Ziegler 2006) and four newly identified RCTs (Boyanov 2003, DeYoung 2012, Hatzichristou 2008, Kamenov 2011) were reviewed for this guideline development. |
| | Twelve of the studies reported on outcomes on the use of PDEIs, with ten placebo controlled trials (five sildenafil trials, two tadalafil trials and three vardenafil trials), one head-to-head comparison trial (tadalafil versus verdenafil, Kamenov 2011) and one study examining on-demand versus three times a week dosing regimens with tadalafil (Buvat 2006). One study assessed the use of testosterone therapy in the management of erectile dysfunction (Boyanov 2003). No studies assessing the use of alprostadil were available in the evidence review. |
| | The GRADE quality of the available evidence for PDEIs assessing erectile function varied from Very low to Low; GRADE assessment of quality of life measures was Moderate; and GRADE assessment of adverse events was Very low to Moderate. |
| | Only one study was available for the evidence of testosterone therapy use in adults with diabetes and erectile dysfunction, and GRADE quality of this study was Very low. Given the paucity and low quality of the evidence available for testosterone therapy in the treatment of erectile dysfunction in adults with diabetes, the GDG was not able to make any recommendations about its use for erectile dysfunction in individuals with diabetes at the present time. |

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| Other considerations | The GDG considered that men starting treatment should be advised to discuss management options for erectile dysfunction with their partners and the men and their clinicians should enable partners to participate in management decision-making. However, the duty of care is to the patient first and foremost and at the present time the onus is not with the clinician to ensure that these conversations take place between patient and partner before treatment being started for erectile dysfunction in adults with type 1 diabetes. |
|---|---|

## 16.3 Acute painful neuropathy of rapid glycaemic control [2015]

### 16.3.1 Introduction

Sudden insulinisation after a prolonged period of severe insulin deficiency can cause short- and medium-term complications. These are associated with the use of insulin itself and the sudden reduction of chronic hyperglycaemia. They include salt and water retention with weight gain, weight gain due to retention of calories previously lost in glycosuria, deterioration of existing retinopathy (attributed at least in part to a fall in the hyperperfusion of the insulin deficient, hyperglycaemic state) and a very distressing painful acute-onset neuropathy. The neuropathy has been described as "insulin induced neuritis"; "insulin induced neuropathy" and, as here, the more descriptive "acute painful neuropathy of rapid glycaemic control", a term which acknowledged the probable role of the sudden change in ambient glucose. This neuropathy is distinct from other forms of diabetic neuropathy, management of which is described in NICE clinical guideline 173, Neuropathic pain – pharmacological management. Its onset is usually sudden and it is self-limiting. However, the duration of symptoms may be very long and the pain can be very severe. It classically affects the limbs, particularly the lower limbs, and it can be associated with more generalised allodynia (the skin is painful when touched).

Acute painful neuropathy of rapid glycaemic control is not common but it can be very distressing. Because of its aetiology, it may occur when an adult with type 1 diabetes has been able to engage with self-care after a prolonged period of self-neglect, with a negative impact on the person's motivation for on-going self-care, which may also need to be addressed.

The aim of treatment is to reduce the pain felt to tolerable levels, so that the pain does not interfere with daily function, while continuing the insulin treatment regimen. The pain is often resistant to simple analgesia. The GDG therefore addressed the question: In adults with type 1 diabetes, what is the most effective treatment for acute painful neuropathy of rapid glycaemic control/insulin-induced neuropathy?

### 16.3.2 Updated review question: In adults with type 1 diabetes, what is the most effective treatment for acute painful neuropathy of rapid glycaemic control?

For full details see review protocol in Appendix C.

**Table 178: PICO characteristics of review question**

| Population | Adults with type 1 diabetes and insulin-induced neuropathy |
|---|---|
| Intervention/s | <ul><li>Analgesia, for example, Duloxetine, tramadol</li><li>Anti-epileptics, antidepressants - tricyclic antidepressants (SNRIs and duloxetine), anti-convulsants (gabapentin, pregabalin), pump therapy</li><li>Lidocaine/lignocaine (anaesthetics)</li><li>Capsaicin</li><li>Insulin pump</li></ul> |

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| | |
|---|---|
| **Comparison/s** | • Anything<br>• None |
| **Outcomes** | Outcomes<br>• Pain scores (continuous)<br>• Retinopathy – incidence (dichotomous)<br>• Low-level (micro) albuminuria - incidence (dichotomous)<br>• Resolution of symptoms (continuous)<br>• Improvement in pain scores (dichotomous) |
| **Study design** | RCTs, observational studies, case-series |

### 16.3.3    Clinical evidence

One study was included in the review[246]. Evidence from this study is summarised in Table 2. This study was a non-comparative observational study (case-series), and therefore were not able to be combined in a meta-analysis or GRADE profile, and was graded as Low quality (due to the study design). However, a summary of the quality and limitations of this study can be found in Appendix G. The study details and the full results have been summarised in the tables below. See also the study selection flow chart in Appendix D, study evidence tables in Appendix G and exclusion list in Appendix K.

A number of RCTs were identified in the literature search. However, these were conducted in a mixed population of type 1 diabetes and type 2 diabetes patients who had chronic diabetic neuropathy and/or did not refer not acute painful neuropathy of rapid glycaemic control. These studies were therefore excluded from the review.

The included study was a prospective case-series of n=16 diabetic patients (n=9, type 1 diabetes) reporting acute onset of insulin-induced neuropathy associated with improved glycaemic control. All patients had historically poor glycaemic control either due to anorexia and/or treatment non-adherence. The patients in the study were on different combinations of treatments and there was no direct comparison of the intervention and comparators listed in the protocol. The results from this study have been reported narratively in Table 165.

Data were available for the following outcomes:

• Improved pain scores: reported as duration of treatment for a 50% reduction in pain

• Pain Scores: reported at baseline (after intensive glycaemic control) and at follow-up

• Resolution of symptoms reported as:

  o Neuropathy impairment scores in the lower limb (NIS-LL) at baseline and 18 months

  o Autonomic symptom scores at baseline and 18 months

  o % of patients with abnormal autonomic function at baseline and 18 months

• Deterioration of other complications associated with sudden onset of diabetes control such as:

  o Retinopathy[q]: reported as no. of patients at baseline and after 6 months of intensive glycaemic control

  o Low-level (micro) albuminuria[q]: reported as no. of patients at baseline and after 1 year of intensive glycaemic control

All outcomes (except for the following) were reported from a mixed population of type 1 diabetes and type 2 diabetes patients and are, therefore, not an exact match (that is, considered indirect) to

<div style="text-align: right;">**Update 2015**</div>

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q    Retinopathy and microalbuminuria outcomes are complications alongside acute painful neuropathy of rapid glycaemic control and not outcomes for the interventions used for the treatment of the neuropathy itself.

the protocol population. Results from these have been included in this review due to the scarcity of evidence. Type 1 diabetes subgroup data were only reported in the following outcomes:

- Resolution of symptoms reported as:
  - o Neuropathy impairment scores in the lower limb (NIS-LL) at baseline and 18 months
  - o Autonomic symptom scores at baseline and 18 months

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**Table 179: Summary of studies included in the review**

| Study | Intervention/comparison | Population | Outcomes | Results |
|---|---|---|---|---|
| GIBBONS 2010[246]<br><br>Prospective case-series | Various medications (alone or in combination):<br>Anti-epileptics + TCA + Tramadol n=2<br>Anti-epileptics + TCA n=1<br>Anti-epileptics + SNRI n=1<br>Anti-epileptics + SNRI + tramadol n=2<br>Anti-epileptics + tramadol n=1<br>Anti-epileptics + SNRI + methadone n=1<br>SNRI + tramadol n=1 | n=16 (n=9 type 1 diabetes)<br>Acute painful neuropathy after rapid and sustained glycaemic control<br><br>Setting: US<br><br>7/9 patients had a remote history of diabetic anorexia and other 2 subjects had historically poor BG control due to treatment non-compliance | **Improved pain scores**[a]<br>Duration of treatment for a 50% reduction in pain | At 15 months (range 12-28) |
| | | | **Pain scores**[a]<br>Pain, 0-10 Likert scale, 0=no pain; 10=worst pain imaginable) | Baseline, mean (SD) = 10 (0)<br>• At Follow-up: 7-9 |
| | | | **Resolution of symptoms**[b]<br>Neuropathy impairment score in lower limb (NIS-LL; muscle strength graded as normal, zero, to max score of 64 if paraplegic, reflexes graded zero to 8 and sensation graded 0 to 16) | • Baseline: 5.1(1.4)<br>• At 1 year: 5.3 (1.3)<br>Reported NS |
| | | | **Resolution of symptoms**[b]<br>Autonomic symptoms (11 point Likert scale; (0=no symptoms; 10=severe symptoms), baseline vs. 18 months | **SS improvement reported in the following scores:** orthostatic lightheadedness, orthostatic dizziness, pre-syncope, syncope, orthostatic symptoms worse with standing, nausea, vomiting, diarrhoea, early satiety<br>**NS difference reported in the following scores:**<br>Orthostatic symptoms after meals, loss of appetite, urinary frequency, nocturia, hyperhidrosis, anhidrosis, erectile dysfunction. |
| | | | **Resolution of symptoms**[a]<br>Autonomic dysfunction | **Abnormal HR response deep breathing**<br>• Baseline: 69%<br>• At 18 months: 48%<br>**Abnormal inspiratory-expiratory ratio**<br>• Baseline: 62%<br>• At 18 months: 19% |

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| Study | Intervention/comparison | Population | Outcomes | Results |
|---|---|---|---|---|
| | | | | **Valsalva ratio** |
| | | | | • Baseline: 56% |
| | | | | • At 18 months: 43% |
| | | | | **Orthostatic hypotension** |
| | | | | • Baseline: 69% |
| | | | | • At 18 months: 31% |
| | | | **Retinopathy**[a,c]<br>Retinopathy, no. of patients | • Baseline: 7/16<br>• At 6 months of sustained BG control:16/16 |
| | | | **Low-level (micro) albuminuria**[a,c]<br>Low-level (micro) albuminuria, number of patients | • Baseline: 8/16<br>• At 1 year 13/16 |

*(a) Data from mixed population of type 1 diabetes and type 2 diabetes*

*(b) Data from type 1 diabetes subgroup analysis*

*(c) Retinopathy and Low-level (micro) albuminuria outcomes are complications alongside insulin-induced neuritis due to intensive glycaemic control and not outcomes for the interventions used for the treatment of insulin induced neuritis*

### 16.3.4 Economic evidence

**Published literature**

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix E.

**Unit costs**

Relevant unit costs are as follows. These have been taken from NICE CG173: Neuropathic pain – pharmacological management.

**Table 180: Daily dosages and cost of recommended drugs – CG173 [503]**

| Drug | Daily dosage[a] | Cost per electronic drug tariff[b] | Cost per day | Annual cost[d] |
|---|---|---|---|---|
| Amitriptyline | 50 mg[c] once daily | 50-mg tablets – £0.99 for 28 | £0.03 | £10.95 |
| | | 40-mg tablets - 4 x 10-mg - £0.87 for 28 | £0.12 | £43.80 |
| Gabapentin | 1800 mg (600 mg three times daily) | 600-mg capsules – £11.50 for 100 | £0.35 | £127.75 |
| | | 300-mg capsules – £3.54 for 100 | £0.21 | £76.65 |
| | | 400-mg capsules x 4 + 2 x 100-mg capsules - £4.53 and £2.56 for 100 respectively | £0.23 | £83.95 |
| Duloxetine | 60 mg once daily | 60-mg capsules – £27.72 for 28 | £0.99 | £361.35 |
| Pregabalin | 300 mg (150 mg twice daily) | 150-mg capsules – £64.40 for 56 | £2.30 | £839.50 |
| Tramadol | 400 mg (100 mg four times daily) | 50-mg capsules – £3.73 for 100 | £0.30 | £109.50 |
| Capsaicin cream (0.075%) | 4 g (1 g four times daily) | 45-g tube – £14.58 | £1.32 | £481.80 |
| Carbamazepine | 800 mg (200 mg four times daily) | 200-mg tablets – £5.78 for 28 | £0.80 | £292.00 |

(a) The Guideline Development Group (GDG) provided estimates of the most common doses for each drug. The GDG pharmacist checked and confirmed drug prices and formulations (table F15 of Appendix F of the full guideline CG173).
(b) The drug costs are taken from the NHS Electronic Drug Tariff[517]
(c) The mean daily dose for amitriptyline is 37.5 mg. This has been rounded up to 50 mg for the purpose of calculating the cost per dose, as this is the nearest whole-tablet dosage.
(d) The GDG advised that the administration costs of the drugs would be equal in a primary care setting, so these have excluded from the costs above.

### 16.3.5 Evidence statements

**Clinical [2015]**

Low quality evidence from a very small case-series (n=16) showed that compared with baseline, treatment for acute insulin induced neuritis using anti-epileptics alone or in combination with other medications, resulted in a 50% reduction in pain, occurring at a median of 15 months treatment, and an improvement in and resolution of some symptoms of the neuropathy. However, treatment of the neuropathy did not seem to have any beneficial effect on other complications of rapid glycaemic control in people with a long history of poor control, such as the further development of retinopathy

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or of low-level (micro) albuminuria. All outcomes were reported at either 6 months, 1 year, or 18 months

**Economic [2015]**

No relevant economic evaluations were identified.

### 16.3.6  Recommendations and link to evidence

<table>
<tr><td rowspan="2">**Recommendations**</td><td>

**144. Reassure adults with type 1 diabetes that acute painful neuropathy resulting from rapid improvement of blood glucose control is a self-limiting condition that improves symptomatically over time. [new 2015]**

**145.  Do not relax diabetes control to address acute painful neuropathy resulting from rapid improvement of blood glucose control in adults with type 1 diabetes. [new 2015]**

**146.  If simple analgesia does not provide sufficient pain relief for adults with type 1 diabetes who have acute painful neuropathy resulting from rapid improvement of blood glucose control, offer treatment as described in the NICE guideline on neuropathic pain – pharmacological management. Simple analgesia may be continued until the effects of additional treatments have been established. [new 2015]**

**147.  When offering medicines for managing acute painful neuropathy resulting from rapid improvement of blood glucose control to adults with type 1 diabetes, be aware of the risk of dependency associated with opioids. [new 2015]**

**148. Explain to the person that the specific treatments for acute painful neuropathy resulting from rapid improvement of blood glucose control:**

- **have the aim of making the symptoms tolerable until the condition resolves**
- **may not relieve pain immediately and may need to be taken regularly for several weeks to be effective. [new 2015]**

</td></tr>
<tr><td>

</td></tr>
<tr><td>Relative values of different outcomes</td><td>

To determine the optimum treatment for acute painful neuropathy of rapid glycaemic control in individuals with type 1 diabetes, the GDG reviewed whether the following UK licensed interventions had any influence on clinical outcome for the condition:

- Antidepressant therapies, including tricyclic antidepressants and duloxetine
- Anti-epileptic treatments, including gabapentin, pregabalin
- Analgesia, including opiates
- Topical therapies, including topical anaesthetics (lignocaine), capsaicin cream
- Intensive insulin therapy, including use of insulin pump

The impact of treatment interventions on acute painful neuropathy of rapid glycaemic control was assessed by the following clinical parameters:
Pain score: reported at baseline (after intensive glycaemic control) and at follow-up

- Improvement in pain scores: reported as duration of treatment for a 50 % reduction in perceived pain versus pre-intervention pain scores

</td></tr>
</table>

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| | |
|---|---|
| | • Time to resolution of symptoms: reported as neuropathy impairment scores in the lower limb at baseline and at 18 months post-treatment. |
| Trade off between clinical benefits and harms | The GDG recognised that acute painful neuropathy of rapid glycaemic control has a natural history of being a self-limiting condition. Although it is a result of rapid glycaemic control, the available evidence does not suggest that glycaemic control needs to be relaxed for resolution of the condition or symptomatic relief. The GDG therefore wanted clinicians to be confident in reassuring individuals diagnosed with the condition that they could expect their symptoms to improve with time, and not to relax glycaemic control in individuals diagnosed with the condition with all the potential deleterious effects that might follow from allowing higher blood glucose levels. |
| | Only one study specific to acute painful neuropathy of rapid glycaemic control was included in the evidence review (Gibbons 2010). The study assessed the impact of treatment interventions in 16 adults with diabetes (9 with type 1 diabetes) reporting acute onset of the painful neuropathy of rapid glycaemic control. All patients in the study had historically poor glycaemic control as a consequence of anorexia and/or treatment non-adherence before study entry. Treatments used in the study included tricyclic antidepressants (amitriptyline, nortriptyline or desipramine), anti-epileptics (gabapentin, pregabalin, lamotrigine or topirmate), and the analgesics tramadol and methadone. No more than two patients used the same combination of treatments in each intervention group, and therefore direct comparison of interventions was not possible. |
| | The available evidence did not indicate that any pharmaceutical intervention had an advantage over any other in the management of acute painful neuropathy of rapid glycaemic control. A 50 % reduction in pain was achieved at a median of 15 (range 12-28) months following treatment initiation. |
| | Treatment of neuropathy did not seem to have any beneficial effect on other complications of rapid glycaemic control in people with a long history of poor control, such as the further development of retinopathy or of low-level (micro) albuminuria. |
| | Clinical experience acquired by members of the GDG reflected that there was often a propensity for individuals diagnosed with painful neuropathies to be treated with opioid therapies, and that this might put a treated individual at risk of dependence. There was no evidence in the available literature to suggest that opioid therapies were any more effective than other therapeutic interventions in providing symptomatic relief. Given that acute painful neuropathy of rapid glycaemic control is normally a self-limiting condition, members of the GDG were keen to stress in their recommendations that alternative interventions be selected in preference to opioid therapies in the management of the condition. |
| | No evidence about the use of topical anaesthetics, capsaicin cream or insulin pump therapy was found in the literature review about the management of acute painful neuropathy of rapid glycaemic control. |
| Economic considerations | No economic evaluations about management of acute painful neuropathy of rapid glycaemic control were identified by the GDG. In order to make an assessment of the cost-effectiveness of the pharmaceutical interventions available for the management of neuropathic pain, the GDG referred to the relevant unit costs provided in NICE Care Guideline 173: 'Neuropathic pain – pharmacological management'[503]. |
| | As a result of the severity of the pain reported by individuals with acute painful neuropathy of rapid glycaemic control, the GDG recognised that a combination of medications might be used more readily in individuals with this conditions than that used for the management of chronic painful neuropathy. |
| | The GDG recognised that acute painful neuropathy of rapid glycaemic control is reported to be associated with a pain that is much more intense than that of chronic painful peripheral neuropathy experienced by individuals with long-term diabetes. Therefore, the GDG recognised that any reduction in subjective pain in individuals |

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| | |
|---|---|
| | was likely to produce a substantial improvement in quality of life. Given the cost of the treatment interventions available, all were likely to be of cost-benefit in the management of the condition. |
| Quality of evidence | Randomised controlled trial evidence about the management of chronic painful peripheral neuropathy in populations of adults with type 1 and type 2 diabetes was identified by the GDG but excluded from the review as they did not specifically address the management of acute painful neuropathy of rapid glycaemic control. Only one study specific to acute painful neuropathy of rapid glycaemic control was included in the evidence review (Gibbons 2010). This study was a case series design and therefore could not be GRADE rated. |
| Other considerations | The term "acute painful neuropathy of rapid glycaemic control" was preferred by the GCG over "insulin-induced neuropathy" or "insulin induced neuritis" to establish the link between a rapid fall in glycated haemoglobin and to avoid the implication that the condition is driven by insulin itself, for which there is no evidence. Expert opinion from the GDG recognised that acute painful neuropathy of rapid glycaemic control is an uncommon condition and that the natural history of the condition is that it is likely to resolve spontaneously, even when treatment is not administered. However, all members of the GDG acknowledged that individuals developing the condition subjectively reported pain that was of a high intensity, and that clinical interventions aimed at reducing the intensity of the pain were warranted. This guidance specifically addresses the management of acute painful neuropathy of rapid glycaemic control only, and not the management of chronic painful peripheral neuropathy experienced by a proportion of adults with long-standing type 1 diabetes. Nonetheless, the range of drugs available for treating the two conditions is the same, and the GDG therefore took note of NICE Guidance 173 [503], in addition to the more limited evidence available on acute painful neuropathy, in developing their recommendations. Although the SSRI-related antidepressant duloxetine was not included in the case series of Gibbons (2010), the GDG included it here because of evidence of benefit in other forms of painful neuropathy as recommended in NCG 173. |

149. **Use of simple analgesics (paracetamol, aspirin) and local measures (bed cradles) are recommended as a first step, but if trials of these measures are ineffective, discontinue them and try other measures. [2004]**

### 16.3.7 Research recommendations [2015]

33. **What is the clinical and cost-effectiveness of constructing a national database and centralising supervision of the management of adults with type 1 diabetes who have painful neuropathy of rapid glycaemic control?**

## 16.4 Thyroid disease –frequency of monitoring [2015]

### 16.4.1 Introduction

Thyroid disease is common in the general population, and the prevalence increases with age. The assessment of thyroid function by modern assays is both reliable and inexpensive. People with type 1 diabetes have a higher prevalence of thyroid disorders compared with the non-diabetic population in

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both cross-sectional and longitudinal studies. This is because patients with one organ-specific autoimmune disease are at increased risk of developing other autoimmune disorders. Thyroid disorders are more common in females and up to 30% of female with type 1 diabetes may have some thyroid disease (1). Transient thyroid dysfunction is common in the postpartum period and the rate of postpartum thyroiditis in those with diabetes is three times that in normal women (2).

The presence of thyroid dysfunction may affect diabetes control. Hyperthyroidism is typically associated with worsening glycaemic control and increased insulin requirements. There is underlying increased hepatic gluconeogenesis, rapid gastrointestinal glucose absorption, and probably increased insulin resistance. Treatment of the hyperthyroidism may increase the risk of hypoglycaemia in adults with type 1 diabetes, as insulin requirements fall. Though wide-ranging changes in carbohydrate metabolism are seen in hypothyroidism, clinical manifestation of these abnormalities is seldom conspicuous. However, the reduced rate of insulin degradation may lower the exogenous insulin requirement, increasing the risk of hypoglycaemia.

Thyroid dysfunction cannot be diagnosed solely on clinical manifestations.. The highly sensitive immunoassay for serum thyroid stimulating hormone or TSH, with a detection limit of less than 0.1 mU/litre, is commonly used to test for thyroid dysfunction and allows both hypothyroidism and hyperthyroidism to be diagnosed. Subclinical thyroid dysfunction may be diagnosed by an abnormal TSH, when serum T3 and T4 are near-normal and, by definition, the patients are asymptomatic. Given the potential for hypo- or hyperthyroidism to affect glucose control and the increased risk for autoimmune thyroid disease in people with type 1 diabetes, it is appropriate to screen for thyroid dysfunction in the adult type 1 diabetic population, as well as testing when there is a clinical indication of it. In addition to testing for biochemical evidence of thyroid dysfunction, tests are also available to detect the presence of autoimmune thyroid disease, including antibodies against thyroid antigens such as anti-TPO.

**The GDG therefore addressed these questions:**

- How should adults with type 1 diabetes be monitored for thyroid disease, and, in the absence of symptoms of thyroid disease, how frequently?
- In addition, the GDG examined the performance of the different tests available for screening adults with type 1 diabetes for thyroid disease.

### 16.4.2 New review question: How should adults with type 1 diabetes be monitored for thyroid disease, and, in the absence of symptoms of thyroid disease, how frequently?

For full details see review protocol in Appendix C.

**Table 181: PICO characteristics of review question**

| Population | Adults with type 1 diabetes |
| --- | --- |
| | • Adult defined as aged >18 years |
| Intervention/s | Thyroid disease monitoring |
| | Thyroid function tests |
| | Thyroid autoantibodies/antibodies (for example, peroxidase) |
| Comparison/s | • As for intervention but at a different frequency |
| | • Standard care/no monitoring |
| | • No comparison (non-comparative studies) |
| Outcomes | • Detection of thyroid disease |
| | • Incidence of thyroid disease |
| | • Frequency of treatment |
| Study design | RCTs, observational studies, prognostic studies, prevalence studies |

### 16.4.3    Clinical evidence

For this review on thyroid disease monitoring in adults with type 1 diabetes we searched for RCTs, observational studies, prognostic studies or prevalence studies that reported information on any of the following three topics:

- which tests should be used to monitor thyroid disease in a type 1 diabetes population?
- the prevalence of thyroid disease in a type 1 diabetes population
- the frequency of monitoring thyroid disease in a type 1 diabetes population

For topic one (which tests to use) and topic two (prevalence of thyroid disease) we found 22 relevant studies[26,69,75,105,150,182,213,256,279,353,361,400,446,540,554,571,585,705,725,728,740]. These studies included 7 cohort studies (retrospective or prospective, and prevalence in studies)[182,279,353,540,554,585,740], three cross-sectional studies (also prevalence information included in one study)[540,571,728] and 12 case studies (also prevalence information included in these studies)[26,69,105,150,213,256,361,400,446,705,725,755,757]. No studies were found directly addressing the remaining topic, the frequency of monitoring for thyroid disease in people with type 1 diabetes.

It was decided that studies with population size less than 20 were excluded from the review.

All studies were observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below.

**Table 182: Summary of studies included in the review for thyroid disease and type 1 diabetes**

| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| ALLEN 2008 [25,26] | Retrospective Case series  Evaluation of antiTPO and thyroid receptor antibody | n=328 (n=180 adult onset, n=148 childhood onset) type 1 diabetes | 5 years | TPO: Prevalence of positive TPO antibodies in childhood onset=11.8% (11/93) Prevalence of positive TPO antibodies was: 11.5% (13/113) in adult onset TRAB Prevalence of positive TRAB antibodies in childhood onset=1.9% (1/54) Prevalence of positive TRAB antibodies in adult onset=9.1%(5/55) |
| BIANCHI 1995 [69] | Case control (cross-sectional) study  Prevalence of thyroid nodules by ultrasound and also measurement of anti- | n=45 adults with type 1 diabetes without overt thyroid disease n=45 control group (matched for sex and age, residing in the same geographical area, admitted to department for functional | No follow-up reported | Cases vs. controls: Increased thyroid volume Prevalence of antimicrosome and antithyroglobulin antibodies=33% and 16% vs. 0% and 2% |

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| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| | thyroid antibodies | gastrointestinal tract or kidney disorders, and who did not have diseases known to influence thyroid function or size | | |
| CARDOSO 1995[105] | Case-control study Prevalence of thyroid autoantibodies  Thyroid function and prevalence of thyroid autoantibodies in an African diabetic population | n=40 type 1 diabetes n=60 type 2 diabetes n=100 control group | No follow-up reported | Cases vs. control: Prevalence of serum thyroid autoantibodies=46% type 1 diabetes (13/28) vs. 1.43% controls (1/70) T3 serum concentration in type 1 diabetes within normal range, lower than control group T4 serum concentration in type 1 diabetes within normal range ,lower than control group TSH concentration in type 1 diabetes within normal, higher than control group |
| DAGDELEN 2009[150] | Case control study  Prevalence of positive thyroid antibodies and clinical presentation of glutamate decarboxylase antibody, coeliac disease and thyroid disease | n=65 type 1 diabetes n=124 first degree relatives n=65 control group | No follow-up reported | Cases vs. controls: Prevalence of positive TPO antibodies= 24.6% (16/65) type 1 diabetes vs. 4.6% (3/65) controls Prevalence of positive TSH antibodies 1.5% (1/65) type 1 diabetes vs. 0% (0) in controls |
| DUFAITRE 2006[182] | Cohort study (prospective)  Prevalence of clinical and subclinical autoimmune diseases According to treatment type Continuous intraperitone | Adults with type 1 diabetes+ CIPII n=154 Adults with type 1 diabetes+ CSII n=121 | 1 year after inclusion | Clinical disease in treatment groups: CIPII group=8.4% (13/154) Hashimoto's thyroiditis and 1.3% (2/154) Graves' disease CSII group=7.5% (9/121) Hashimoto's thyroiditis and 2.5% (3/121) Graves' disease  Subclinical disease in treatment groups: TPO >60 ml/U in CIPII group= 25/9% (36/139) vs. CSII=30.6% |

| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| | al insulin infusion vs. continuous subcutaneous insulin infusion using an external pump | | | (33/108)<br><br>Incidence of autoimmune disease according treatment mode:<br>7.2% (5/69) developed TPO positivity in CIPII group vs. 7.3% (3/41) in CSII group at T=1<br><br>Prevalence and incidence regardless of treatment:<br>Whole group prevalence of thyroid disease=9.8% (clinical disease) and 28% (subclinical disease)<br>Combined total prevalence of clinical and subclinical autoimmune disease=31%<br>Combined total incidence of clinical and subclinical autoimmune disease=7.3%<br><br>No new cases after T=0<br><br>Prevalence of autoimmune disease is not correlated with age, duration of diabetes or duration of external or implanted pump treatment<br>Prevalence of thyroid autoimmune disease=41.1% in females and 20.5% in males |
| FIALKOW 1975[213] | Case series<br><br>Prevalence thyroid autoantibodies<br><br>Evaluation of insulin status | n=52 type 1 diabetes (n=1 Graves' disease n=1 Surgery or goitre or both)<br><br>n=48 type 2 diabetes (n=1 hypothyroidism) | Duration=2 years | Prevalence of clinical disease:<br>Prevalence of thyroid antibodies type 1 diabetes =35% (18/52)<br><br>Prevalence of type 1 diabetes and Graves' disease= 1.9% (1/52), type 1 diabetes and Hashimoto's thyroiditis=1.9% (1/52)<br>20-39 year subgroup:<br>60% (18/30) patients tested positive for thyroid antibodies:<br>23% (7/30)= TPO+ (low titre)<br>4/30= TPO+ (high titre),<br>5/30=TGab+ (low titre),<br>2/30=TGab+ (high titre)<br><br>40-59 year subgroup:<br>27% (6/22) patients tested positive for thyroid antibodies:<br>27% (2/22)= TPO+ (low titre)<br>27% (2/22)= TPO+ (high titre),<br>27%(2/22)=TGab+ (low titre), |

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| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| | | | 495 | 27 %(0/22)=TGab+ (high titre)<br><br>Frequencies of antibodies to thyroglobulin and to thyroid cytoplasm were equally elevated in type 1 diabetes<br><br>Presence of antibodies was not correlated significantly with duration of disease or of insulin therapy |
| GOMEZ 2003[256,257] | Case control<br><br>Prevalence<br><br>Measurement of thyroid volume by ultrasonography | n=65 adults with newly diagnosed type 1 diabetes<br><br>n=65 healthy matched controls | Recruited over4 years | Basal TSH levels in type 1 diabetes males and females vs. control group:<br>Type 1 diabetes males =1.6%±1.14 vs. control group=1.5%±0.78 (95%CI -0.56 to 0.41; P=0.76)<br><br>Type 1 diabetes females=1.69%±1.08 vs. control group=1.59%±0.96 (P=0.48) |
| HANUKOGLU 2003[279] | Cohort study<br>Prevalence<br>Prevalence rates of autoimmune thyroiditis diagnosed by abnormally high TPO and Tg antibodies | Probands=109<br>Relatives screened=100<br>Relatives interviewed=312<br>Control subjects=78 | Study over 3 years | Prevalence of autoimmune thyroid disease as determined by positive TPO<br>and/or TG antibody rates among type 1<br>diabetes probands was 27%, with 6%<br>of those being hypothyroid<br><br>The corresponding rates among screened first-degree relatives (positive<br>TPO and/or TG 25%, hypothyroid Hashimoto<br>disease 8%) did not significantly differ from the rates found in probands, but were higher than rates in control subjects<br><br>The frequencies of positive TPO and<br>TG antibodies alone and together were<br>18, 19, and 11%, respectively, in probands.<br>The corresponding rates among first-degree relatives were quite similar<br>(19, 17, and 10%, respectively) |

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| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| | | | 496 | TPO titres in three control subjects were only slightly elevated (1/84, 1/118, and 1/98), in most probands and family members TPO was elevated ( 5-fold in 13 probands and 12 relatives and 2.5-fold in 3 probands and 6 relatives) In first degree relatives who were screened, medical history revealed pre-existing Hashimoto thyroiditis in five and Graves disease in one The frequency of pre-existing autoimmune thyroiditis detected by interview only, was low (1%) Probands with Hashimoto thyroiditis did not have more relatives with positive antibodies than probands with normal antibody titres. Among 50 probands whose relatives were screened, 12 probands with thyroiditis had 8 relatives with positive antibodies and 13 relatives with normal antibody titres. Among 13 probands without thyroiditis, the corresponding numbers were 16 (positive) and 17 (normal) relatives |
| JIN 2011[353] | Cohort study (prospective) Prevalence Evaluation of genetic and immunological factors involved in the development of thyroid | n=190 type 1 diabetes n=135 LADA | 4 years | Prevalence of thyroid antibodies at start type 1 diabetes: TGab =23.7% TPOab =24.7% Prevalence of thyroid antibodies at 4 years follow-up type 1 diabetes: TGab=24.5% TPOab =25.5%. Prevalence of thyroid antibodies at start in LADA: TGab=16.3% TPOab =18.5% Prevalence of thyroid antibodies at |

| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| | autoimmunity | | | 4 years follow-up in LADA: TGab=17.7% TPOab=20.0% |
| JUNIK 2006[361] | Case control study<br><br>Intervention: ultrasound, TSH, T4, free T3, Free T4 | n=30 type 1 diabetes<br>n=98 type 2 diabetes<br>n=50 matched controls treated in department at same time for diseases other than diabetes mellitus and thyroid disorders | No follow-up | Ultrasound and thyroid volume (type 1 diabetes vs. control group):<br>type 1 diabetes = 20% relative increase in thyroid volume vs. control group<br>Thyroid volume exceeded reference range for 13% (4/30) type 1 diabetes vs. 3% (1/38) control group<br>Hormone measurement (type 1 diabetes vs. control group):<br>7% (2/30) type 1 diabetes = subclinical hyperthyroidism vs. 3% (1/38) control group<br>3% (1/30) type 1 diabetes =subclinical hypothyroidism vs. 5% (2/38) control group<br>TSH levels =0.97 (range 0.61-1.58) mIU/litre type 1 diabetes vs. 1.66 (range 0.76-2.09) mIU/litre control group |
| KUCERA 2003[400] | Case-control study<br>Prevalence of thyroid autoantibodies | n=153:<br>n=68 type 1 diabetes<br>n=85 type 2 diabetes<br>n= 62 controls selected randomly from a common population of older people and from a senior's home with no signs of severe metabolic disease, matched by age and sex | No Follow-up reported | Prevalence of thyroid autoantibodies:<br>8.82% (6/68) type 1 diabetes =positive thyroglobulin antibodies vs. 3.5% (3/85) type 2 diabetes 22.1% (15/68) type 1 diabetes =positive TG antibodies vs. 9.4% (8/85) type 2 diabetes<br><br>Prevalence of positive thyroglobulin and TPO antibodies=higher in type 1 diabetes group vs. type 2 diabetes group |
| LUPI 2013[446] | Case control study<br><br>Assessment of antiTPO, antiTG<br>type 1 diabetes with Hashimoto's thyroiditis or Graves' | n=111 adults with type 1 diabetes<br>n=110 type 2 diabetes<br>n=214 controls | No follow-up reported | Clinical disease in type 1 diabetes:<br>Hashimoto's disease =31% (35/111)<br>Grave's disease=6% (7/111) |

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| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| | disease | | | |
| PALMA 2013[540] | Cohort study (cross-sectional)<br><br>Prevalence of thyroid dysfunction by testing for anti-TPO, FT4 and TSH | n=386:<br>n=82 type 1 diabetes<br>n=304 type 2 diabetes | Follow-up not reported | Prevalence thyroid antibodies in type 1 diabetes:<br>Anti-TPO positivity=14.6% (12/82) vs. 9.9% (30/304) type 2 diabetes<br>Subclinical hypothyroidism without previous thyroid disease =13%<br>Incidence of new subclinical hypothyroidism without prior thyroid disease =13% (9/70)<br>Thyroid hormones in type 1 diabetes:<br>TSH and FT4 levels = normal range in type 1 diabetes with prior thyroid disease was 50% (6/12) |
| PERROS 1995[554] | Cohort study (prospective)<br>Assessment of prevalence and incidence of thyroid dysfunction | n=1310:<br>n=406 adults with type 1 diabetes<br>n=904 type 2 diabetes | Blood tests at year 1 after recruitment, and then retested after 12 months | Prevalence of thyroid disease:<br>Overall 13% (176/1310) of study population had previous or present thyroid disease<br>Prevalence of thyroid disease in type 1 diabetes males was 12.4% and type 1 diabetes females was 31.4%, prevalence peak at 60-70 years of age<br>Annual incidence of new thyroid disease:<br>New thyroid disease =6.7% (89/1310)<br><br>Annual risk of thyroid disease =12.3% in type 1 diabetes females<br><br>Thyroid antibodies:<br>64% study population =positive thyroid antibodies<br>80% hypothyroid cases=positive thyroid antibodies<br>44.4% hyperthyroid cases=positive thyroid antibodies<br>90.9% sub clinical hypothyroid cases=positive thyroid antibodies<br><br>Clinical management influence in 4% (49/1310) of the study population |
| PRAZNY 1999[571] | Cross-sectional study<br>Evaluation of thyroid and islet | n=55 type 1 diabetes | No follow-up | Thyroid autoantibodies:<br>18% (10/55) patients had positive anti-TPO antibodies |

| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| | autoantibodies | | | |
| RATTARASA RN 2000[585] | Cohort study Clinical significance of thyroid autoantibodies Prediction of thyroid dysfunction in Thai patient group | n=50 type 1 diabetes n=29 non-diabetic patients with hyperthyroid Graves' disease or Hashimoto's thyroiditis as control group | Up to 3 years | Thyroid autoantibodies: 18% (9/50)=TGab positivity 30% (15/50)=TPOab positivity 16% (8/50)= positive for both antibodies

2/16 type 1 diabetes with positive TGab or TPOab had hyperthyroidism before diabetes onset

2 patients newly diagnosed hyperthyroidism (1 patient with clinical hypothyroidism and elevation of serum TSH; 1 patient with mild elevation of serum TSH without hypothyroidism)

In 8 patients with TGab or TPO positivity and without thyroid dysfunction (2 patients developed hypothyroidism during follow-up 19±8 months; serum TSH increased from 10.0 to 20.75 mU/litre after 20 months in 1 patient and 4.64 to 33.87 mU/litre after 35 months in another patient)

21 patients tested for thyroid antibodies remained negative for thyroid dysfunction during 16.4±6.3 months follow-up

3/14 type 1 diabetes patients without previous a previous history of thyroid diseases had a significantly higher frequency of thyroid dysfunction at the start of the study and tended to have a higher risk of developing thyroid dysfunction up to approximately 3 years of follow-up

Antibody positivity was higher in females than males |
| UMPIERREZ 2003[705] | Case series (prospective) Evaluation of thyroid status and presence | n=58 type 1 diabetes | 18 years (TSH, thyroxine and triiodothyronine measured every | Prevalence of clinical disease and thyroid antibodies: 18/58 patients had hypothyroidism Hypothyroidism was more common in females (41%) than males (19%) |

| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| | of TPO antibodies | | year TPO antibodies measured at 4 year intervals) | and in patients with positive TPO antibodies Type 1 diabetes with TPO positive antibodies were 18 times more likely to develop hypothyroidism

Presence of TPO antibodies was associated with an increased risk of hypothyroidism Most patients with positive TPO antibodies at the beginning of the study remained positive throughout the study One patient who was negative for TPO antibodies developed low TPO titres after 12 years follow-up No differences in TSH values on diagnosis of hypothyroidism between patients with positive or negative antibodies |
| VONDRA 2004[725] | Case series (prospective)

Subgroups of patients were compared over 12 years thyroid autoantibodies | n=109 adults with type 1 diabetes Subgroup 1: positive for both thyroid autoantibodies Subgroup 2: Positive antiTPO antibody only Subgroup 3: thyroid autoimmunity not present) | 12 years | Clinical disease, thyroid antibodies, and thyroid hormones: Cumulative incidence of positivity of thyroid antibodies during 12 follow-up was 51% Hypoechogenic thyroid was detected in 59% of group 1 compared with 25% of group 2 TSH levels above 4.5 mlU/litre were found in 30% of group 1 compared with 7% of group 2 At 4 years of follow-up, subclinical hypothyroidism was found in 100% of group 1 compared with 11% of group 2 Cumulative incidence peaked in group 1 during 4-12 years of follow-up of antiTPO and antiTgI positivity (25%) compared with 9-12 years antiTPO positivity (26%) in group 2 |
| WALTER 2007[728] | Cross-sectional study Prevalence of autoimmune disease in type 1 diabetes | n=124 type 1 diabetes | No follow-up reported | Prevalence of thyroid disease: 31% (38/124) of type 1 diabetes patients had thyroid disease The detection rate for new cases as 5.8% (true prevalence 35%) Thyroid disease was more common in women than men (33/77 vs. 10/47) |
| WHITEHEAD 2010[740] | Cohort study. Prevalence Screening for | n=400 type 1 diabetes n=400 type 2 | Type 1 diabetes (median range) 9.5 years | Prevalence of clinical hypothyroidism: Prevalence of autoimmune |

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| Study | Intervention/ comparison | Population | Follow-up | Results |
|---|---|---|---|---|
| | hypothyroidism | diabetes | | hypothyroidism (including subclinical hypothyroidism) in type 1 diabetes was 10.8% (43/400) Prevalence of hypothyroidism requiring thyroxine treatment in type 1 diabetes was 6.8%, and increased with age, particularly after 50 years age Dose of treatment: Average dose of thyroxine replacement in type 1 diabetes patients requiring thyroxine treatment was 134ug (SD 62) Routine thyroid hormone testing done at annual review detected hypothyroidism requiring thyroxine treatment in 1.8% of patients with type 1 diabetes. |
| YAMAGUCHI 199[754,755] | Case control Investigation of islet cell antibodies and insulin dependent diabetes in patients with autoimmune disease Prevalence of insulin dependent diabetes in Japan | n= 316 patients with autoimmune disease Group I: type 1 diabetes +Graves' disease Group II: type 1 diabetes +Hashimoto's thyroiditis Group III: type 1 diabetes only Group IV: healthy control group | Study duration=6 years | Prevalence of thyroid autoantibodies: 87.5% (18/21) type 1 diabetes patients were positive for anti-thyroidal autoantibodies |
| YASMIN 2006[757] | Case control study | n=163: n=51 type 1 diabetes n=61 type 1 diabetes n=51 controls | Followed for 1 year from recruitment | Thyroid antibodies: 39% had normal anti-TPO levels, 21% had mild level of anti-TPO, 20% had moderate levels of anti-TPO 20% had high levels of anti-TPO. Levels of anti-TPO and TSH in type 1 diabetes were higher than in the control group Thyroid hormones: Levels of FT4 were lower in the type 1 diabetes compared with the control group |

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**Table 183: Summary table showing the prevalence results from all the studies.**

| Study | Frequency of monitoring | Thyroid auto anti-body positive | Hashimoto's disease | Graves' disease | Sub-clinical/clinical hypothyroidism | Sub-clinical/ clinical hyperthyroidism | TPO antibody positive | Tg antibody positive | TSH positive | FT4/T4 positive | T3/ FT3 positive | TRAB (receptor antibody) positive |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ALLEN 2008 (childhood onset and adult onset type 1 diabetes) | | | | | | | 11.5% (adult onset) 11.8% (child onset) | | | | | 9.1% (adult onset) 1.9% (child onset) |
| BIANCHI 1995 (type 1 diabetes with no previous thyroid disorder) | | | | | | | 33% | 16% | 8.8% =below detection threshold (Ab negative) | 8.8% high FT4 | 8.8% high FT3 | |
| CARDOSO 1995 (adult onset of type 1 diabetes) | | 46.6% | | | | | | | | | | |
| DAGDELEN 2009 (adult onset of type 1 diabetes) | | | | | | | 24.6% | | 1.5% | | | |

| Study | Frequency of monitoring | Thyroid auto anti-body positive | Hashimoto's disease | Graves' disease | Sub-clinical/clinical hypothyroidism | Sub-clinical/clinical hyperthyroidism | TPO antibody positive | Tg antibody positive | TSH positive | FT4/T4 positive | T3/FT3 positive | TRAB (receptor antibody) positive |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DUFAITRE 2006 (unclear onset of type 1 diabetes) | Monitored at 1 year after inclusion, No new cases of autoimmune disease recorded at 1 year FU | | 8.4% (CIPII patients) 7.4% (CSII patients) | 1.3% (CIPII patients) 2.4% (CSII patients) | Subclinical disease (all patients): 28% | | 25.9% (CIPII patients) 30.6% (CSII patients) | | | | | |
| FIALKOW1975 (unclear duration of type 1 diabetes) | | 35% 40-59 years: 9% | | 1.9% | | | 20-30 years: positive and low titre= 23.3%; positive and high titre= 13% | 20-30 years: positive and low titre= 16.6%; positive and high titre= 6% | | | | |
| GOMEZ 2003 (newly diagnosed type 1 diabetes) | | | | | | | | | Basal level: 1.6% (men); 1.7% (women) | | | |
| HANUKOGLU 2003 (type 1 diabetes | . | Probands =27% First- | | 0 | | | Probands=18% First-degree relatives=19% | Probands =19% First | | | | |

| Study | Frequency of monitoring | Thyroid auto anti-body positive | Hashimoto's disease | Graves' disease | Sub-clinical/clinical hypothyroidism | Sub-clinical/ clinical hyperthyroidism | TPO antibody positive | Tg antibody positive | TSH positive | FT4/T4 positive | T3/FT3 positive | TRAB (receptor antibody) positive |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| diagnosed before 18 years age) | | degree relatives= 25% | | | | | | degree relatives= 17% | | | | |
| JIN 2011 (late onset of type 1 diabetes) | TPO At 4 years =25.5% Tg At 4 years =24.5% | Baseline= 27.4% 95% patients Ab positive at baseline were also positive during FU | | | 9.5% | | Baseline= 24.7% | Baseline= 23.7% | | | | |
| JUNIK 2006 (unclear onset and duration of type 1 diabetes) | | | | | Subclinical: 3% | Subclinical: 7% | Normal range | | | | | |
| KUCERA 2003 (late onset of type 1 diabetes) | | | | | | | 22.1% | 8.8% | | | | |
| LUPI 2013 (unclear | | | 31.5% | 6.3% | | | | | | | | |

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| Study | Frequency of monitoring | Thyroid auto anti-body positive | Hashimoto's disease | Graves' disease | Sub-clinical/clinical hypothyroidism | Sub-clinical/ clinical hyperthyroidism | TPO antibody positive | Tg antibody positive | TSH positive | FT4/T4 positive | T3/FT3 positive | TRAB (receptor antibody) positive |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| onset of type 1 diabetes) | | | | | | | | | | | | |
| PALMA 2003 (Adult onset of type 1 diabetes) | | | | | Subclinical without dysfunction: 13% | | 14.6% | | | | | |
| PERROS 1995 (Adult onset of type 1 diabetes) | Annual incidence of new thyroid disease=6.7% | | | | 5.9% (men); 14.5% (women)-hypothyroidism  Sub-clinical: 5.4% (men); 9.5% (women) | 1.1% (men); 6.4% (women)-hyperthyroidism  Sub-clinical: 0% (men) 0.9% (women) | | | | | | |
| PRAZNY 1999 (Adult onset of type 1 diabetes) | | | | | | | 14% (men); 21% (women)  11% positive for both TPO and TgAb | Higher in women | | | | |
| RATTARASARAN 2000 (Childhood and adult | At 19 months FU: TGab or TPO | 16% | | | | | 30% | 18% | | | | |

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| Study | Frequency of monitoring | Thyroid auto anti-body positive | Hashimoto's disease | Graves' disease | Sub-clinical/clinical hypothyroidism | Sub-clinical/clinical hyperthyroidism | TPO antibody positive | Tg antibody positive | TSH positive | FT4/T4 positive | T3/ FT3 posit ive | TRAB (recep tor antibo dy) positiv e |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| onset of type 1 diabetes) | without obvious thyroid disease=25 %<br><br>At 20 months FU: 13% elevated TSH<br><br>25% were at higher risk of developing thyroid dysfunction at 3 years FU | | | | | | | | | | | |
| UMPIEREZ 2003 (Adult onset of type 1 diabetes) | Patients TPO+ 17.9x likely to develop hypothyroi dism vs. TPO-patients. | | | | Average: 31%<br><br>19% (men); 44% (women) | | | | | | | |
| VONDRA 2004 | Annual new cases of | | | | | | 26% (group 1 TPO positive only) | | | | | |

| Study | Frequency of monitoring | Thyroid auto anti-body positive | Hashimoto's disease | Graves' disease | Sub-clinical/clinical hypothyroidism | Sub-clinical/clinical hyperthyroidism | TPO antibody positive | Tg antibody positive | TSH positive | FT4/T4 positive | T3/FT3 positive | TRAB (receptor antibody) positive |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (Newly diagnosed type 1 diabetes) | TPO+ during FU = 26% (at year 9); 0% (at years 10, 11, and 12) Cumulative incidence of positive TPO and Tg=25% in the study and at FU | | | | | | 25% (group 2 TPO+Tg positive) | | | | | |
| WALTER 2007 (Adult onset of type 1 diabetes) | | Autoimmune thyroid disease=31% More common in women (43%) vs. men (21%) | | | | | | | | | | |
| WHITEHEAD 2010 (Adult | Annual thyroid hormone testing to | | | | 10.8% Subclinical: 4% Hypothyroidism | 1% Hypothyroidism requiring | | | | | | |

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| Study | Frequency of monitoring | Thyroid auto anti-body positive | Hashimoto's disease | Graves' disease | Sub-clinical/clinical hypothyroidism | Sub-clinical/clinical hyperthyroidism | TPO antibody positive | Tg antibody positive | TSH positive | FT4/T4 positive | T3/FT3 positive | TRAB (receptor antibody) positive |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| onset of type 1 diabetes) | detect hypothyroidism for thyroxine treatment= 1.8% | | | | due to surgery: 2% | Thyroxine treatment: increased with age after 50 years | | | | | | |
| YAMAGUCHI 1991 (Adult onset of type 1 diabetes) | | 87.5% | | | | | | | | | | |
| YASMIN 2006 (childhood and adult onset of type 1 diabetes) | | | | | | | 61% Higher in women | | | 84% | | |
| MEDIAN % (RANGE) | | 33% (16 - 88) | 8.4% (7.4 – 31.5) | 2.2% (1.3– 6.3) | SUBCLINICAL (all): 4% (3-13) SUBCLINICAL (men): 5.4% (5.4) SUBCLINICAL (women): 9.5% (9.5) CLINICAL (all): 10.8% (6-31) | SUBCLINICAL (all): 7% (7) SUBCLINICAL (men): 0% (0) SUBCLINICAL (women): 0.9% (0.9) CLINICAL (all): | 25.9% (11.5 – 61) Higher in women; similar for child and adult onset | 16% (6-23.7) Higher in women | 1.6% (1.5 – 1.7) Similar in men and women | 46% (8.8 – 84) | 8.8% (8.8) | 5.5% (1.9 - 9.1) Lower in child onset |

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| Study | Frequency of monitoring | Thyroid auto anti-body positive | Hashimoto's disease | Graves' disease | Sub-clinical/clinical hypothyroidism | Sub-clinical/clinical hyperthyroidism | TPO antibody positive | Tg antibody positive | TSH positive | FT4/T4 positive | T3/FT3 positive | TRAB (receptor antibody) positive |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CLINICAL (men): 12.5% (5.9-19) CLINICAL (women): 29.3% (14.5-44)  Higher in women | 1% (1) CLINICAL (men): 1.1% (1.1) CLINICAL (women): 6.4% (6.4)  Higher in women | | | | | | |

*Percentages are the prevalence of people with type 1 diabetes who had the marker or disease of interest.*

### 16.4.4 Economic evidence

**Published literature**

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

### 16.4.5 Evidence statements

**Clinical**

**16.4.5.1 Prevalence of thyroid antibodies ([25,26], [69], [105], [150], [182], [213], [279], [571], [585], [705], [725], [754,755], [757])**

- Low quality evidence from 7 studies reported prevalence of multiple thyroid autoantibodies in type 1 diabetes patients and ranged from 1.43% to 87.5 %.[69,105], [213], [554], [585], [754,755],

- Low quality evidence from 6 studies reported prevalence of antiTPO positivity of 11.5%, 14.6%, 18%, 22.1%, 24.6%, and 30% in type 1 diabetes patients [25,26], [150], [540], [585], [571], [400] and one study reported 21% type 1 diabetes with mild levels of ant-TPO antibody, 20% type 1 diabetes patients with moderate levels of anti-TPO antibody, and 20% type 1 diabetes patients with high levels of anti-TPO antibody.[757]

- Low quality evidence from one study reported prevalence of autoimmune thyroiditis determined by high TPO and/or Tg titres was 27 and 25% for probands and relatives respectively. [279]

- Low quality evidence from one study reported 23% type 1 diabetes patients (20-39 years) with low and 13% with high levels of anti-TPO antibody.[213] In the older subgroup (40-59 years) with type 1 diabetes, 27% had low and 27% had high levels of anti-TPO antibody. This study also showed an increase in anti-TPO antibodies in type 1 diabetes patients over 4 years from 24.7% to 25.5%.

- Low quality evidence showed that the presence of TPO antibodies was associated with an increased risk of hypothyroidism; type 1 diabetes patients with TPO positive antibodies were 18 times more likely to develop hypothyroidism. Most patients with positive TPO antibodies at the beginning of the study remained positive throughout the study.[705],

- Low quality evidence from one study showed that the prevalence of anti-TPO antibody positivity was higher in females than males.[585]

- Low quality evidence from two studies reported prevalence of thyroglobulin antibody positivity of 8.8% and 18%.[400], [571]

- Low quality evidence from one study reported 17% type 1 diabetes patients (20-39 years) to have low levels of thyroglobulin antibody positivity and 6.6% type 1 diabetes patients to have high levels of thyroglobulin antibody positivity compared with higher levels in 40-59 years subgroup of type 1 diabetes patients (27% low levels and 27% high levels of thyroglobulin antibody positivity).[213]

- Low quality evidence from one study reported a prevalence of 23.7% of thyroglobulin antibody positivity at the start of the study which increased to 24.5% prevalence after 4 years.[353]

**16.4.5.2 Prevalence of thyroid hormones [105], [150], [256,257], [361], [540], [725], [757]**

- Low quality evidence from one study reported prevalence of positive TSH to be higher in patients with type 1 diabetes compared with the control group.[150]

- Low quality evidence from one study reported FT4 and TSH concentrations to be lower in type 1 diabetes compared with control group

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- Low quality evidence from two studies reported FT4 and TSH levels to be within the normal range in 50% patients.[540] with type 1 diabetes and also in type 1 diabetes patients with previous thyroid disease [554]

- Low quality evidence from one study reported T3 and T4 concentrations to be within normal range, but lower than in the control group, and TSH concentration was within normal range but higher than in the control group.[105]

- Low quality evidence from one study reported TSH levels above 4.5mU/litre in 30% of patients who were positive for both thyroid antibodies compared with 7% of patients who were positive for TPO antibody only.[725]

- Low quality evidence from one study reported TSH levels to be lower in type 1 diabetes patients (0.97 (range 0.61-1.58) mlU/litre) compared with control group (1.66 (range 0.76-2.09) mlU/litre).[361]

- Low quality evidence from one study showed that basal levels of TSH were higher in females compared with males (1.6%±1.14 versus 1.69%±1.08) and higher in type 1 diabetes patients compared with the control group (type 1 diabetes males =1.6%±1.14 versus control group=1.5%±0.78; type 1 diabetes females=1.69%±1.08 versus control group=1.59%±0.96).[256,257]

### 16.4.5.3 Prevalence of thyroid disease [182], [213], [446], [554], [705], [725], [728], [740]

- Low quality evidence from one study reported 31% type 1 diabetes patients to have thyroid disease. [728]

- Low quality evidence from two studies reported overall prevalence of previous or present thyroid disease was 13% [554] and 9.8% [182]. The combined total prevalence of clinical and subclinical disease was 31%. [182]

- Low quality evidence from one study reported hypo-echogenic thyroid in 59% type 1 diabetes patients positive for both thyroid antibodies. At 4 years follow-up, 100% of people with type 1 diabetes who were positive for both TPO and Thyroglobulin antibodies had subclinical hypothyroidism compared with 11% of those with type 1 diabetes positive for TPO antibody only.[725]

- Low quality evidence from two studies reported prevalence of 10.8% and 31% for hypothyroidism (including subclinical hypothyroidism) in patients with type 1 diabetes.[740], [705]

- Low quality evidence from three studies reported that prevalence of thyroid disease was higher in females (43%, 41%, and 31.4%) than males (21%, 19%, and 12.4%).[728], [554], [740]

- Low quality evidence showed that the prevalence of Hashimoto's thyroiditis (two studies) was 31% and 1.9%, and Graves' disease 6% and 1.9% in type 1 diabetes patients.[446], [213]. In another study the prevalence of Hashimoto's thyroiditis was 8.4% and 7.5%, and 1.4% and 2.5% for Graves' disease in type 1 diabetes patients treated different insulin treatments.[182]

- Low quality evidence from one study reported that prevalence of autoimmune disease was not correlated with age, duration of diabetes or duration of treatment. [182]

### 16.4.5.4 Tests for monitoring thyroid disease[705,740]

**T4, T3, TSH tests**

The tests used in the included studies were T4, T3, TSH, with TSH and T4 measured more frequently

- Low quality evidence from one study, that measured TSH, T3, T4 every year, and TPO antibody every 4 years, over an 18 year period. Presence of TPO antibodies was associated with an increased risk of hypothyroidism. Most patients with positive TPO antibodies at the beginning of the study remained positive throughout the study. One patient who was negative for TPO

antibodies developed low TPO titres after 12 years follow-up. No differences in TSH values on diagnosis of hypothyroidism between patients with positive or negative antibodies. [705]

- Low quality evidence from one study found that routine thyroid hormone testing done at annual review detected hypothyroidism requiring thyroxine treatment in 1.8% of patients with type 1 diabetes. [740]

#### 16.4.5.5 Antibody tests [26,182,213,353,554,585,725,757]

Tests for thyroid disease studies included anti-TPO and anti-thyroglobulin positivity.

- Low quality evidence from one study that measured anti-TPO positivity in type 1 diabetes patients over 4 years and resulted in mild increase in the number of patients that were positive either anti-TPO or anti-TG antibodies.[353]

- Low quality evidence from one study that measured anti-TPO antibody in type 1 diabetes patients over 5 years and reported positive antibodies in 13 patients.[25,26]

- Low quality evidence from one study that measured anti-TPO antibody over one year and reported that anti-TPO positivity developed in 7.2% after one year.[182]

- Low quality evidence from one study that measured anti-TPO and anti-TG antibodies over two years reported that frequencies of antibodies to thyroglobulin and TPO were equally elevated. [213]

- Low quality evidence from one study that measured thyroid antibodies over one year and reported an annual risk of thyroid disease of 12.3% in females with type 1 diabetes. The annual incidence of new thyroid disease was 6.7%. Clinical management was influenced in 4% of the study group. [554]

- Low quality evidence from one study in patients with TGab or TPO positivity and without thyroid dysfunction, found that 2 patients developed hypothyroidism during follow-up 19±8 months; serum TSH increased from 10.0 to 20.75 mU/litre after 20 months in 1 patient and 4.64 to 33.87 mU/litre after 35 months in another patient. 21 patients tested for thyroid antibodies remained negative for thyroid dysfunction during 16.4±6.3 months follow-up. Subjects with positive antibodies had a higher risk of developing thyroid dysfunction up to approximately 3 years of follow-up.[585]

- One study measured thyroid antibodies over 12 years and reported cumulative incidence of positivity of thyroid antibodies during 12 follow-up of 51%. Hypoechogenic thyroid was detected in 59% type 1 diabetes patients positive for both antibodies compared with 25% type 1 diabetes patients who were positive for one antibody. TSH levels above 4.5 mlU/litre were found in 30% type 1 diabetes patients positive for both antibodies compared with 7% type 1 diabetes patients who were positive for one antibody. At 4 years of follow-up, subclinical hypothyroidism was found in 100% o type 1 diabetes patients positive for both antibodies compared with 11% type 1 diabetes patients who were positive for one antibody. Cumulative incidence of concomitant positivity of both antibodies (anti-Tgl and antiTPO) in type 1 diabetes patients, peaked at 25% in year 8 of follow-up and did not change during the remaining 4 years of the 12 years total follow-up time. In patients with type 1 diabetes who were only positive for antibody (anti-TPO), the cumulative incidence of positivity varied over the follow-up period and peaked at 26% at year 9, and did not change and did not change during the remaining 3 years of the 12 years total follow-up time.[725]

- One study measured thyroid autoantibodies for one year after recruitment and reported 39% with normal anti-TPO levels, 21% with low levels of anti-TPO, 20% with moderate levels of anti-TPO, 20% with high levels of anti-TPO. Measurement of T4 was lower, and TSH and TPO were higher in subjects with type 1 diabetes compared with a control group without diabetes.[757]

**Economic**

No relevant economic evaluations were identified.

## 16.4.6 Recommendations and link to evidence

| | **150. Measure blood thyroid-stimulating hormone (TSH) levels in adults with type 1 diabetes at annual review. [new 2015]** |
|---|---|
| **Recommendations** | |
| Relative values of different outcomes | The GDG agreed that the purpose of this question was to look at the detection of. This is because adults with autoimmune type 1 diabetes are at increased risk for primary auto-immune thyroid disease and the detection of subclinical disease will allow appropriate treatment to start without delay. Secondary causes of thyroid disease are much less common and not specific to adults with type 1 diabetes. Their routine detection may be more complex, especially if thyroid function monitoring is by measurement of TSH alone, and this does not fall within the remit of routine diabetes management. Among primary thyroid diseases, hypothyroidism is more common than hyperthyroidism, but the screening tests are the same for both and both were considered |
| | Ideally this question would be informed by RCTs evaluating different screening strategies for thyroid disease against one another and against no screening. No such RCTs were found. The GDG therefore looked for cohort studies, case-control studies or observational studies which provided data about the incidence of thyroid disease in people with type-1 diabetes. Data on frequency of testing were also sought, but no study was found that directly addressed this. |
| | The marker of thyroid disease used was different between studies. Some looked at clinical thyroid disease, some at thyroid antibodies (presence of thyroid antibodies is an established risk factor for development of thyroid disease), some at abnormal thyroid function tests (TSH +/- thyroid hormones) and some at combinations of these. The GDG agreed that it was appropriate to consider detection before thyroid disease is clinically apparent, because sub-clinical disease has a very high rate of conversion to clinical disease which can be avoided with appropriate treatment. |
| | The data of particular interest were therefore: |
| | Rate of development of thyroid auto-antibodies (thyroid Ab) over time in people with type 1 diabetes |
| | Rate of development of abnormal thyroid function tests (TFT) over time in people with type 1 diabetes |
| | The relationship between these two, that is, how reliably does the development of thyroid Ab predict the development of abnormal TFT, and what is the associated time-scale. This is relevant to the issue of whether both thyroid Ab and TFT need to be measured. |
| Trade off between clinical benefits and harms | The studies confirmed the expected high prevalence of thyroid dysfunction in people with type 1 diabetes. Many of the studies reported at one time point only. Among the studies which reported thyroid Ab and/or TFT results at more than one time point, it was noted that: |
| | Perros[554] re-measured TFT at 12 months in 1,310 adult diabetic patients (the largest cohort in the available evidence) including 406 with type 1 diabetes. The incidence of new thyroid disease (clinical plus sub-clinical) at 12 months was 6.7% |
| | Jin [353] found a positive TPO antibody test in 24.7% of 190 patients with type 1 diabetes. At re-test 4 years later this had risen only slightly to 25.5%, and virtually all of the positive results were in those who had been positive at first test (95% remained Ab positive). Less than 1% of the antibody negative subjects became positive. |
| | Vondra[725] followed 109 subjects with type 1 diabetes for 12 years. Those with |

| Recommendations | 150. Measure blood thyroid-stimulating hormone (TSH) levels in adults with type 1 diabetes at annual review. [new 2015] |
|---|---|
| | thyroid Ab had a substantially greater risk of developing sub-clinical or clinical thyroid disease (All patients with repeated positivity of both thyroid autoantibodies – T-Ab and anti-TgL – developed subclinical hypothyroidism within 4 years after the first detection of T-Ab, whereas this figure was only 11% in patients with isolated antiTPO positivity). <br><br> Umpierrez[705] in a smaller study over 4 years also showed that those with type 1 diabetes who have thyroid Ab are much more likely to develop thyroid disease (OR 17.91) <br><br> As already noted, there is value in picking up thyroid dysfunction because symptomatic deterioration can be avoided, in the case of hypothyroidism using simple replacement therapy which is generally extremely well tolerated. The GDG considered there to be very little risk in screening people with type 1 diabetes. A blood test is required, but as this can be part of the annual metabolic screen; there is no need for an additional blood test |
| Economic considerations | There were no economic studies of screening for, or early detection of, thyroid disease in type 1 diabetes. <br> The cost of the most commonly tested thyroid Ab (TPO antibody) is approximately £7.50. The cost of a TSH measurement is approximately £3.50. <br> The GDG recognised that thyroid screening blood tests could be carried out as part of the annual metabolic screening and therefore do not incur additional phlebotomy costs, so only the cost of the assay need be considered. . <br><br> Carrying out the test would improve the detection and treatment of thyroid disease, reducing its symptoms and complications. Therefore testing for thyroid disease is likely to have a positive effect on quality of life and it is likely to justify its cost. |
| Quality of evidence | There were no RCTs, and the GDG had to develop their recommendations by inference from the available cohort and cross-sectional studies. <br><br> There were differences between studies in the characteristics of the subjects in terms of age (and whether or not both children and adults were included); duration of diabetes (this information was generally not available); and country of origin. <br> The antibody tests under consideration also differed between studies. Antibodies against thyroid antigens can logically be used to predict risk of hypothyroidism (in hyperthyroidism anti-TSH receptor antibodies are used to diagnose autoimmune hyperthyroidism once the diagnosis has been established). In screening for hypothyroidism the most commonly used antibodies were anti-peroxidase (TPO) and anti-thyroglobulin antibodies. Expert opinion within the GDG was that TPO antibodies are better predictors of the subsequent development of hypothyroidism. <br><br> Most of the available studies measured thyroid Ab and/or TFT at only one time point. Moreover, all but one of studies reporting repeat measurement made only one further measurement within the study, and this additional measurement was not made at a similar time point in all studies. Only the study by Vondra and colleagues (ref) in 109 people with type 1 diabetes reported thyroid measurements at multiple time-points. |

| Recommendations | **150. Measure blood thyroid-stimulating hormone (TSH) levels in adults with type 1 diabetes at annual review. [new 2015]** |
|---|---|
| Other considerations | The GDG agreed that monitoring for thyroid disease in people with type 1 diabetes was worthwhile given the marked increase in risk in this population.<br><br>There was debate about the optimum strategy. The evidence suggests that the risk of sub-clinical or clinical thyroid disease is much greater in those who are thyroid Ab positive, and that routine measurement of TFT in antibody-negative people is less obviously beneficial. One study (Vondra) suggested the rate of TPO positivity rises after diagnosis of type 1 diabetes but plateaus at 10 -12 years. A further study (Umpierrez) showed TPO negativity stable after 12 years diabetes duration. One strategy would therefore be to measure for the presence of thyroid antibodies annually for the first 10-12 years after diagnosis of type 1 diabetes. In those who develop antibodies, annual TFT measurement should be performed. In those without antibodies TFT may not be necessary. An alternative strategy is to measure TSH (which the GDG considered was the only TFT required in monitoring for primary thyroid disease) annually; this takes into account the very low cost of a TSH measurement. In this strategy annual TSH measurement is offered to all people with type 1 diabetes, irrespective of antibody status which therefore does not need to be measured routinely at all. The majority view was that annual TFT for all was preferable because it is much simpler and therefore more likely to be successfully implemented. |

Update 2015

## 16.5   Eye disease [2004]

### 16.5.1    Retinopathy surveillance programmes

#### 16.5.1.1    Rationale

Diabetes eye damage is the single largest cause of blindness before old age. The success of laser therapy in the treatment of sight-threatening retinopathy is an accepted part of ophthal-mological care and has not been assessed for this guideline. Appropriate issues which need to be addressed are, however, how people with developing retinopathy can be selected for ophthalmological referral in time for optimal treatment, and whether preventative therapy other than good blood glucose and good blood pressure control can be useful in people with type 1 diabetes. This section deals with the structure and success of surveillance programmes, while the methods used for detection of early retinopathy, the use of alternative preventative therapies and referral guidelines to ophthalmology are considered below.

#### 16.5.1.2    Evidence statements

The SIGN guideline suggested from two comparative studies that screening is effective at detecting unrecognised sight-threatening retinopathy.[638] Onset of pre-proliferative retinopathy was identified in one study 3.5 years after diagnosis of type 1 diabetes in post-puberty patients, and within two months of onset of puberty (IIa).

There are discrepancies in the recommended optimal frequency of testing for diabetic retinopathy. Annual review was considered appropriate by consensus in two guidelines.[337,338,638] Testing for other diabetic complications takes place annually, and this is considered an appropriate schedule for retinopathy screening (IV).

The NICE guidelines for type 2 diabetes reached consensus on a more frequent need for screening (three to six months) in patients who experienced worsening of lesions or scattered exudates more than one disc diameter from the fovea or in a person with changes in blood glucose control suggesting higher risk of progression of retinopathy (NICE).[505,522]

Further research is needed in increasing this screening interval for low-risk patients. Evidence from non-randomised controlled studies considered in a systematic review found that patients with no retinopathy at baseline have a less than 1% chance of developing any retinopathy within two years (IIa).[638]

Evidence from patient focus groups and the grey literature suggests that success of screening depends on continued consistently high levels of uptake. Patients expressed importance in discussing fear of blindness and benefits of attending regular screening. Explanations of techniques and technologies for screening including new technologies under investigation were requested. The need for eye drops and transient effects on vision should also be communicated. Multiple patient reminders did not improve attendance at screening sessions. A range of education methods is needed to encourage non-attendees (IV).

SIGN guidelines cite cohort studies with high risk of potential confounding in their design and expert opinion indicating that patients prefer screening to be performed at a site convenient to them.[638] Low vision clinics and community self-help groups can improve the quality of life and functional ability of patients with visual impairment. Community support, low vision aids and training, and assistance to register as blind/partially sighted should be provided to people with diabetes and visual impairment (IV).

### 16.5.1.3  Health economic evidence

The health economic searches produced nine papers of potential interest to the guideline that fall into three distinct sets. The first set of five papers present US and Swedish simulations of the cost-effectiveness of the screening for and treatment of diabetic retinopathy using a similar model structure.[210,210,348-351,351,351,351,351] All these papers consider retinopathy screening at a yearly or more frequent interval. Three of the papers relate to a government perspective within the US, where the cost of federal benefits for blindness is argued to be greater than the costs of a yearly (or more frequent) screening regimen for those with retinopathy.[349-351,351,351,351] A fourth paper relates the model to Sweden, where it is argued that retinopathy screening is cost-saving to the government.[210] A final paper, also US based, considers only medical costs (a health insurer standpoint) and finds a cost-effectiveness ratio of $1,996 per QALY (1990 prices) for the yearly screening of those without retinopathy and a six-monthly screening for those with retinopathy.[348,351]

Two other related papers consider national retinopathy screening using an alternative model.[142,142,567,567] In one of these papers, only minimal glycaemic control is assumed (HbA1c at 10%) when evaluating retinopathy, whilst the other gives insufficient details of the model or alternative strategies to allow analysis. Both papers appear to produce findings consistent with the cost-effectiveness of screening for and treatment of diabetic retinopathy.

None of the above papers consider the potential role of digital photography in detecting diabetic retinopathy at low marginal cost.

Two papers consider the screening methods used in dispersed or isolated populations.[73,73,452,452] Of these, one relates to a mixed population with a very low proportion of type 1 diabetes,[452] whilst the other uses highly-specific cost estimates.[73] As no large dispersed or isolated subgroup exists within the UK, the results of these papers are not relevant for the guideline.

#### 16.5.1.4 Consideration

Members of the group recognised that some people with long-standing stable eye condition (and unchanging metabolic and blood pressure control) did not necessarily justify annual eye surveillance, but that currently the practicalities and knowledge base for identification and selection and recall of such people meant that a universal minimum recommendation of annually was the correct judgement. More frequent assessment of some individuals with changing retinopathy was noted to be cost-effective as they would otherwise have to be referred to ophthalmologists. The group were aware that future developments in the evidence base may allow for longer intervals between assessments for low-risk individuals. The importance of education of people with diabetes as to the purpose of the surveillance was agreed, while the issue of convenience of site was noted to have significant cost consequences.

#### 16.5.1.5 Recommendations

**151. Start eye screening for adults newly diagnosed with type 1 diabetes from diagnosis. [2004]**

**152. Depending on the findings, follow structured eye screening by:**
- **routine review in 1 year or**
- **earlier review or**
- **referral to an ophthalmologist [2004]**

**153. Explain the reasons and success of eye screening systems to adults with type 1 diabetes, so that attendance is not reduced by lack of knowledge or fear of outcome. [2004]**

### 16.5.2 Screening tests for retinopathy

#### 16.5.2.1 Rationale

The success of laser therapy in the treatment of sight-threatening retinopathy is an accepted part of ophthalmological care and has not been assessed for this guideline. The appropriate issue to be addressed is, but how people with developing retinopathy can be selected for ophthalmological referral in time for optimal treatment. This section deals with the methods used for detection of early retinopathy, the structure of surveillance programmes having been covered in the previous section, while other therapy issues are covered in 9.3.

#### 16.5.2.2 Evidence statements

**Ophthalmoscopy**

Direct ophthalmoscopy does not usually meet the required standards for retinopathy screening and review.[505,522]Sensitivity achieved by GP and optometrist screening with ophthalmoscopes is very low (NICE).[285,505,522]

**Ultra-wide angle screening laser ophthalmoscope**

Little evidence is available in this area. One comparative study conducted on healthy individuals reported in a systematic review is of limited applicability clinically (Ia).[285]

**Slit lamp biomicroscopy**

A diagnostic study quoted in a systematic review found that slit lamp biomicroscopes with dilated indirect ophthalmoscopy used by properly-trained individuals can achieve sensitivities similar to retinal photography, with a lower technical failure rate (DS).[285]

A systematic review concluded that slit lamps are always needed for those not amenable to digital photography (IV).[285]

**Retinal photography**

Retinal cameras have the highest level of accuracy of any practical screening method, and provide permanent images for quality control.[18] Retinal photography is more effective than direct ophthalmoscopy and can regularly achieve a sensitivity of 80% (DS).[638]

Photography is more accurate at detecting the presence of microaneurysms than ophthal- moscopy and may be of use in milder disease states (Ib).[18]

A low percentage of retinal photographs are ungradeable, although this may be improved by digital imaging. Accuracy is not dependent on the type of professional involved, but data from non-randomised controlled studies underlines the need for training in reading the photographs or images (IIa).[285]

Limited evidence exists on the number of fields that should be viewed with a retinal camera. One systematic review considering diagnostic studies showed that single-field studies gave marginally better results than those with two or more fields (DS).[285]

Digital cameras show similar accuracy to conventional photography but have advantages in image transfer and potential for automated grading.[285] Technical failure rates are lower with digital cameras (DS).

Further evaluation of digital imaging techniques is needed to prove the usefulness of this screening method (IV).[638]

There are inconsistent results and conclusions from randomised trials regarding the use of mydriasis in retinal photography reported in a systematic review (Ia).[285]

The Health Technology Board for Scotland assessment report states that there is no clear evidence that mydriasis or the routine use of more than one image significantly alters the sensitivity or specificity of screening for the detection of sight-threatening retinopathy.[285] The review concludes that there is little difference between the accuracy and failure rates of modern cameras when used with or without mydriasis; but the analysis of failure after non-mydriatic photography may have favoured no difference to outcome. Comparable screening accuracy is achieved with digital cameras, with or without mydriasis, but direct comparisons suggest that mydriasis may occasionally result in a successful image when non-mydriatic imaging fails (DS).

A large diagnostic study of screening services in both hospital and district settings found screening tests by trained retinal screeners to have a high sensitivity and very high specificity to detect sight-threatening diabetic retinopathy as assessed by slit lamp examination (DS).[546]

NICE type 2 diabetes guidelines suggest that mydriatic 45° retinal photography is the most effective test when screening for diabetic retinopathy (NICE).[505,522]

If more than one image per eye is required for screening then mydriasis is essential because of constriction of the pupil caused by the first photographic flash (IV).

Tropicamide (0.5%–1%), administered by a trained professional is a safe and appropriate way to perform mydriasis (NICE).[638]

The use of pilocarpine to reduce mydriasis is potentially harmful (IV).[285]

Blurred vision and sensitivity to light are complications of the instillation of eye drops for mydriasis. Other related side effects such as glaucoma and allergic reactions are rare (IV).[456]

**Table 184: Mydriasis with tropicamide**

| Mydriasis with tropicamide: |
| --- |
| • reduces the failure rate (inadequately interpretable photographs) in around 5% of eyes of people with diabetes (in particular in the second eye and in older people), and thus, the need for recall for a further examination when tropicamide will be necessary |
| • allows follow-up ophthalmoscopy to be optimised reducing false-negative referrals to ophthalmologists |
| • carries no detectable risk to the eye except in the post-surgical period |
| • is briefly uncomfortable (stings) |
| • paralyses accommodation (near vision) and pupil constriction for 30–60 minutes (low dose), but in some people for much longer, giving problems with glare and bright light sufficient to impair vision to unsafe levels for some tasks (for example driving). |

No studies reported whether differences found in sensitivities of healthcare professionals undertaking tests were statistically significant. Comparable sensitivity is achieved by GPs and optometrists using a direct ophthalmoscope through dilated pupils. Optometrists using slit lamp biomicroscopy only achieved moderate sensitivity (62% sensitivity at 95% specificity). The greatest sensitivity was found in comparative studies used in a systematic review with trained graders using mydriatic and non-mydriatic photography (DS).[285]

Initial data indicates that high-resolution automated grading systems compared to conventional grading can identify the absence of microaneurysms on digital images with a high sensitivity (Ia).[285]

A systematic review included a descriptive study evaluating a system for referring photo- graphs to the next level of expertise.[260] Referral when the grader identified any potential sign of retinopathy, with the more experienced professionals involved in the second and third levels, helped maintain effective analysis of images (IV).

Diabetes UK consensus is that an effective screening system should achieve a technical failure rate of less than 5% (IV).[682,683]

A systematic review reported inconsistent findings from controlled studies of the impact of disease condition and progression of disease on test failure rates (IIa).[285]

Lower technical failure rates are achievable with digital photography compared to conventional slide photography. Failure rates for ophthalmoscopy do not differ greatly from photography in controlled studies reported within a systematic review (IIa).[285]

There is a lack of discrete evidence about the role and usefulness of visual acuity testing. The NICE type 2 diabetes guideline retinopathy working-group supported the consensus guidelines from the Royal College of Ophthalmologists on the usefulness of visual acuity testing as part of the overall eye care approach (NICE).[505,522]

Diagnosis of macular oedema rests on the use of stereoscopic, slit lamp, indirect ophthalmoscopy in expert hands. Due to the difficulty of differentiating non-significant and clinically significant macular oedema, the use of visual acuity testing is recommended for screening in routine practice. Reduced visual acuity is an indication for specialist referral (NICE).[505,522]

#### 16.5.2.3  Consideration

The group felt that earlier judgements (for example NICE Inherited type 2 diabetes guideline) that digital photography best met the needs of appropriate sensitivity/selectivity, feasibility and opportunities for quality assurance were clearly endorsed by the evidence review and personal experience of Group members. Mydriasis was noted to be of particular importance in particular groups of people in whom some form of ophthalmoscopy was commonly required to complete a quality examination after photography, and appears safe if inconvenient to some people. It was strongly endorsed. Patient preference studies have suggested that mydriasis may reduce attendance for retinopathy screening because of its temporary effect on vision, but there is no recorded clinical evidence to suggest this. Visual acuity testing, while ill-evidenced, was noted to be fast and non-invasive (though requiring trained staff to test), and provided a useful function in helping detect unsuspected macular oedema, a critical but treatable condition.

154. **Implement digital retinal photography for eye screening programmes for adults with type 1 diabetes. [2004]**

155. **Use mydriasis with tropicamide when photographing the retina, after prior agreement with the adult with type 1 diabetes after discussion of the advantages and disadvantages, including appropriate precautions for driving. [2004]**

156. <mark>Make</mark> **visual acuity testing a routine part of eye screening programmes. [2004, amended 2015]** *Update 2015*

#### 16.5.3  Referral

#### 16.5.3.1  Rationale

The issues of surveillance programmes, screening technologies and non-blood glucose/non- blood pressure therapies for prevention are considered in the immediately prior and following sections of this guideline. This section considers the issue of how quickly a person with diabetes should be seen by an ophthalmologist once potentially sight-threatening retinopathy is detected.

#### 16.5.3.2  Evidence statements

The SIGN guidelines showed from controlled trials that poor outcomes and severe visual loss are associated with a delay in treatment of over two years from diagnosis of sight-threatening diabetic retinopathy.[638] This figure was one year for vitrectomy (IIa).

#### 16.5.3.3  Consideration

The group felt it inappropriate to derive and recommend new referral guidelines without detailed review of the ophthalmological literature, particularly as such guidelines were already published by the Royal College of Ophthalmologists and the National Screening Committee diabetic retinopathy screening group (www.nscretinopathy.org.uk). In the area of assessment of macular oedema it was noted that retinal screening recommendations using digital photography (see Section 9, 'Screening tests for retinopathy') could not inform the referral process suggested by the RCO guideline; thus use of unexplained change in visual acuity was substituted, reflecting current practice.

#### 16.5.3.4  Recommendations

157. <mark>Ensure that</mark> **emergency review by an ophthalmologist occurs for:**
   - **sudden loss of vision**

*Update 2015*

- **rubeosis iridis**
- **pre-retinal or vitreous haemorrhage**
- **retinal detachment [2004, amended 2015]**

158. <mark>Ensure that</mark> rapid review by an ophthalmologist occurs for new vessel formation. [2004, amended 2015]

159. Refer to an ophthalmologist for:
- **referable maculopathy:**
  i. **exudate or retinal thickening within 1 disc diameter of the centre of the fovea**
  ii. **circinate or group of exudates within the macula (the macula is defined here as a circle centred on the fovea, of a diameter the distance between the temporal border of the optic disc and the fovea)**
  iii. **any microaneurysm or haemorrhage within 1 disc diameter of the centre of the fovea, only if associated with a best visual acuity of 6/12 or worse**
- **referable pre-proliferative retinopathy:**
  i. **any venous beading**
  ii. <mark>**any venous reduplication**</mark>
  iii. **any intraretinal microvascular abnormalities (IRMA)**
  iv. **multiple deep, round or blot haemorrhages**

  **(if cotton wool spots are present, look carefully for the above features, but cotton wool spots themselves do not define pre-proliferative retinopathy)**
- **any <mark>large sudden</mark> unexplained drop in visual acuity. [2004, amended 2015]**

### 16.5.4 Non-surgical treatment of diabetic retinopathy

#### 16.5.4.1 Rationale

The means and systems of detection of diabetic retinopathy in sufficient time to allow successful laser therapy are considered in the previous three sections. However, laser therapy is a destructive salvage therapy, and prevention by good blood glucose and good blood pressure control are not as yet absolutely successful. Accordingly it is important to consider whether other approaches can delay the development of retinopathy in people with type 1 diabetes.

#### 16.5.4.2 Evidence statements

There is a lack of robust evidence for non-surgical, non-laser treatment of diabetic retinopathy. In general, trials in this area have limitations in their methodology.

The SIGN guideline addressed the absence of good evidence for use of ACE inhibitors in diabetic eye disease.[638] One multicentre RCT examined therein is methodologically limited. Trials with ACE inhibitor therapy are ongoing but at present there is inconclusive evidence in this area (Ia).

There is limited evidence from trials with the antiplatelet agents ticlopidine[224,224,689] and dipyridamole[539] that measures for deterioration of retinopathy were significantly lower in patients treated with antiplatelet agents compared to placebo, although potential methodological limitations would prevent this evidence forming the basis of a clinical recommendation. Ticlopidine has a high incidence of side effects (Ib).

One three-year study showed a sevenfold reduction in the number of definite annual microaneurysms compared to placebo in insulin-treated patients, and an inverse relationship

between progression of microaneurysms and hypo-aggregability level in patients treated with ticlopidine.[494] The trial in this treatment area is of moderate size (Ib).

A recent randomised controlled trial showed high dose vitamin E significantly reduced mean circulation time and increased retinal blood flow in diabetic patients.[100,101] No differences were seen in retinopathy level between the placebo and vitamin E groups (Ib).

### 16.5.4.3   Consideration

Issues of blood glucose control, blood pressure control or smoking are covered in chapters 7 and 8. Outside these indications the evidence was not felt to be strong enough to justify any recommendation. As this is in line with current practice, no negative recommendations were felt to be needed.

# 16.6   Diabetic kidney disease: kidney damage [2004]

## 16.6.1   Rationale

Kidney damage in type 1 diabetes is the largest cause of renal failure in the working age group. Primary prevention by good blood glucose and good blood pressure control is considered elsewhere in this guideline while this section deals with the early detection of diabetic nephropathy. For management of detected nephropathy, please refer to ………

## 16.6.2   Evidence statements

### Predictors of nephropathy

One seven-year longitudinal study showed the ability to predict progression to diabetic nephropathy by the presence of microalbuminuria may not be as reliable as previous studies have assumed.[674,675] Approximately 19% to 24% of patients with microalbuminuria develop diabetic nephropathy. Systolic blood pressure, glycated haemoglobin and triglycerides were significantly higher in people with type 1 diabetes who progressed to diabetic nephropathy, than for those who did not (III).

Five year follow-up of microalbuminuric patients with type 1 diabetes showed 19% progressed to diabetic nephropathy and 33% regressed to normoalbuminuria.[28] Progressors had significantly higher HbA1c and mean blood pressure and incidence of proliferative retinopathy compared to non-progressors (III).

Another seven-year prospective study in 148 normotensive people with diabetes showed that baseline albumin excretion rate (AER) is the predominant predictor for the development of microalbuminuria in type 1 diabetes.[460] Raised mean arterial blood pressure and HbA1c also were significantly related to progression to microalbuminuria (III).

A cohort study of two years follow-up showed in sex-specific analysis that HbA1c, age and baseline AER were particularly important predictors of progression to nephropathy in men, whereas duration of diabetes and triglycerides were particularly important in women.[132] Low- density lipoprotein (LDL) cholesterol was particularly important in people with shorter duration of diabetes and triglycerides in those with a longer diabetes duration (IIa).

A case-controlled study with 10-year follow-up showed that baseline glomerular filtration rate (GFR), although not a predictor of end-point AER or microalbuminuria, was a significant predictor of end-of-study blood pressure level.[758] Levels of AER and blood pressure were the main risk factors for renal outcome. A further five-year prospective study showed that in patients with microalbuminuria

decline in GFR was independently correlated to onset of diabetic nephropathy and baseline systolic blood pressure (IIa).[461]

**Screening and diagnosis**

The SIGN diabetes guidelines include one comparative study showing that measurements of albumin loss and serum creatinine are the best screening tests for diabetic nephropathy (III).[638]

Urine albumin concentration compared to urine albumin:creatinine ratio in a screening accuracy test showed specificity and sensitivity for microalbuminuria of 77% and 82% and 77% and 92% and for macroalbuminuria levels of 84% and 90%, and 88% and 90%.[23] No statistically significant difference was seen when comparing the performance of these two measures in detecting nephropathy (DS).

Both albumin concentration and albumin:creatinine ratio measured on a first-pass morning urine sample and compared against timed collection of urinary albumin excretion rate, showed high sensitivity and specificity for normal and elevated albuminuria.[121] Combining the two tests together in the same urine sample revealed the highest sensitivity (98%) and specificity (100%) (DS).

A comparative study reported in the SIGN guidelines reports that first-pass morning urine samples best reflect a timed collection and provide adequate assessment of urinary albumin loss (III).[638]

One test accuracy study comparing 24-hour urine collection with spot-urine samples showed both samples were accurate for the screening and diagnosis of diabetic nephropathy.[765] Urinary protein better correlates with the reference standard (urinary AER) in macro- albuminuric (0.95) and microalbuminuric (0.80) samples, than in normoalbuminuric samples (0.61) (DS).

A 10-year follow-up study showed the predication of microalbuminuria is most effective in a four-hour morning urine collection with a greater specificity than 24-hour collection (positive predictive value 91% vs 79%), and is similar to the overnight collection, but with a greater sensitivity (DS).[191,192]

One screening test study showed significant intraindividual variation of urinary albumin excretion between samples taken in triplicate for seven days.[476] Mean coefficient of variation was 49%. Urinary albumin excretion more than 1.0 mg/mmol on the first specimen had a sensitivity of 97% and specificity of 82% for detection of those with a three sample mean more than 2.5 mg/mmol (DS).

A microalbumin analyser was shown in one screening test accuracy study to have sensitivity, specificity, negative predictive and positive predictive values of 92%, 100%, 93% and 100% respectively, suggesting a high reproducibility and reliability for microalbuminuria detection.[129,130] Another accuracy study showed a different device to have sensitivity, specificity and negative and positive predictive value of 100%, 97%, 100% and 96% respectively (DS).[649]

A semi-quantitative diagnostic test reported sensitivity of 86% and specificity of 67% to estimate albumin excretion rate as a screening tool for microalbuminuria.[731] This was consider- ably lower than the reference standard of albumin concentration (sensitivity 75% and specificity 94%) using the Micral test, which itself is not an effective screening tool for microalbuminuria. A further three studies of similar design, predominantly comparing Micral test with urinary albumin excretion rates returned varying results in terms of accuracy.[15,16,20,21,261] However, all suggested a lower sensitivity of Micral test for the detection of albuminuria (DS).

One correlation study reporting on self-testing with the Micral test found that 80% of patients classified themselves correctly.[560] Using at least two positive test results increased the specificity and sensitivity to 81% and 92% with a positive predictive value 71% leading to 90% of all patients classifying themselves correctly (III).

One correlation study showed that the dipstick testing method was insensitive or not adequately specific to detect abnormal overnight albumin excretion rate.[393,394] This study had potential internal validity limitations and should not be used as the basis for a positive clinical recommendation (III).

One diagnostic study of a Clinitek microalbumin test method performed in 302 people with diabetes demonstrated sensitivity and specificity of 79% and 81% and negative and positive predictive values of 46% and 95% for determining microalbuminuria (DS).[419]

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### 16.6.3   Health economic evidence

The health economic literature relating to the method of surveillance for emerging kidney damage produced four papers.[209,209,417,433,434,552,552] Three of these papers concentrated on the costs of testing, and largely ignored later outcomes. The fourth of these papers presents a cost-utility analysis of laboratory testing vs double dipstick testing plus laboratory assays where either result is positive.[417] However, this paper employs a non-standard QALY measure and this limits the robustness of the conclusions.

Five studies consider ACE inhibitor use for those found to have proteinuria following screening.[123,123,240,240,297,297,596,596,714,714] One paper was excluded as it was predicated on a significantly different healthcare system than that of the UK.[123] The remaining four papers argued that ACE inhibitor treatment will be cost-saving in those found to exhibit proteinuria.

The cost-effectiveness of ACE inhibitor treatment of those with microalbuminuria[79,372,372,543,545,653,653] is also analysed in four papers based outside of the UK, of which two consider benefits from arterial disease in addition to the benefits of delaying or preventing nephropathy.[543,545,653,653] Two papers suggest ACE inhibitor treatment will be cost-effective on both base case and sensitivity analysis.[79,653,653] One cost-utility study (interpretation of which is limited by possible typographic errors in the calculations) considers nephropathy benefits only and suggests ACE inhibitor treatment is cost-effective on their base case analysis but not in sensitivity testing.[372] A final paper considers both nephropathy and arterial benefits and finds a high cost per life year saved.[543,545]

### 16.6.4   Consideration

The issue of blood glucose control and its role in the development of microvascular complications is considered elsewhere in this guideline.

While there was no formal evidence on frequency of testing in the individual without previous evidence of nephropathy, organisational issues and the slow time course of progression of nephropathy suggested yearly surveillance in concert with eye and foot surveillance. For perceived reasons of convenience and adherence, spot urine specimens were considered more useful than timed collections, and, because of the effects of activity on albumin excretion rate, first-pass specimens on rising ('early morning urine') the most desirable. As urine concentration varies considerably between and within individuals, the general recom- mendation to measure an albumin:creatinine ratio was accepted, but if this was not organisationally practical a specific and sensitive concentration test could be used. Once positive, confirmation is recommended given the variability of albumin excretion rate from day to day. It was not felt that confirmation required a further clinic visit if one was already scheduled at three to four month intervals, unless there was evidence of renal impairment or non-diabetic renal disease. It seems sensible to measure serum creatinine annually at the same time. There is a need to consider the possibility of renal disease unrelated to diabetes.

Effectiveness and cost-effectiveness evidence suggests that ACE inhibitors should be used as first-line therapy in people with type 1 diabetes once albumin excretion rate is detectably abnormal. Discussion of side effects noted the more serious of these (hyperkalaemia and acute renal impairment) related mostly to people with type 2 diabetes. No direct evidence for angiotensin 2 receptor antagonists in type 1 diabetes had been found, but as the microvascular complications of diabetes seem independent of aetiology of diabetes, the Group felt that evidence from type 2 diabetes could be extrapolated. However, being more expensive, these should be reserved as second-line therapy. Combination therapy seems likely to be effective but no recommendation is appropriate until more evidence on benefit and risk in this area is available.

While it was not found that a low protein diet was sufficiently well supported to be recommended for people with evidence of established diabetic nephropathy, it was felt that formal advice on a non-high protein diet should be given. In the absence of useful evidence, the group were unable to set an arbitrary referral cut-off based on one biochemical measure, but agreed to leave this to local collaborative arrangements between specialists.

### 16.6.5    Recommendations

See also recommendations for blood pressure in section 15.4.

160. **For guidance on managing kidney disease in adults with type 1 diabetes, see the NICE guideline on chronic kidney disease. [new 2015]**

161. **Ask all adults with type 1 diabetes with or without detected nephropathy to bring in the first urine sample of the day ('early morning urine') once a year. Send this for estimation of albumin:creatinine ratio. Estimation of urine albumin concentration alone is a poor alternative. Serum creatinine should be measured at the same time. [2004]**

162. **Suspect other renal disease:**
     - **in the absence of progressive retinopathy**
     - **if blood pressure is particularly high**
     - **if proteinuria develops suddenly**
     - **if significant haematuria is present**
     - **in the presence of systemic ill health. [2004]**

163. **Discuss the significance of a finding of albuminuria with the person concerned. [2004, amended 2015]** <span>Update 2015</span>

164. **Start angiotensin-converting enzyme (ACE) inhibitors and, with the usual precautions, titrate to full dose in all adults with confirmed nephropathy (including those with low-level albuminuria [microalbuminuria] alone) and type 1 diabetes. [2004]**

165. **If ACE inhibitors are not tolerated, substitute angiotensin 2 receptor antagonists. Combination therapy is not recommended. [2004, amended 2015]** <span>Update 2015</span>

166. **Maintain blood pressure below 130/80 mmHg by addition of other anti-hypertensive drugs if necessary. [2004]**

167. **Advise adults with type 1 diabetes and nephropathy about the advantages of not following a high-protein diet. [2004]**

168. **Referral criteria for tertiary care should be agreed between local diabetes specialists and nephrologists. [2004]**

## 16.7 Diabetes foot problems [2004]

For guidance on diabetic footcare, please see the NICE clinical guideline on diabetic foot problems (add link to diabetic foot care guideline when published).

The recommendations and text from the 2004 guideline pertaining to foot care can be found in Appendix S.

169. **For guidance on managing foot problems in adults with type 1 diabetes, see the NICE guideline on diabetic foot problems. [new 2015]**

## 16.8 Diagnosis and management of autonomic neuropathy [2004]

Treatments for two aspects of autonomic neuropathy – gastroparesis and erectile dysfunction – have been re-reviewed and revised in 2015. Sections relating to these two topics have been removed from this reprise of the 2004 guideline. The updated evidence for gastroparesis and erectile dysfunction can be found in sections 16.1 and 16.1.7.

### 16.8.1 Rationale

Autonomic neuropathy is a late complication of diabetes that presents in diverse ways and affects a variety of organ symptoms including the skin (sweating), blood vessels (orthostatic hypotension), gastrointestinal tract (gastroparesis, diarrhoea), heart (cardiac arrest), bladder and sexual function. It may blunt the symptoms of hypoglycaemia. Considerable morbidity occurs as a result of many of these problems.

### 16.8.2 Evidence statements

#### Progression of autonomic neuropathy

A long-term follow-up study measured the progression of symptoms of autonomic neuropathy in 76 people with type 1 diabetes and over nine years.[431,432] This study found that of all the symptoms of autonomic neuropathy only gastroparesis was found to have increased in prevalence from baseline. At nine years after entering the study the only other symptoms reported were diarrhoea, impotence, loss of vaginal lubrication, hypoglycaemia unawareness and postural hypotension, and these were reported in not more than 9% of the study sample. There was a tendency for many symptoms such as hypoglycaemia unawareness to recover with time (III).

#### Symptoms of autonomic neuropathy

Two descriptive reviews were located that suggested possible symptoms due to autonomic neuropathy across diabetes populations. One review suggested impotence, unexplained diarrhoea, faecal incontinence, unexplained urinary symptoms (increased period between micturition, muted sensation of bladder fullness, frequency, urinary incontinence, unexplained bladder dilation), postural dizziness or faintness, gustatory sweating, dry feet, unexplained bloating, early satiety, fullness, nausea, vomiting, unexplained dysphagia and unexplained ankle oedema.[612,613] The authors suggested that tests for autonomic neuropathy may help in defining neuropathic aetiology. Another review found that autonomic symptoms can be vague and may present insidiously, and that nerve damage can be found in people without symptoms being manifest.[202] It is suggested that a mixed presentation is usual with a combination of postural hypotension, nocturnal diarrhoea, gastric

problems, bladder symptoms, abnormal sweating, impotence or a failure to recognise that hypoglycaemia is likely. In addition people with severe symptoms may also have advanced retinopathy, nephropathy and somatic neuropathy (IV).

### Aldose reductase inhibitors

Three randomised controlled trials have investigated the effect of ponalrestat on autonomic nerve function in mixed diabetes cohorts. Two small and short-term studies found no benefit of ponalrestat over placebo in terms of heart rate variability[248,249] or standard tests of autonomic function,[203] although a vibration perception measure or peripheral neuropathy did show a significant improvement with the intervention drug after 16 weeks of therapy.[248,249] However the potential methodological limitations of this study would not recommend it for the basis for recommendations (Ib).

A larger multicentre trial also testing the effect of 600 mg of ponalrestat compared to placebo found heart rate response to standing was significantly greater on the intervention drug while HbA1c remained constant throughout the period, and with no effect on frequency of adverse events, although only a third of the study population displayed abnormal autonomic neuropathy from tests, with the sample being drawn from people with diabetes and peripheral neuropathy (Ib).[672]

A long-term study found that there was a significant increase in indices of postural index and heart rate variability after two years of treatment with tolrestat compared with placebo, with changes in autonomic function not being influenced by changes in HbA1c level.[177,178] This study was conducted in people with diabetes who displayed abnormalities in two or more standard autonomic function tests and used a dose of 200 mg/day tolrestat (Ib).

### ACE inhibitors

Two small studies with medium-term follow-up investigated the potential of the angiotensin converting enzyme inhibitor quinapril to improve the heart rate variability of people with diabetic autonomic neuropathy. One study found total heart power (by 24-hour ECG) to be improved with quinapril compared to placebo as was high frequency power at six months.[389] In addition there was a significant increase in the level of heart rate variability at both three and six months. A similar study for 12 months found quinapril to have beneficial effects on all heart rate frequency domains, and the low frequency to high frequency power ratio to be lower (improved) with quinapril than placebo, and this held for analysis of morning, evening, or night-time comparisons.[50] The study also found quinapril to reduce heart rate to 12 months although no effect was seen on blood pressure. No complications of diabetic autonomic neuropathy or hospitalisations were reported (Ib).

No studies were identified that determined the effects of quinapril on symptoms of autonomic neuropathy.

### Indirect cholinergic agent cisapride

A small crossover trial of 20 mg cisapride compared to placebo in a mixed diabetes population found no increase in antral or duodenal motility with the intervention drug; but antral-duodenal coordination was significantly improved when fasting, and at other meals (Ib).[732]

### Erythromycin

Three small crossover trials of erythromycin compared to placebo in people with Type 1 diabetes and documented gastroparesis found short-term improvement in emptying of solids and mixed results with liquids with oral[169,617] or intravenous[347] administration, without side effects. However no improvements in symptoms scores were reported and larger scale and longer trials will be required to prove efficacy (Ib).

### 16.8.3    Health economic evidence

No health economic papers were found regarding the diagnosis of either autonomic neuropathy or gastroparesis. One paper was identified in the cost-effectiveness of management for painful neuropathy.[397] However, as a review of other evidence, specific cost-effectiveness data was limited to recommending intensive treatment to reduce complications.

### 16.8.4    Consideration

The group noted that the manifestations of autonomic neuropathy often occurred independently of each other, with very significant overlap into many other super-specialties of medicine (for example dermatology, gastroenterology, urology). Accordingly, the topic addressed a wider range of diagnostic and management issues than could be tackled in a diabetes guideline. Nevertheless the importance of alertness to, and detection of, these conditions was clearly relevant to the practice of the diabetes team. Of specific relevance is gastroparesis because of the effect of this condition on blood glucose control, but the group recognised that the diagnosis of this condition was not easy or reliable, and the treatments available only partially and erratically successful.

### 16.8.5    Recommendations

170. In adults with type 1 diabetes who have unexplained diarrhoea, particularly at night, the possibility of autonomic neuropathy affecting the gut should be considered. [2004]

171. Take care when prescribing antihypertensive medicines not to expose people to the risks of orthostatic hypotension as a result of the combined effects of sympathetic autonomic neuropathy and blood pressure lowering medicines. [2004]

172. In adults with type 1 diabetes who have bladder emptying problems, investigate the possibility of autonomic neuropathy affecting the bladder, unless other explanations are adequate. [2004]

173. When managing the symptoms of autonomic neuropathy, include standard interventions for the manifestations encountered (for example, for abnormal sweating and postural hypotension). [2004, amended 2015]

174. Anaesthetists should be aware of the possibility of parasympathetic autonomic neuropathy affecting the heart in adults with type 1 diabetes who are listed for procedures under general anaesthetic and who have evidence of somatic neuropathy or other manifestations of autonomic neuropathy. [2004]

## 16.9    Chronic diabetic neuropathy [2004]

175. For guidance on treating chronic diabetic neuropathy, see the NICE guideline on neuropathic pain – pharmacological management.[new 2015]

## 16.10   Management of special situations [2004]

**Adults who are newly diagnosed**

### 16.10.1   Rationale

The time following diagnosis is one of marked stress for many adults with diabetes. However, decisions taken at this time may have a long-term impact, and to be accurate and effective would appear to need fairly complete assessment of medical and lifestyle factors. These can be expected to affect choice of therapy and monitoring requirements, educational requirements, input from different members of the multidisciplinary team, site of care and the need for involvement of other health-related services and perhaps employers and other institutions.

### 16.10.2   Evidence statements

**Organisation of initial assessment planning**

Consensus in the ADA guidelines suggests that medical evaluation is made to classify the person presenting as a basis for a management plan and to assess complications.[29] This is echoed by Diabetes UK recommendations for management in primary care which indicate that a planned programme of diabetes care should include systems for ensuring assessment and acute management of all newly-diagnosed patients.[171,172] In addition, American guidelines from the Department of Veterans Affairs identify initial assessment as a useful tool to review systems and set priorities for care (IV).[167]

**Content of the initial assessment plan**

All of the guidelines reviewed are aimed at a mixed diabetic population and do not specify any specific features of initial assessment that are particular to people with type 1 diabetes. All guidance[29,30,167,171,172] suggests that assessment should look for co-morbid conditions that people with diabetes are more commonly at risk from and should consider factors that may affect the management of diabetes such as COPD, substance misuse and depression.[29,30,167] Factors that may precipitate diabetes secondary to other medical conditions should also be considered (IV).[167]

Other factors of initial assessment that can aid management planning that are widely suggested included physical examinations, laboratory tests including lipid profile, urinalysis and ECG.[29,167,171,172] Consideration for referral is advised for (IV):

- urgent hospitalisation if patient is clearly unwell,[171,172] or
- where specialist examination is required for eye exam, family planning, diabetes education, behavioural advice or foot disorders.[29]

Consistent documentation of assessment is widely recommended,[167,171,172] and initial assessment should be used for the baseline of an individualised management plan (IV).[29,171,172]

**Adults who are newly diagnosed**

### 16.10.2.1   Rationale

The time following diagnosis is one of marked stress for many adults with diabetes. However, decisions taken at this time may have a long-term impact, and to be accurate and effective would appear to need fairly complete assessment of medical and lifestyle factors. These can be expected to affect choice of therapy and monitoring requirements, educational requirements, input from

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#### Benefit of initial assessment plan

No interventional studies were identified that assess the effect on outcomes of improved initial assessment planning. It may be assumed that benefits may accrue in terms of understanding and satisfaction with care, and potentially with adherence to management plans, although these cannot be quantified at this time (IV).

### 16.10.3 Health economic evidence

The health economic searches produced no studies giving guidance on appropriate insulin regimens for those newly diagnosed with type 1 diabetes.

### 16.10.4 Consideration

The group noted that this was not an area in which to expect RCT evidence of different styles of initial management planning, and endorsed in general the views expressed in other recent guidelines for people with type 1 diabetes. An overlap with the education recommendations of this guideline (see Chapter 7) was noted.

### 16.10.5    Recommendations

176. At the time of diagnosis (or if necessary after the management of critically decompensated metabolism), the diabetes professional team should develop with and explain to the adult with type 1 diabetes a plan for their early care. To agree such a plan will generally require:

- medical assessment to:
  i.   ensure security of diagnosis of type of diabetes
  ii.  ensure appropriate acute care is given when needed
  iii. review and detect potentially confounding disease and medicines
  iv.  detect adverse vascular risk factors
- environmental assessment to understand:
  i.   the social, home, work and recreational circumstances of the individual and carers
  ii.  their preferences in nutrition and physical activity
  iii. other relevant factors, such as substance use
- cultural and educational assessment to identify prior knowledge and to enable optimal advice and planning about:
  i.   treatment modalities
  ii.  diabetes education programmes
- assessment of emotional state to determine the appropriate pace of education.

The results of the assessment should be used to agree a future care plan. Some items of the initial diabetes assessment:

- acute medical history
- social, cultural and educational history/lifestyle review
- complications history/symptoms
- long-term/recent diabetes history
- other medical history/systems
- family history of diabetes/arterial disease
- medication history/current medicines
- vascular risk factors
- smoking
- general examination
- weight/BMI
- foot/eye/vision examination
- urine albumin excretion/urine protein/serum creatinine
- psychological wellbeing
- attitudes to medicine and self-care
- immediate family and social relationships and availability of informal support. [2004]

177. Elements of an individualised and culturally appropriate plan will include:

- sites and timescales of diabetes education, including nutritional advice (see 'Structured education programmes', Section 7.2, and 'Dietary management', Section 7.3)
- initial treatment modalities, including guidance on insulin injection (see 'Insulin regimens', Section 9.2, and 'Insulin delivery', Section 9.3)

- means of self-monitoring <mark>and targets</mark> (see 'Self-monitoring of glucose level', Section 14)
- <mark>symptoms, risk and treatment of hypoglycaemia</mark>
- <mark>management of special situations, such as driving</mark>
- means and frequency of communication with the diabetes professional team
- management of arterial risk factors (see Arterial risk control', Section 14)
- <mark>for women of childbearing potential, implications for pregnancy and family planning advice</mark>
- follow-up consultations, including <mark>frequency of review of HbA1c levels and experience of hypoglycaemia, and</mark> surveillance at annual review (see Section 16) [2004, amended 2015]

178. After the initial plan is agreed, put arrangements in place to implement it without inappropriate delay, and to provide for feedback and modification of the plan over the ensuing weeks. [2004]

# 16.11   Psychological problems [2004]

## 16.11.1   Rationale

The management demands of insulin therapy, the risks of late complications of diabetes, and the problems of hypoglycaemia and social discrimination, can place significant emotional stress on people with type 1 diabetes. This might precipitate or exacerbate psychological difficulties present for other reasons. Additionally, the stresses might in themselves be expected to interfere with a person's ability to self-manage their diabetes.

## 16.11.2   Evidence statements

### Depressed mood and glycaemic control

A small cohort study examining depressed mood as a factor in glycaemic control in type 1 diabetes found a strong positive correlation between mood and glycaemic control.[715] As the depression scores for this sample were mainly in the normal range, the results of this study indicate that mood, rather than clinical depression per se, is associated with significant differences in glycaemic control (IIa).

A medium-sized cohort study316 examined depression and its effect on reporting diabetes symptoms in type 1 diabetes. The study found that seven of nine symptoms attributed to diabetes (hyperglycaemic symptoms, hypoglycaemic symptoms and non-specific symptoms of poor control) were associated with depression whereas only one of nine symptoms attributed to diabetes was related to HbA1 (IIa).

A meta-analysis of cross-sectional studies examined whether depression is associated with glycaemic control.[447,448] A weak correlation was found between depression and glycaemic control. However, the study has certain potential issues with the methodology used. No systematic quality appraisal has been given for those studies included in the meta-analysis. Effect size estimates may be unstable due to the small number of studies and the small sample sizes of some studies (III).

### Injection anxiety and glycaemic control

One medium-sized cohort study examined 'fear of blood and injury' and its association with glycaemic control in type 1 diabetes.[66,67] The study shows that Type I diabetes adults with poorer glycaemic control perform fewer blood glucose measurements per day. The relationship between

poor glycaemic control and fewer blood glucose measurements is mediated by fear of blood and injury (IIa).

Another medium-sized cohort study examined injection anxiety in type 1 and type 2 diabetes.[763] The study found a significant negative correlation between injection anxiety and the number of insulin injections. However, no significant difference was found in the degree of glycaemic control between diabetes patients with high vs low anxiety scores. The results of this study are not analysed separately for people with type 1 and type 2 diabetes (III).

One meta-analysis[320] examined whether or not anxiety is associated with poor glycaemic control in adults with type 1 and type 2 diabetes. The studies that were limited to type 1 diabetes found a weak correlation between anxiety and glycaemic control. However, the study has some possible methodological limitations which may have introduced bias into analysis. No systematic quality appraisal has been given for those studies included in the meta-analysis. Effect size estimates may be unstable due to the small number of studies and the small sample sizes of some studies (III).

**Prevalence of depression in Type I diabetes**

One recent meta-analysis of prevalence studies examining the prevalence of depression in type 1 diabetes found a significantly higher prevalence of depression in type 1 diabetes (21.7%) than in non-diabetes control subjects (8.6%).[35,37] Potential methodological factors inherent to the study may limit the validity of the results derived from the meta-analysis (III).

One retrospective cross-sectional case-control study examined the prevalence of antidepressant use in type 1 diabetes compared to age- and sex-matched controls.[414] The study found a significantly higher proportion of type 1 diabetes patients (12.8%) had received a prescription for antidepressants in the past twelve months compared to controls (7.4%). The data for this study was derived from a localised computerised database of 28 GP practices so caution needs to be taken when generalising these results to other geographical areas (III).

**Management of depression**

A medium-sized prospective 12-month follow-up study in type 1 diabetes evaluated whether a blood glucose awareness training programme (BGAT-2) would improve mood.[136,140] No significant improvement in mood was detected in baseline scores at six and 12 months. This is attributed to baseline scores being within the normal limits. When subjects who feel within the range of mild depression were examined separately, these individuals did demonstrate a significant reduction in baseline scores at six and 12 months (IIb).

A small randomised controlled trial evaluated the efficacy of nortriptyline for depression and poor glycaemic control in a mixed (type 1 and type 2) diabetes population with poor glycaemic control.[448,451] The study found that the nortriptyline group were significantly less depressed after eight weeks than the placebo-treated patients. Of the nortriptyline-treated patients, 57% successfully remitted compared to 35.7% of the placebo-treated patients. No significant difference in response rate was found between type 1 and type 2 diabetes. Further- more, in the sample as a whole (type 1 and type 2) there was a non-significant trend towards worsened glycaemic control, both in patients who received nortriptyline and those who received placebo (Ib).

A small randomised controlled trial evaluated the antidepressant efficacy of fluoxetine in diabetic patients (mixed population type sample) with major depressive disorder.[448,449] At the conclusion of the eight-week treatment period, a significant reduction in symptoms of depression was found in the fluoxetine-treated group compared to the placebo group. However, no significant difference in the improvement of glycaemic control was found between patients who received fluoxetine and those who received placebo (Ib).

A small random two-group parallel comparison with a pre-test and nine and 15 months follow- up study compared the effects of a standard intensive treatment, patient education and distress reduction programme, with a standard treatment and patient education.[665] Outcomes examined were psychological variables and metabolic control. At nine months follow-up, depression improved significantly in the intensive treatment group compared to the standard treatment group. No significant difference was found in metabolic control between the two groups. At 15 months follow-up, improvement in depression faded and metabolic control was worsened (Ib).

**Management of anxiety in type 1 diabetes**

A small double-blind randomised controlled trial in a mixed (type 1 and type 2) diabetes population examined the effects of alprazolam on glucose regulation in anxious and non- anxious patients with poor glycaemic control.[448,450] Patients treated with alprazolam had a significantly greater reduction in GHb levels than those receiving placebo, regardless of anxiety. Both alprazolam and placebo similarly improved anxiety among anxious patients. Results were not analysed separately for type 1 and type 2 diabetes (Ib).

### 16.11.3    Consideration

It was felt that, whether or not depression and other psychological illness was more common in people with type 1 diabetes, the literature being inconclusive, the interaction with self-management demanded professional alertness to such problems. A degree of competence in managing these problems at least matching that of an experienced general practitioner is clearly desirable.

### 16.11.4    Recommendations

179. **Members of diabetes professional teams providing care or advice to adults with type 1 diabetes should be alert to the development or presence of clinical or subclinical depression and/or anxiety, in particular if someone reports or appears to be having difficulties with self-management. [2004]**

180. **Diabetes professionals should:**
    - **ensure that they have appropriate skills in the detection and basic management of non-severe psychological disorders in people from different cultural backgrounds**
    - **be familiar with appropriate counselling techniques and drug therapy, while arranging prompt referral to specialists of those people in whom psychological difficulties continue to interfere significantly with wellbeing or diabetes self-management.**

    **See also the NICE guidelines on common mental health disorders, generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults and depression in adults with a chronic health problem. [2004, amended 2015]**

*Update 2015*

## 16.12    Eating disorders [2004]

### 16.12.1    Rationale

Due to the inadequacies of subcutaneous insulin therapy, dietary self-management is an inevitable consequence of the optimal self-care of type 1 diabetes. Eating disorders are not uncommon in the general population, while type 1 diabetes is most commonly diagnosed at an age (12–20) when consciousness of own body image is high. Accordingly, eating disorders are seen in people with type 1 diabetes, and will interfere with self-management.

A review of the management of eating disorders is outside the scope of this guideline. A systematic search of the literature was, however, undertaken to review the types and relevant prevalence of eating disorders, and whether any specific issues of management had been identified in the type 1 diabetes population.

### 16.12.2    Evidence statements

Many papers on eating disorders in diabetes include people with type 2 diabetes. Extrapolation to type 1 diabetes from such populations is not safe. Assessment of eating disorders can be by interview (specific, low prevalence) or questionnaire (non-specific, high prevalence), and may or may not include manipulation of insulin dosage (dose omission or reduction). Accordingly published prevalence and odds ratio vs matched populations vary. Furthermore there may be cultural variations depending on attitudes to obesity and peer pressure. People with diabetes often are in continued contact with professional care teams, and the input of those teams might be expected to have influence on behavioural disorders (IV).

A follow-up study using interview methods in a clinic population found no eating disorders at all.[96] Nevertheless a proportion of young people did use insulin dose manipulation to control weight, and appeared to have worse outcomes (markers of late complications of diabetes) as a result (III).

A group in Toronto published a series of papers over the last decade, including a non-systematic review.[305,597] They note the odds ratio for eating disorders in young people compared to non-diabetic controls is around 2.0, with an excess prevalence of 2%–5%. The principal disorders described are bulimia nervosa and insulin dose manipulation, the conditions tend to be chronic even under care, and diabetes outcomes relatively poor compared to peers (III).

A review, described as a meta-analysis of prevalence studies, concurred with these figures for bulimia and dose manipulation, and could not find evidence of increased prevalence of anorexia nervosa (III).[525,526]

One small randomised controlled trial of a group psycho-education programme to improve sub-clinical disordered eating in women with type 1 diabetes found no significant differences between the intervention and control (standard care) in outcomes of metabolic control with both groups showing improvements from baseline.[27] There was also no significant difference in concordance with diabetes treatment or eating disorder symptomology at six weeks (Ib).

A position statement of the American Dietetic Association and the Dietitians of Canada found evidence that the prevalence of eating disorders among young adult women with type 1 diabetes to be about 5% to 11%.[19] It is suggested that dietetic professionals have a vital role in the management of diabetes as they have an understanding of the health issues that affect women with diabetes (IV).

### 16.12.3    Consideration

The group felt that the evidence on the whole suggested that eating disorders were more prevalent in people with type 1 diabetes, and particularly in young adults. Insulin dose manipulation of calorie loss accounted for much of this, and perhaps the long-term follow-up study's results were influenced by the benefits of the good long-term support offered. Experience of eating disorders in clinical practice was that in the context of insulin therapy they can have serious short- and long-term impacts, sometimes fatal.

### 16.12.4    Recommendations

**181. Members of diabetes professional teams should be alert to the possibility of bulimia nervosa, anorexia nervosa and insulin dose manipulation in adults with type 1 diabetes with:**

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- **over-concern with body shape and weight**
- **low BMI**
- **hypoglycaemia**
- **poor overall blood glucose control.**

**See also the NICE guideline on eating disorders. [2004, amended 2015]**

182. **The risk of morbidity from the complications of poor metabolic control suggests that consideration should be given to early, and occasionally urgent, referral of adults with type 1 diabetes to local eating disorder services. [2004]**

183. **Make provision for high-quality professional team support at regular intervals with regard to counselling about lifestyle issues and particularly dietary behaviour for all adults with type 1 diabetes from the time of diagnosis (see 'Structured education programmes, Section 7.2 and Dietary management, Section 7.3). [2004]**

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# 18 Acronyms and abbreviations

| Acronym or abbreviation | Description |
| --- | --- |
| ADA | American Diabetes Association |
| anti-TGL | anti-triglyceride Lipase |
| BGAT | Blood Glucose Awareness Training |
| BMI | Body mass index |
| CGM | Continuous glucose monitoring |
| CHO | Carbohydrate |
| CSII | Continuous subcutaneous insulin infusion |
| COPD | Chronic obstructive pulmonary disease |
| CV | Cardiovascular |
| DAFNE | Dose adjustment for normal eating |
| DKA | Diabetic ketoacidosis |
| GAD/GADA/GAD65 | Glutamic acid decarboxylase autoantibodies |
| GI | Glycaemic index |
| HbA1c | Glycated haemoglobin |
| HFS | Hypoglycaemia fear survey |
| IA2A | Inslet antigen 2 antibody 2A |
| IAA | Insulin autoantibodies |
| IAH | Impaired awareness of hypoglycaemia |
| ICA | Islet cell antibodies |
| ICU | Intensive care unit |
| LADA | Latent autoimmune diabetes of adulthood |
| MI | Myocardial infarction |
| MODY | Maturity onset diabetes of the young |
| NICE | National Institute for Health and Care Excellence |
| NCGC | National Clinical Guideline Centre |
| PAID | Problem areas in diabetes |
| SMBG | Self-monitoring of blood glucose |
| SIGN | Scottish Intercollegiate Guideline Network |
| TA | Technology appraisal |
| T-Ab | Thyroxine Antibody |
| TSH | Thyroid stimulating hormone |
| TPO | Thyroid peroxidase antibodies |
| TFT | Thyroid function tests |
| UCPCR | Urine C-peptide creatinine ratio |
| VAS | Visual analogue scale |

# 19 Glossary

| Term | Definition |
|---|---|
| Abstract | Summary of a study, which may be published alone or as an introduction to a full scientific paper. |
| Acute painful neuropathy of rapid glycaemic control | A very small proportion of individuals with diabetes who achieve a rapid improvement in blood glucose levels with insulin therapy develop a painful paraesthesia in limbs, especially the legs and feet, that can have a considerable impact on sleep and activities of daily living. The aetiology has not been clearly identified and no satisfactory explanation for the phenomenon has been agreed; symptoms usually improve over time but individuals may require additional treatments for pain relief. |
| Algorithm (in guidelines) | A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows. |
| Allocation concealment | The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants. |
| Applicability | How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered. |
| Arm (of a clinical study) | Subsection of individuals within a study who receive one particular intervention, for example placebo arm. |
| Association | Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal. |
| Autonomic neuropathy | Late stage complication of diabetes where the neurons of the autonomic nervous system become damaged following exposure to chronically raised blood glucose levels. Manifestations include gastroparesis, diarrhoea, sweating, orthostatic hypotension, cardiac arrest, erectile dysfunction, bladder dysfunction and cardiac arrest. |
| Baseline | The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared. |
| Bias | Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias. |
| Blinding | A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.

A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received. |
| Carer (caregiver) | Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability. |

| Term | Definition |
|------|-----------|
| Case–control study | A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition.

For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition. |
| Case series | Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients. |
| Clinical efficacy | The extent to which an intervention is active when studied under controlled research conditions. |
| Clinical effectiveness | How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials.

Clinical effectiveness is not the same as efficacy. |
| Clinician | A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist. |
| Cochrane Review | The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration). |
| Cohort study | A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study. |
| Comorbidity | A disease or condition that someone has in addition to the health problem being studied or treated. |
| Comparability | Similarity of the groups in characteristics likely to affect the study results (such as health status or age). |
| Concordance | This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence. |
| Confidence interval (CI) | There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population.

The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.

A wide confidence interval indicates a lack of certainty about the true effect |

| Term | Definition |
|------|------------|
| | of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a lot of patients have been studied). |
| Confounding factor | Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. |
| | For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor. |
| Consensus methods | Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques. |
| Continuous subcutaneous infusion insulin infusion (or insulin pump therapy) | A device that delivers rapid-acting insulin constantly into subcutaneous tissue for blood glucose control. The device requires input from the user to administer bolus insulin doses with food but has the advantage that it can be set up to deliver a variable basal rate of rapid-acting insulin according to the user's needs. |
| Control group | A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. |
| | Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment. |
| Cost-effectiveness analysis (CEA) | Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention). |
| Cost-effectiveness model | An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes. |
| Cost–utility analysis (CUA) | Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility. |
| Credible interval (CrI) | The Bayesian equivalent of a confidence interval. |
| Decision analysis | An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes. |
| Diabetic ketoacidosis | A medical emergency which occurs when the body is unable to use glucose as an energy source due to a lack of insulin. The body breaks down fat as an alternative source of energy. Ketone formation is a by-product of this process and contributes to the development of an acidotic state. Diabetic ketoacidosis is a medical emergency as it can lead to coma and death. It requires urgent treatment with intravenous fluids, insulin and electrolyte replacement, typically in a hospital setting. |
| Diabetic nephropathy | A microvascular complication of diabetes that results in progressive kidney disease caused by angiopathy of capillaries in kidney glomeruli. |

| Term | Definition |
|---|---|
| Diabetic retinopathy | An ocular manifestation of diabetes that occurs as a result of microvascular retinal changes in response to chronic hyperglycaemia exposure. It can be associated with visual loss, although, screening programmes aim to detect early changes and time specialist referral for treatment interventions. |
| Discounting | Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present. |
| Economic evaluation | An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals.<br><br>There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost–minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention. |
| Effect<br>(as in effect measure, treatment effect, estimate of effect, effect size) | A measure that shows the magnitude of the outcome in one group compared with that in a control group.<br><br>For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%.<br><br>The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant). |
| Effectiveness | How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care. |
| Efficacy | How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care. |
| Epidemiological study | The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions. |
| EQ-5D (EuroQol 5 dimensions) | A standardised instrument used to measure health-related quality of life. It provides a single index value for health status. |
| Evidence | Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients). |
| Exclusion criteria (literature review) | Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence. |
| Exclusion criteria (clinical study) | Criteria that define who is not eligible to participate in a clinical study. |
| Extrapolation | An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics. |
| Follow-up | Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables. |
| Gold standard | A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease. |

| Term | Definition |
|------|-----------|
| GRADE, GRADE profile | A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile. |
| Harms | Adverse effects of an intervention. |
| Health economics | Study or analysis of the cost of using and distributing healthcare resources. |
| Health-related quality of life (HRQoL) | A measure of the effects of an illness to see how it affects someone's day-to-day life. |
| Heterogeneity or Lack of homogeneity | The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity. |
| Hyperglycaemia | Abnormally high blood glucose level, typically considered to be >7.0 mmol/litre fasting and >11.1 mmol/litre post-prandially. Prolonged hyperglycaemia can lead to osmotic symptoms of thirst, passing urine frequently and weight loss in the short term, and retinopathy, nephropathy and neuropathy in the long-term. |
| Hypoglycaemia | Abnormally low blood glucose level, typically considered to be a level of <3.5 mmol/litre. An individual with a hypoglycaemic blood glucose level typically experiences autonomic symptoms (sweating, palpitations, tremor) and neuroglycopenic symptoms (emotional lability, paraesthesia, blurred vision, incoordination, reduced orientation) that warn them to consume carbohydrate to correct their glucose levels. |
| Impaired awareness of hypoglycaemia | Repeated episodes of hypoglycaemia can result in reduced autonomic and neuroglycopenic warning signs when low blood glucose levels occur in individuals with diabetes. Eventually, an individual with diabetes can develop hypoglycaemia awareness such that they do not have any warning signs that they have a low blood glucose level, and this can predispose them to episodes of severe hypoglycaemia. |
| Imprecision | Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect. |
| Inclusion criteria (literature review) | Explicit criteria used to decide which studies should be considered as potential sources of evidence. |
| Incremental analysis | The analysis of additional costs and additional clinical outcomes with different interventions. |
| Incremental cost | The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently. |
| Incremental cost-effectiveness ratio (ICER) | The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another. |
| Indirectness | The available evidence is different from the review question being addressed, in terms of PICO (population, intervention, comparison and outcome). |
| Intervention | In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet. |
| Long-term care | Residential care in a home that may include skilled nursing care and help |

| Term | Definition |
|------|-----------|
| | with everyday activities. This includes nursing homes and residential homes. |
| Ketogenesis | The process by which ketone bodies are produced as a result of fatty acid breakdown. In individuals with type 1 diabetes, this typically occurs when blood glucose cannot be taken up by cells as a consequence of insufficient insulin levels; ketone body production is then initiated to make energy available to cells from the breakdown of stored fatty acids. |
| Ketosis | Ketosis occurs when ketogenesis is happening at an abnormally high level to form raised concentrations of acetone, acetoacetate and β-hydroxybutyrate from acetyl-CoA to provide energy supplies to the body. Acetoacetate and β-hydroxybutyrate are acidic, and high levels result in ketoacidosis, a medical emergency which can lead to a comatose state, if left untreated. |
| Latent autoimmune diabetes of adulthood (LADA) | A form of diabetes mellitus that is caused by autoimmune destruction of pancreatic β cells, but typically the destruction is considerably slower than that seen in classic presentations of type 1 diabetes, and it presents in adults rather than in childhood. Clinical onset of osmotic symptoms is therefore slower (over several years), and in its early stages good glycaemic control can be achieved with very small doses of insulin. LADA has been likened to a slow onset form of type 1 diabetes. |
| Lipolysis | The breakdown of fat (lipid) cells. |
| Macrovascular complications of diabetes | Diabetes is associated with disease of large blood vessels in the body, including the coronary arteries, aorta, carotid arteries and peripheral vascular arteries to the limbs. Chronic exposure to hyperglycaemia leads to an increased incidence of coronary heart disease, cerebrovascular disease and peripheral vascular disease. |
| Markov model | A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle). |
| Maturity onset diabetes of the young (MODY) | Rare forms of diabetes different from type 1 and type 2 diabetes caused by mutation of a single gene – it is thought that 1-2% of people with diabetes in the UK have this form of diabetes. Key features are:<br>Presentation with diabetes at <25 years of age<br>Diabetes in at least two preceding generations, with diagnosis at <25 years of age<br>Absence of ketones at diagnosis such that insulin may not be immediately required for management of the diabetes in its early stages |
| Meta-analysis | A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment. |
| Microalbuminuria | An increase in the level of albumin in the urine (>30 to 300 mg/litre, >30-300 mg/24 hours, urine albumin/creatinine ratio of >2.5 mg/mmol in men and >3.5 mg/mmol in women) that occurs when the permeability of the renal glomerulus is abnormally increased in response to chronic hyperglycaemia exposure. The diagnosis of microalbuminuria should be confirmed on a repeat urine sample within 3 to 6 months of the first positive test. Microalbuminuria is an important prognostic marker for kidney disease, and its detection should prompt a clinical review of treatment options in adults with diabetes mellitus. |
| Microvascular complications of diabetes | Diabetes is associated with disease of small blood vessels in the body caused by direct damage from hyperglycaemia, with microvascular complications, including damage to the eyes (retinopathy), kidneys (nephropathy) and nerves (neuropathy). Treatments aimed at improving glycaemic control aim to reduce the incidence of each of these complications in individuals with diabetes. |

| Term | Definition |
|---|---|
| Micturition | Passing urine from the body; urination. |
| Observational study | Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening.

There is a greater risk of selection bias than in experimental studies. |
| Odds ratio | Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another.

An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group.

Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio. |
| Outcome | The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins. |
| P value | The p value is a statistical measure that indicates whether or not an effect is statistically significant.

For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant.

If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be. |
| Perioperative | The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods. |
| Peripheral sensory neuropathy | Damage or disease affecting the sensation nerves of the peripheral nervous system. In individuals with diabetes, this can occur as a microvascular complication in response to chronic hyperglycaemia exposure. The condition results in reduced sensation, classically in a stocking distribution in the lower limbs and feet, and can be associated with symptoms of painful paraesthesia, especially at night. Its diagnosis is important as it is associated |

| Term | Definition |
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| | with increased risk of skin injury and ulcer formation in individuals with diabetes. |
| Placebo | A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention. |
| Postoperative | Pertaining to the period after patients leave the operating theatre, following surgery. |
| Preoperative | The period before surgery commences. |
| Primary care | Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians. |
| Primary outcome | The outcome of greatest importance, usually the one in a study that the power calculation is based on. |
| Problematic hypoglycaemia | Hypoglycaemia is defined as problematic in any of the following circumstances:<br><br>more than 1 episode per year of severe hypoglycaemia with no obviously preventable precipitating cause<br><br>complete loss of awareness of hypoglycaemia<br><br>frequent (more than 2 episodes per week) asymptomatic hypoglycaemia that is causing problems with daily activities<br><br>extreme fear of hypoglycaemia. |
| Prodrome | Early phase of an illness before the full array of disease-specific symptoms occur |
| Prospective study | A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies. |
| Publication bias | Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot. |
| Quality of life | See 'Health-related quality of life'. |
| Quality-adjusted life year (QALY) | A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.<br><br>QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance. |
| Randomisation | Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention. |
| Randomised controlled trial (RCT) | A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the |

| Term | Definition |
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| | experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias. |
| RCT | See 'Randomised controlled trial'. |
| Receiver operated characteristic (ROC) curve | A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal. |
| Reference standard | The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice. |
| Relative risk (RR) | The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). |
| | If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than one means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio. |
| Review question | In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations. |
| Secondary outcome | An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes. |
| Sensitivity | How well a test detects the thing it is testing for. |
| | If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). |
| | For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. |
| | If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). |
| | Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed. |
| Sensitivity analysis | A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. |
| | One-way simple sensitivity analysis (univariate analysis): each parameter is |

| Term | Definition |
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| | varied individually in order to isolate the consequences of each parameter on the results of the study. |
| | Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. |
| | Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. |
| | Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation). |
| Severe hypoglycaemia | Severe hypoglycaemia is defined as a blood glucose level that is sufficiently low to cause a reduced level of function in an individual such that they are unable to self-manage a hypoglycaemia episode and require help from another individual to achieve normoglycaemia. |
| Significance (statistical) | A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p < 0.05$). |
| Specificity | The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. |
| | See related term 'Sensitivity'. |
| | In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers. |
| Stakeholder | An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: |
| | • manufacturers of drugs or equipment |
| | • national patient and carer organisations |
| | • NHS organisations |
| | • organisations representing healthcare professionals. |
| Systematic review | A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis. |
| Time horizon | The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation. |
| Univariate | Analysis which separately explores each variable in a data set. |
| Utility | In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs). |