Internal Clinical Guidelines Team

Final version

Type 2 diabetes in adults

Type 2 diabetes in adults: management

NICE's original guidance on Type 2 diabetes in adults was published in 2015.
It was updated in 2016, 2018, 2019, 2020, 2021 and 2022. See the NICE website for the guideline recommendations and the evidence reviews for these updates. This document preserves evidence reviews and committee discussions for areas of the guideline that have not been updated since 2015.

Clinical Guideline Update (NG28)

Methods, evidence and recommendations

December 2015

Commissioned by the National Institute for Health and Care Excellence

Disclaimer

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.

Update information

February 2022: The section on drug treatment to control blood glucose was updated in 2015 and used as part of the evidence base for the 2022 update. See http://www.nice.org.uk/guidance/ng28/evidence for the 2022 evidence review and guideline recommendations.

November 2021: We have reviewed the evidence and made new recommendations on SGLT2 inhibitors for adults with type 2 diabetes and chronic kidney disease.

December 2020: We have amended recommendations 1.7.20 and 1.7.23 to bring them in line with the diabetic eye screening programme.

August 2019: The section on blood pressure therapy was updated and replaced by the NICE guideline on hypertension in adults. Recommendations on blood pressure therapy have been removed.

April 2016: Text on sodium–glucose cotransporter 2 (SGLT-2) inhibitors was added to the section on initial drug treatment. The algorithm for blood glucose lowering therapy in adults with type 2 diabetes was also updated to revise footnote b with links to relevant NICE guidance on SGLT-2 inhibitors, and new information on SGLT-2 inhibitors was also added to the box on action to take if metformin is contraindicated or not tolerated.

July 2016: Recommendation 89 has been reworded to clarify the role of GPs in referring people for eye screening and also to add information on when this should happen. Minor corrections to project team lists.

December 2016: The algorithm for blood glucose lowering therapy in adults with type 2 diabetes was updated to include reference to NICE TA418 on dapagliflozin in triple therapy for treating type 2 diabetes.

Minor changes since publication

June 2018: Recommendation 1.3.11 was added to the short version to provide a link to NICE's advice on bariatric surgery. This change can be seen in the short version of the guideline (https://www.nice.org.uk/guidance/NG28).

January 2018: Footnotes were added with links to MHRA warnings about sodium–glucose cotransporter 2 (SGLT-2) inhibitors. These changes can be seen in the short version of the guideline (https://www.nice.org.uk/guidance/NG28).

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Summary Section

1.1 GDG membership and ICG technical team

1.1.1 Guideline Development Group 2015

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For a full list of guideline development group declarations of interest, see Appendix A.

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1.2 Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the Guideline Development Group is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Recommendation wording in guideline updates

NICE began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations ending **[2009]** (see 'Update information' below for details about how recommendations are labelled). In particular, for recommendations labelled **[2009]**, the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Update information

This guidance is an update of NICE guideline CG87 (published May 2009) and replaces it. This guidance also updates and replaces NICE technology appraisal guidance 203 and NICE technology appraisal guidance 248.

It has not been possible to update all recommendations in this update of the guideline. Areas for review and update were identified and prioritised through the scoping process and stakeholder feedback. Areas that have not been reviewed in this update may be addressed in 2 years' time when NICE next considers updating this guideline. NICE is currently considering setting up a standing update committee for diabetes, which would enable more rapid update of discrete areas of the diabetes guidelines, as and when new and relevant evidence is published.

Recommendations are marked as **[new 2015]**, **[2015]**, **[2009]** or **[2009, amended 2015]**:

- **[new 2015]** indicates that the evidence has been reviewed and the recommendation has been added or updated.
- **[2015]** indicates that the evidence has been reviewed but no change has been made to the recommended action.
- **[2009]** indicates that the evidence has not been reviewed since 2009.
- **[2009, amended 2015]** indicates that the evidence has not been reviewed since 2009, but either changes have been made to the recommendation wording that change the meaning or NICE has made editorial changes to the original wording to clarify the action to be taken.

1.3 Key Priorities for Implementation

1.3.1 Patient education

Offer structured education to adults with type 2 diabetes and/or their family members or carers (as appropriate) at and around the time of diagnosis, with annual reinforcement and review. Explain to people and their carers that structured education is an integral part of diabetes care. **[2009]**

Ensure that any structured education programme for adults with type 2 diabetes includes the following components:

- 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. **[2015]**

1.3.2 Dietary advice

Integrate dietary advice with a personalised diabetes management plan, including other aspects of lifestyle modification, such as increasing physical activity and losing weight. **[2009]**

1.3.3 Blood pressure management

This section was updated and replaced by recommendations in the 2019 NICE guideline on hypertension in adults. See www.nice.org.uk/guidance/ng136 for the updated recommendations.

1.3.4 Blood glucose management

1.3.4.1 Targets

Involve adults with type 2 diabetes in decisions about their individual HbA1c target. Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life. **[new 2015]**

In adults with type 2 diabetes, if HbA1c levels are not adequately controlled by a single drug and rise to 58 mmol/mol (7.5%) or higher:

- reinforce advice about diet, lifestyle and adherence to drug treatment **and**
- support the person to aim for an HbA1c level of 53 mmol/mol (7.0%) **and**
- intensify drug treatment. **[new 2015]**

1.3.4.2 Self-monitoring of blood glucose

Do not routinely offer self-monitoring of blood glucose levels for adults with type 2 diabetes unless:

- the person is on insulin **or**
- there is evidence of hypoglycaemic episodes **or**
- the person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery **or**
- the person is pregnant, or is planning to become pregnant. For more information, see the NICE guideline on diabetes in pregnancy. **[new 2015]**

1.3.5 Drug treatment

Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. **[new 2015]**

In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment[a] with:

- a dipeptidyl peptidase-4 (DPP-4) inhibitor **or**
- pioglitazone[b] **or**
- a sulfonylurea. **[new 2015]**

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[a] Be aware that, if metformin is contraindicated or not tolerated, repaglinide is both clinically effective and cost effective in adults with type 2 diabetes. However, discuss with any person for whom repaglinide is being considered, that there is no licensed non-metformin-based combination containing repaglinide that can be offered at first intensification.

[b] When prescribing pioglitazone, exercise particular caution if the person is at high risk of the adverse effects of the drug. Pioglitazone is associated with an increased risk of heart failure, bladder cancer and bone fracture. Known risk factors for these conditions, including increased age, should be carefully evaluated before treatment: see the manufacturers' summaries of product characteristics for details. Medicines and Healthcare products Regulatory Agency (MHRA) guidance (2011) advises that 'prescribers should review the safety and efficacy of pioglitazone in individuals after 3–6 months of treatment to ensure that only patients who are deriving benefit continue to be treated'.

1.4 Algorithm for blood glucose lowering therapy

This section was updated in 2022. The updated algorithm can be found at https://www.nice.org.uk/guidance/ng28/resources

1.5 Recommendations

This section was partially updated in 2015.

The current recommendations can be found at www.nice.org.uk/guidance/ng28

1.6 Research recommendations

The Guideline Development Group (GDG) has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

1. What is the effectiveness of low carbohydrate diets in adults with type 2 diabetes?

Why this is important

Type 2 diabetes is associated with obesity, and lifestyle interventions including diet and physical activity are thought to be useful in helping to control the condition and improve patient outcomes such as reducing the risk of long-term complications and increasing quality of life. Low carbohydrate diets have been a source of discussion over the past two decades and there is much debate regarding its effectiveness and safety in controlling blood glucose levels, particularly in the longer-term. Specifically, there is little consensus on the optimal intake of daily carbohydrates, where the risk of adverse effects such as hypoglycaemia is minimised. A randomised controlled trial addressing this clinical question would help to provide a better understanding of the effects of low carbohydrate diets on diabetes control and maintenance to inform appropriate management strategies.

2. What is the natural history of individuals who are diagnosed with type 2 diabetes in childhood in terms of long-term complications/consequences in adulthood?

Why this is important

Type 2 diabetes has historically been associated with adults, with research largely focused on this population. However, there is growing concern of the increasing incidence of type 2 diabetes in younger people, thought to be linked to the rising levels of obesity. In order to improve clinical management of people diagnosed in childhood, a better understanding of the early progression of the condition is needed, particularly in terms of its effects on the long-term risks of developing microvascular and macrovascular complications. A prospective longitudinal 10 year cohort study of children diagnosed with type 2 diabetes would help improve understanding of whether diabetes spanning the growth spurt would result in long-term complications occurring at a different rate compared to individuals who are diagnosed during adulthood.

3. What is the effectiveness of short-term self-monitoring of blood glucose during acute intercurrent illnesses in adults with type 2 diabetes?

Why this is important

There is an increased risk of hyperglycaemia during acute intercurrent illnesses in adults with type 2 diabetes. However, there is little evidence on the clinical and cost effectiveness of short-term self-monitoring of blood glucose levels during acute illnesses. Robust evidence from randomised controlled trials is needed to determine the comparative effectiveness of self-monitoring with no self-monitoring during episodes of acute illnesses. Outcomes should include change in treatment and prevention of hospital admissions.

4. What is the optimal frequency for self-monitoring of blood glucose in adults with type 2 diabetes?

5. What are the optimal blood glucose targets for self-monitoring in adults with type 2 diabetes?

Why this is important

It is widely recognised that self-monitoring of blood glucose is a multicomponent intervention. As well as being educated about how to use a self-monitoring device to assess blood glucose levels, adults with type 2 diabetes need to be able to understand their results and act on the observed readings. In adults for whom self-monitoring is appropriate, there is limited evidence to guide clinical practice in prescribing self-monitoring regimens, in terms of frequency of testing and optimal blood glucose targets. Given the inconvenience and expense of self-monitoring, robust evidence from randomised controlled trials is needed to guide the optimal use of this intervention.

6. In adults with type 2 diabetes, what treatment combinations (for example, glucagon-like peptide-1 [GLP-1] mimetics and insulin, combination therapy with meglitinides) are most effective when initial drug treatment with non-metformin monotherapy fails to adequately control blood glucose levels?

Why this is important

Although it is recognised that metformin therapy is suitable for most adults with type 2 diabetes, its use is contraindicated or not tolerated in approximately 15% of individuals. To date, research evidence has largely focused on metformin-based treatment combinations. Given the progressive nature of the condition, in which intensification of blood glucose lowering drug therapies are indicated over time, there is little evidence, for some adults, to guide management strategies on treatment combinations that do not include metformin. Randomised controlled trials are therefore needed to better understand the treatment choices that are available which improve blood glucose control and long-term risks of complications associated with diabetes.

7. In adults with type 2 diabetes, what are the effects of early use of insulin and glucagon-like peptide-1 (GLP-1) mimetics?

Why this is important

Poor blood glucose control is associated with increased risk of vascular complications. Glucagon-like peptide-1 (GLP-1) mimetics are a new class of blood glucose lowering drugs that target the incretin system, regulating insulin and glucagon. It is associated with low rates of hypoglycaemia and some weight loss. Its effectiveness and safety in combination with insulin early on in the drug treatment pathway is unknown. Randomised controlled trials are needed to understand the short and long-term effects of early use of GLP-1 agonists with insulin in terms of blood glucose control, adverse effects, diabetes-related complications and mortality. Research on its use could have a significant impact on the management of adults with type 2 diabetes.

8. When third intensification of treatment is indicated, which blood glucose lowering therapies should be used to control blood glucose levels?

Why this is important

As the incidence of type 2 diabetes increases in the younger population and as blood glucose control declines naturally over time, it is likely that further intensification of therapies would be needed. Currently, there is evidence up to second intensification of drug therapies, that is, when 2 or more non-insulin based treatment combinations fail to adequately control blood glucose levels. Randomised controlled trials are needed to improve understanding of alternative treatment options for adults at second intensification whose blood glucose is inadequately controlled with insulin and/or triple non-insulin based drug therapies.

9. In adults with type 2 diabetes, what are the effects of stopping and/or switching drug treatments to control blood glucose levels, and what criteria should inform the decision?

Why this is important

There is a lack of evidence on the effects of stopping and/or switching drug treatments to control blood glucose levels. The current practice of 'stopping rules' is typically motivated by either inadequate blood glucose control (rising HbA1c levels) or intolerable side effects. There is limited understanding of the short- and long-term effects of stopping a therapy and switching to another in terms of diabetes control (HbA1c levels), hypoglycaemic risk, weight gain, and cardiovascular morbidity and mortality. In addition, there is limited understanding of how quickly consideration should be given to stopping and switching to another drug treatment and, if stopping and switching may be needed, what the optimal sequencing is of drug treatments. Randomised controlled trials examining these different issues would help to improve diabetes care.

10. In adults with type 2 diabetes, what are the long-term effects of blood glucose lowering therapies such as dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium–glucose cotransporter 2 (SGLT-2) inhibitors and meglitinides?

Why this is important

There is limited evidence in relation to the long-term effects (at least 5 years) of blood glucose lowering therapies, particularly newer agents in terms of efficacy and adverse events (for example, cardiovascular outcomes). Randomised controlled trials and prospective longitudinal studies are needed to better understand the long-term efficacy and safety issues surrounding these medicines.

11. In adults with type 2 diabetes and chronic kidney disease, what is the safety and effectiveness of metformin?

Why this is important

Type 2 diabetes and renal impairment are closely associated, with prevalence increasing with age. Metformin is not recommended for individuals with an estimated glomerular filtration rate (eGFR) of less than 30 ml/minute/1.73m^2. Currently, there are no systematic reviews that have evaluated the safety of administering metformin at a reduced dose for people with an eGFR of less than 30 ml/minute/1.73m^2. Given the well-recognised cardiovascular benefits, research is needed to determine the safety and effectiveness of applying metformin in this group of individuals.

12. In adults with type 2 diabetes, what patient characteristics predict response or non-response to pharmacological blood glucose lowering therapies?

Why this is important

There is little understanding of the prognostic characteristics that determine the likelihood that a person would benefit and respond or not respond to treatment. Increased understanding of important predictive criteria would better help clinicians target drug therapies and improve overall patient care. Prospective longitudinal cohort studies examining various types of prognostic factors such as demographic, disease-specific and comorbid are needed to identify characteristics that are likely to predict treatment response or non-response to blood glucose lowering therapies in adults with type 2 diabetes.

13. In adults with type 2 diabetes and multimorbidity, what are the optimal blood glucose lowering treatment strategies?

Why this is important

The evidence reviewed in this guideline commonly excluded participants with type 2 diabetes whose disease is complicated by significant coexisting conditions, although this is a common presentation in real-world practice. As a result, it is difficult to account for the impact of different comorbid conditions on the effectiveness of blood glucose lowering treatment strategies. A systematic review is needed to ascertain the optimal treatment strategies for blood glucose control in adults with type 2 diabetes and a range of comorbid conditions. Multimorbidity covers a wide range of conditions (for example, heart failure, chronic obstructive pulmonary disease and depression) and each would have different implications. Therefore, analyses should consider whether the optimal treatment strategies differ according to specific comorbid conditions.

14. What is the optimal dosing of different phosphodiesterase-5 (PDE-5) inhibitors for people with type 2 diabetes and erectile dysfunction?

Why this is important

Although phosphodiesterase-5 (PDE-5) inhibitors have been shown to be effective compared to placebo in improving erectile function in men with type 2 diabetes, there is little understanding of the optimal dosing strategies for the different drugs available in this class. Double-blind randomised controlled trials in this area could help inform clinical practice.

15. What is the effectiveness of pharmacological treatment strategies for people with type 2 diabetes and erectile dysfunction who do not respond to phosphodiesterase-5 (PDE-5) inhibitors, for example PDE-5 inhibitor plus prostaglandins?

Why this is important

There is limited understanding of alternative treatment strategies available to men who do not respond to phosphodiesterase-5 (PDE-5) inhibitors. Double-blind randomised controlled trials of combination therapies and other pharmacological treatments could help inform clinical practice.

16. What is the effectiveness of treatment strategies (pharmacological and non-pharmacological) for sexual dysfunction related to type 2 diabetes in women?

Why this is important

Sexual dysfunction affect women with type 2 diabetes and there is limited understanding of available effective treatment strategies. A systematic review is needed examining the clinical and cost-effectiveness of available treatment strategies for women with type 2 diabetes and sexual dysfunction.

17. What is the effectiveness of treatment strategies (pharmacological and non-pharmacological) for sexual dysfunction in adults with type 2 diabetes in same-sex relationships?

Why this is important

Sexual dysfunction in adults with type 2 diabetes in same-sex relationships is an important area, where there is a limited understanding about effective treatment strategies. A systematic review is needed examining the clinical and cost-effectiveness of available treatment strategies for adults with type 2 diabetes and sexual dysfunction in same-sex relationships.

2 Overview

2.1 Introduction

This section was updated in 2015

Diabetes is a group of disorders with a number of common features, of which raised blood glucose (hyperglycaemia), by definition is the most evident. In England and Wales, the four commonest types of diabetes are:

● Type 1 diabetes

● Type 2 diabetes

● Secondary diabetes (from pancreatic damage, hepatic cirrhosis, endocrinological disease/therapy, or anti-viral/anti-psychotic therapy)

● Gestational diabetes (diabetes in pregnancy).

This guideline focuses on the management of type 2 diabetes in adults (18 years and over).

The World Health Organization's (WHO) definition of diabetes updated in 2011, was used in this guideline (International Diabetes Federation 2006). Although, no specific definition for type 2 diabetes is provided, the general definition refers to a state of high blood glucose levels that is sufficient to put the person at risk of specific microvascular complications associated with the condition. In 2009, the WHO recommended that a glycated haemoglobin (HbA1c) threshold of 48 mmol/mol (6.5%) be used to diagnose diabetes. A person is normally thought to have type 2 diabetes if he or she does not have type 1 diabetes (characterised by a rapid onset, often in childhood, insulin-dependence, and ketoacidosis if neglected), monogenetic diabetes or other medical conditions or treatment suggestive of secondary diabetes. Diagnosis is not addressed in this guideline.

The underlying disorder of type 2 diabetes is usually that of a background of insulin insensitivity where the body is unable to respond to normal levels of insulin, and insulin deficiency where the pancreas is unable to secrete enough insulin to compensate for this resistance. Insulin insensitivity is usually evidenced by excess body weight or obesity, and is exacerbated by overeating and inactivity. It is commonly associated with raised blood pressure, a disturbance of blood lipid levels, and a tendency to develop thrombosis. This combination is often recognised as 'metabolic syndrome', and is associated with fatty liver and abdominal adiposity (increased waist circumference). Insulin deficiency is progressive over time, such that the high glucose levels usually worsen relentlessly over a period of years, requiring continued escalation of blood glucose lowering therapy.

Type 2 diabetes is associated with long-term complications, reduced quality of life and life expectancy. The UK Prospective Diabetes Study (UKPDS) found that approximately 50% of people newly diagnosed with type 2 diabetes already have complications. Type 2 diabetes is notable for the increased cardiovascular risk that it carries: coronary artery disease (leading to heart attacks, angina); peripheral artery disease (leg claudication, gangrene); and carotid artery disease (strokes, dementia). In addition, prolonged hyperglycaemia can lead to irreversible microvascular complications such as diabetic retinopathy, nephropathy and neuropathy (resulting in amputation, painful symptoms, erectile dysfunction and other problems).

This section was updated in 2015

Multiple vascular risk factors and wide-ranging complications make diabetes care complex and time-consuming, and many areas of healthcare services must be involved for optimal management. Necessary lifestyle changes, the complexities and possible side effects of therapy make patient education and self-management important aspects of diabetes care.

2.2 Prevalence

This section was updated in 2015

In 2013, over 3.2 million adults were diagnosed with diabetes, with prevalence rates of 6% and 6.7% in England and Wales respectively. It is estimated that about 90% of adults currently diagnosed with diabetes have type 2 diabetes. Type 2 diabetes is more common in people of African, African-Caribbean and South Asian family origin. It can occur in all age groups and is increasingly being diagnosed in children. People who are overweight or obese, have inactive lifestyles or have a family history of diabetes are at risk. It is also more common in the less-affluent.

2.3 Health and resource burden

This section was updated in 2015

Type 2 diabetes can result in a wide range of complications with repercussions for both the person and the NHS. The economic impact of this condition includes at least 3 factors:

- direct cost to the NHS and associated healthcare support services
- indirect cost to the economy, including the effects of early mortality and lost productivity
- personal impact of diabetes and subsequent complications on people and their families.

It is estimated that diabetes account for approximately 15 to 16% of deaths in England, with life expectancy for people with type 2 diabetes reduced by an average of up to 10 years. Diabetes care is estimated to account for at least 5% of UK healthcare expenditure, and up to 10% of NHS expenditure. The presence of diabetic complications can lead to a 5-fold increase in a patient's NHS costs and people with diabetes can experience prolonged stays in hospital.

This guideline contains recommendations for managing type 2 diabetes in adults and focuses on patient education, dietary advice, managing cardiovascular risk, managing blood glucose levels, and identifying and managing long-term complications. The guideline does not cover diagnosis, secondary diabetes, type 1 diabetes in adults, diabetes in pregnancy and diabetes in children and young people.

2.4 Reasons for the update

This section was updated in 2015

Since the publication of the 2009 guideline, availability of new evidence and several key developments have prompted an update in the following areas: managing blood glucose levels, antiplatelet therapy and erectile dysfunction. In particular, reasons included safety concerns surrounding some blood glucose lowering medicines, new evidence on novel dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, new indications and licensed combinations for licensed class members and the potential impact of drugs coming off patent on health-economic issues. In addition, new evidence and safety issues relating to the off-label use of antiplatelet therapy (aspirin and clopidogrel) in the primary prevention of cardiovascular disease motivated an update of this review.

2.5 Medicines

This section was updated in 2015

The guideline will assume that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

This guideline recommends some medicines for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient (or those with authority to give consent on their behalf) should provide informed consent, which should be documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. Where recommendations have been made for the use of medicines outside their licensed indications ('off-label use'), these medicines are marked with a footnote in the recommendations.

2.6 Patient-centred care

This section was updated in 2015

This guideline offers best practice advice on the care of adults with type 2 diabetes.

When caring for older adults with type 2 diabetes, particular consideration should be given to their broader health and social care needs. Older people are more likely to have co-existing conditions and to be on a greater number of medicines. Their ability to benefit from risk-reduction interventions in the longer term may also be reduced.

Much of the evidence base used to inform this guideline has been generated from studies involving younger adults (study mean ages ranged from 45 to 68 years). While the Guideline Development Group (GDG) considered that the recommendations are applicable to a wider age group, they highlighted that there needs to be flexibility, to ensure that the care of older people with diabetes also addresses their broader health and social care needs.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. If it is clear that the child or young person fully understands the treatment and does not want their family or carers to be involved, they can give their own consent. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

3 Methods

This section was updated in 2015

This guideline update [2015] was developed in accordance with the process and methods outlined in 'The guidelines manual (2012)', which are different to those used to develop CG66 [2008] and CG87 [2009]. Chapters 7, 8, and 9.3 have been updated in 2015 and systematic reviews for each clinical question followed the review protocols (see Appendix C) agreed by the Guideline Development Group (GDG). GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology was used and/or adapted for appraising the quality of the evidence, and the Linking Evidence to Recommendations (LETR) framework was adopted to transparently document the GDG's decision making process. In instances where the guidelines manual does not provide advice, additional methods were used and are described in detail.

There is more information about how NICE clinical guidelines are developed on the NICE website. A booklet, 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS' is available.

3.1 Population

The guideline focused on adults (aged 18 years and older) with type 2 diabetes. Studies with at least 85% of people with type 2 diabetes were included, unless otherwise stated. Evidence on specific patient subgroups for whom the management of type 2 diabetes may vary were considered where available. These included (but were not restricted to):

- adults aged 65 years and older
- people with renal impairment
- people in specific ethnic groups
- people in specific cardiovascular risk groups.

3.2 Outcomes

The outcomes prioritised in the review questions reflect the treatment objectives in the management of type 2 diabetes such as controlling blood glucose levels, reducing cardiovascular risk, minimising associated complications and improving life expectancy. Unless otherwise stated, the minimal important difference (MID) for dichotomous outcomes was defined as a relative risk reduction or an increase of 25% or more.

3.2.1 Change in blood glucose levels

This section was updated in 2015

Glycated haemoglobin (HbA1c) is commonly used in clinical practice to monitor glycaemic control as it provides a measure of average plasma glucose over the preceding 8 to 12 weeks (Nathan et al. 2007), and therefore captures fluctuations including hypoglycaemic events. For this reason, the GDG agreed that change in HbA1c would be the main outcome measure used to reflect glycaemic control and a difference of 5 mmol/mol (0.5%) was considered to be clinically important. This blood test can be administered at any time and overcomes the issues of other tests (for example fasting and postprandial blood glucose) including day-to-day variability of glucose values and the inconvenience of special dietary preparation or fasting period. Since 1995, the International Federation of Clinical Chemistry (IFCC) has worked to standardise HbA1c analysis, establishing 2 reference methods – mass spectroscopy and capillary electrophoresis. Despite its advantages, HbA1c measurement may be affected by different factors such as haemoglobinopathies, illnesses like malaria that are associated with accelerated red blood cell turnover and certain anaemias.

Changes in fasting and postprandial blood glucose levels were included in the self-monitoring of blood glucose levels review (see section 8.3). The minimal important difference for both measures was 1 mmol/L (18 mg/dL).

3.2.2 Cardiovascular risk

This section was updated in 2015

Changes in blood pressure and lipid levels were included in the considered outcomes for the review question on drug treatments to control blood glucose (see review protocol in Appendix C). However, available data were too sparse or too different to allow for meaningful network meta-analyses to be undertaken and are therefore not reported.

3.2.3 Diabetes-related complications

This section was updated in 2015

Mortality, microvascular and macrovascular complications were prioritised by the GDG. These included cardiovascular disease, retinopathy, kidney damage, foot complications and erectile dysfunction specifically in men.

3.2.4 Adverse events

This section was updated in 2015

Across the included studies, adverse events were reported in many different ways. To allow for comparisons of studies and prevent double-counting of events, the following measures were prioritised for data extraction; total dropouts, dropouts because of adverse events and nausea. The GDG prioritised these measures because patients and clinicians are most interested in adverse events that affect treatment compliance and decisions.

3.2.4.1 Hypoglycaemia

This section was updated in 2015

Hypoglycaemia, although a common adverse event, was reported separately because of its significant negative impact on a person's wellbeing and quality of life and its influence on treatment decisions. Reporting of hypoglycaemia varied across the included trials in terms of definition of event and presentation of data. Both rate data (events per unit of person-time at risk) and dichotomous data (proportion of participants experiencing 1 or more event) were extracted. Where available, rate data were preferred to dichotomous data, because it is important to account for people who experience multiple events over time, and this information is lost when trial participants are split into those who have or have not experienced 1 or more event. Where rate data were not directly reported, they were sometimes estimable using the approach described in section 3.4.2.

The GDG also ranked the different types of hypoglycaemic data to reflect what they consider most clinically important. For the review question on drug treatments to control blood glucose (section 8.4), the highest ranking one reported in the trials was extracted. The hierarchy of hypoglycaemic data was:

- All hypoglycaemic events (number of events)
- All hypoglycaemic events (number of patients)
- Symptomatic hypoglycaemia
- Symptomatic (confirmed) hypoglycaemia
- Symptomatic (unconfirmed) hypoglycaemia
- Confirmed hypoglycaemia
- Minor hypoglycaemic events
- Minor (confirmed) hypoglycaemia
- Minor (unconfirmed) hypoglycaemia
- Moderate hypoglycaemia
- Moderate/severe hypoglycaemia
- Major/severe hypoglycaemic event
- Nocturnal hypoglycaemia
- Nocturnal (symptomatic) hypoglycaemia
- Nocturnal (confirmed) hypoglycaemia
- Nocturnal (mild) hypoglycaemia
- Nocturnal (moderate/severe) hypoglycaemia

3.2.4.2 Change in body weight

This section was updated in 2015

Diabetes is related to obesity and some drug treatments are associated with weight gain. Change in body weight was considered separately from other adverse events and hypoglycaemia, because the GDG agreed that it is important to patients' quality of life and self-esteem, which may affect treatment compliance.

3.3 Data extraction

This section was updated in 2015

3.3.1 Time-points

The included evidence reported a variety of follow-up periods. Given the number and heterogeneity of the time-points reported in the literature, it was important to prioritise which time-points were extracted. In order to enable the comparison of studies with different follow-up periods, the GDG considered it important to extract outcomes at common time-points. Based on clinical practice of 3-monthly medication review and the use of HbA1c as the main indicator of glycaemic control, the GDG agreed that the following time-points would provide clinically relevant evidence and enable comparisons across all studies for the review question focusing on drug treatments to lower blood glucose levels (section 8.4):

- 3 months (12 to 16 weeks)
- 6 months (22 to 30 weeks)
- 12 months (44 to 60 weeks)
- 24 months (96 to 112 weeks)

Data were extracted for each relevant timepoint that was reported in the included trials. If a study reported more than 1 data-point in the time ranges outlined above, the one closest to the central figure was extracted. For example, if data were reported at 25 and 28 weeks, the data-point closest to 6 months was extracted, that is 25 weeks. If data-points were equidistant from the time-point, for example 24 and 28 weeks, the later time period, 28 weeks was extracted. A minimum of 12 weeks' follow-up from start of treatment was agreed to be clinically relevant as it coincides with medicine reviews and HbA1c measurements.

For the supplementary review question on the long-term serious adverse effects of blood glucose lowering drug treatments (section 8.5), the GDG agreed that a minimum follow-up period of 2 years was sufficient to allow for adverse events and complications to occur.

For the review question on self-monitoring of blood glucose levels (section 8.3), the GDG agreed that a minimum follow-up period of 4 weeks would allow for important information on short-term outcomes such as hypoglycaemia to be captured.

No time restrictions were placed on the remaining review questions on optimal blood glucose targets (sections 8.1 and 8.2), use of antiplatelet therapy for primary prevention of cardiovascular disease (section 7) and management of erectile dysfunction (section 9.3).

For dichotomous outcomes such as adverse events, data were generally extracted at study end-point.

3.3.2 Conversion of continuous outcome data

Continuous outcomes which reported different units (for example, HbA1c in % or mmol/mol) were converted to a common unit prior to synthesis. Estimates of body weight in kilograms were calculated from studies which only reported body mass index (BMI). Where the mean height of the cohort was available, this was used to estimate weight; where no height data were available the mean height of people in the THIN dataset derived for the health economic model (168 cm; see section 8.4.3.3) was used.

3.3.3 Process

Data were extracted by 1 reviewer and a second reviewer checked the studies included in the analyses. Where numerical data were not reported in tables or text, information was extracted from graphs by digitising the images and using a bespoke electronic ruler in Microsoft Excel. Data were typically extracted from graphs where relevant time-points were not reported (for example, the study reported outcomes at 1 year but provided a graph of changes over time with data-points at 3 and 6 months) and only if measures of dispersion were provided (for example, error bars from graphs were used to estimate standard deviations).

3.4 Data imputation

This section was updated in 2015

3.4.1 Estimating mean change from baseline

Where possible, mean difference from baseline to follow-up was the point of synthesis for continuous measures. If the study did not provide the mean difference, where possible, it was calculated from reported baseline and follow-up scores that is, follow-up score minus baseline value. However, the standard deviation (SD) of mean differences is also required for syntheses. To estimate this, it is necessary to specify the correlation between measurements at the 2 time-points. These were estimated from studies in the effectiveness evidence base. Where a study reports SD at baseline (σ_b), SD at follow-up (σ_f) and the SD of changes between baseline and follow-up (σ_c), the correlation (C) between baseline and follow-up for that study may be estimated by:

$$C = \frac{\sigma_b^2 + \sigma_f^2 - \sigma_c^2}{2 \times \sigma_b \times \sigma_f} \quad \textbf{(1)}$$

C was calculated for each arm (regardless of treatment assignment) in each study reporting the necessary information. These values were combined by a weighted average according to the number of people in the arm, and the resulting average *C* used to impute SDs of mean differences in studies that did not report them, using the formula:

$$\sigma_c = \sqrt{\sigma_b^2 + \sigma_f^2 - (2 \times C \times \sigma_b \times \sigma_f)} \quad \textbf{(2)}$$

In some instances, the correlation coefficient that was estimated from the evidence base was observed to be outside the acceptable values (that is, outside the range of −1 to 1) or were very close to perfect correlation. These were assumed to be a result of inaccuracies in the data, typos in the primary paper and unclear measures of reported variance (SD or standard error, SE), generally estimated from graphs. These estimated correlation coefficients were unlikely to represent true population values. In these cases, and also in syntheses where no studies provided sufficient evidence to estimate a correlation coefficient, a conservative value of 0.5 was used (Follmann et al. 1992).

3.4.2 Estimating person time at risk

This section was updated in 2015

When events are likely to occur to a person more than once (for example, hypoglycaemic events), it is preferable to use count or rate data. To calculate the rate of an event occurring, the total number of events and total person-time at risk are needed. However, papers did not commonly report person-time at risk.

Where papers reported the rate of events occurring and the total number of events, the corresponding person-time at risk was estimated. If studies provided data on specific timings of dropouts for people who withdrew from the trial, these durations were used to estimate the person-time at risk. Where these data were not reported, a crude estimate of person-time at risk for each arm in a trial was obtained from the number of participants (N), the duration of the trial (D) and the number of dropouts in the trial arm (y) using the formula:

$$ND - 0.5Dy. \quad \textbf{(3)}$$

The accuracy of this crude estimation of person time at risk was tested by comparing values obtained using the equation above with values obtained using reported rates and total number of events. Although there were some differences in the values of person-time at risk, there was minimal impact on the overall rate of events.

3.4.3 Approach to missing data

This section was updated in 2015

Many of the included trials that used intention-to-treat (ITT) analyses used the last observation carried forward (LOCF) imputation, which is considered to overestimate treatment effects. Unfortunately, it is difficult to adequately deal with this data for continuous outcomes without individual patient data reported for each study.

3.5 Crossover trials

This section was updated in 2015

The incorporation of data from RCTs of parallel and crossover design in single quantitative syntheses is a subject of methodological debate (Elbourne et al. 2002). The following approaches were considered:

1. The optimal method is to include data from crossover studies in a way that exploits the increased precision the crossover design provides. This is straightforward where within-patient differences from a paired analysis are reported by authors; alternatively, methods are available that can impute these data if the correlation between treatment periods is known (or can be calculated) (Elbourne et al. 2002).
2. Another method sometimes used is to restrict attention to the first period of randomised treatment in each crossover trial only. In this way, a parallel trial of half the size is derived. This approach is suboptimal, as it discards data from the remainder of the trial, and relies on data being reported in a way that facilitates the extraction of data from the initial period only.
3. Another option is to exclude all crossover studies from consideration.
4. Finally, it is possible to ignore the crossover design of the trials, and analyse them as if they had a parallel design. This method is not generally recommended, as it ignores within-patient correlations and therefore discards the design advantages of crossover trials. However, this means that the approach is conservative, as it results in the trials having less weight in syntheses than they would have if paired data were used (or imputed).

The issue of washout period was discussed with the GDG and it was agreed that a minimum of 4 to 6 weeks would be adequate to minimise the influence of existing therapies. Therefore, the following decisions were taken relating to which data from crossover trials were extracted:

- If the trial reported analysis that is considered appropriate for crossover designs and a washout period of 4 to 6 weeks, then the end of treatment data were extracted.
- If the trial reported analysis that is considered appropriate for crossover designs but a washout period of less than 4 weeks, then data from the first treatment period only were extracted.
- If the trial did not report analysis that is considered appropriate for crossover designs, then data from the first treatment period only were extracted.

3.6 Evidence synthesis

3.6.1 Meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For continuous outcomes, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were differences at baseline these studies were not included in any meta-analysis and were reported separately.

3.6.2 Network meta-analyses

Network meta-analyses (NMAs) were conducted to simultaneously compare multiple treatments in a single meta-analysis, preserving the randomisation of the included trials in the reviews. This allows all evidence to be combined in a single internally consistent model.

An extensive series of NMAs was undertaken to synthesise evidence on pharmacological treatments to control blood glucose (see section 8.4). The GDG's preferred approach to identifying and synthesising relevant evidence for these analyses relied on several critical assumptions that are discussed in section 8.4.1.

Hierarchical Bayesian NMA was performed using the software WinBUGS version 1.4.3. The models were based on the approach and code provided in the NICE Decision Support Unit's Technical Support Documents on evidence synthesis, particularly Technical Support Document 2 ('A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials'; see http://www.nicedsu.org.uk/). Model code is provided in Appendix K.

3.6.2.1 Continuous outcomes

Identity-link models, which rely on a normal likelihood, were used for continuous outcomes. It should be emphasised that these models do not assume that the measures being synthesised are, themselves, normally distributed; rather, they assume that the sample means are normally distributed (given sufficiently large samples, this would be expected to be the case regardless of skewness in the underlying data, according to the Central Limit Theorem; in the case in hand, many of the datasets are relatively small and convergence to a normal distribution of means may not have occurred; however, the same lack of data would make it difficult to select an alternative likelihood).

Mean difference from baseline to follow-up was the point of synthesis for continuous measures (see section 3.4.1). We were unable to include the outcomes from studies where continuous data were reported in the form of median differences or as percentage change from baseline in syntheses as it is not possible to combine outcomes with these measures and mean differences (the point of synthesis chosen) without access to individual patient data.

The WinBUGS code used for this model is provided in Appendix K.

3.6.2.2 Dichotomous outcomes

This section was updated in 2015

As advised in NICE DSU TSD 2 (Dias et al. 2012a), dichotomous outcomes can be synthesised using 2 alternative models:

- The most straightforward model adopts a binomial likelihood with a logit link function, and generates output on a log-odds scale, with results transformed to odds ratios for presentation.
- An alternative model incorporates data on duration of follow-up in each underlying RCT, assuming a constant rate of events, to estimate the probability of events occurring over time. Again, a binomial likelihood is assumed, but a complementary log–log ('cloglog') link function is used, which results in outputs on a log-hazard scale (transformed into hazard ratios for presentation).

Where differences in follow-up in the underlying evidence were believed or shown to be minor and/or unimportant, the simpler logit-link model was preferred. Where duration of follow-up was believed to have a potential impact on outcomes, both models were explored, and the choice made on the basis of goodness of fit (see section 3.6.2.7).

The WinBUGS code used for these models is provided in Appendix K.

Zero cells

This section was updated in 2015

In datasets containing studies with 'zero cells' (that is, trials in which no events occurred in 1 or more arm), substantial instability was encountered when performing syntheses. To address this problem, a constant of 0.5 was added to all cell counts (effectively adding 0.5 to the numerator and 1 to the denominator of the proportion). The same approach was used to address instability for datasets containing studies with 100% events reported in all arms.

Studies reporting no events in any arms were excluded from NMAs, as they do not provide any information on the relative likelihood of events occurring.

3.6.2.3 Rate / count outcomes

This section was updated in 2015

For rate data (event per unit of person-time), a Poisson model with a log link function was used, to estimate the probability of events occurring over time. These models produce outputs on a log-hazard scale (transformed into hazard ratios for presentation).

3.6.2.4 Combining dichotomous and rate data

This section was updated in 2015

Because, as noted above, both rate data and dichotomous data (with an estimate of follow-up time) can be synthesised on a log-hazard scale, it is possible to combine both types of data in a hybrid model with appropriate likelihoods and link functions for each type of data. This assumes that, regardless of which way the data are reported, the incidence of events has the characteristics of a homogeneous Poisson process. Models of this type were run to combine heterogeneously reported data on incidence of hypoglycaemia (see section 3.2.4.1).

The WinBUGS code used for the hybrid binomial–cloglog/Poisson–log model is provided in Appendix K.

3.6.2.5 Prior distributions

This section was updated in 2015

Non-informative prior distributions were used in all models. Trial baselines and treatment effects were assigned $N(0, 100^2)$ priors. The between-trial standard deviations used in random-effects models were given U(0, 2) priors for dichotomous outcomes. It was considered that this standard deviation was appropriate as the upper limit of 2 represents a huge range of trial-specific treatment effects. This is recommended in NICE DSU Technical Support Document 2. U(0, 2) priors were also used for syntheses of continuous measures of HbA1c (units in %) – given the relatively limited range in which HbA1c values fall, this was considered to be appropriately vague. Sensitivity analyses with broader priors demonstrated negligible impact. U(0, 10) priors were used for syntheses of continuous measures of body weight (units in kilogram).

3.6.2.6 Running the model

This section was updated in 2015

In the first instance, models were run with 50,000 burn-ins and 10,000 iterations. Three separate chains with different initial values were used. If models did not appear to converge well, they were re-run with more burn-ins and/or observations 'thinned' from a large number of posterior samples (for example, every 20th sample of 200,000 could be used to provide 10,000 iterations with minimised autocorrelation).

Model ouputs were assessed for any points that significantly deviated from the other data-points and the reasons for any deviate points were investigated.

3.6.2.7 Goodness of fit

This section was updated in 2015

Measures of model fit were scrutinised to assess appropriateness of each model. Particular attention was paid to:

- **Total residual deviance**: a calculation of the model's ability to predict the individual data-points underlying it. In every iteration of the model sampling procedure, the amount each model-estimated data-point deviates from the observed evidence is calculated, summed and averaged over all iterations. Each data-point should contribute about 1 to the posterior mean deviance; therefore, the total residual deviance of a well-fitting model will be approximately the same as the number of independent data-points in the model.
- **Deviance information criterion (DIC)**: an estimate of deviance that is 'penalised' according to the number of parameters in the model (adding parameters to a model should increase its ability to predict known data; however, this may come at the expense of reducing its ability to predict external datasets).
- **SD of random-effects term (tau)**: where a random-effects model is fitted, the width of the inter-study heterogeneity distribution estimated by the model is a reflection of heterogeneity in the underlying data. Therefore, while not a measure of goodness of fit *per se*, it is useful to consider as an indication of how broad a model is required to fit the data. Because inter-study heterogeneity is not modelled in fixed-effects models (that is, tau is assumed to be 0), there is no analogous quantity that can be used to compare different fixed-effects models.

3.6.2.8 Choice of model (random- versus fixed-effects)

This section was updated in 2015

For all syntheses, both random and fixed effects models were run and model fit measurements were explored to select the most appropriate model for the specific outcome. If either model had clearly superior residual deviance and/or DIC, it was preferred; if there was little to choose between them, fixed-effects models were preferred for reasons of parsimony and interpretability. In practice, this led to a rule where fixed-effects models were preferred unless the corresponding random-effects model had a DIC that was 3 or more lower. Model fit statistics and selection decisions are shown in Appendix J.1.

An exception to this principle was in instances where there was only 1 study for each link in the network. In this case, no data are available to estimate the random-effects term; therefore, a fixed-effects model was used.

3.6.2.9 Meta-regression

This section was updated in 2015

For some larger datasets, the potential for heterogeneity of treatment effect to be explained by study-level covariates was explored in meta-regression (see NICE DSU TSD 3 [Dias et al. 2012b]). In particular, for analyses of the relative effectiveness of pharmacological treatments (research question 1), it was considered important to account for baseline HbA1c level – it has been suggested that differences in baseline severity may account for some or all of observed differences in treatment effects (Chapell et al. 2009). However, none of these analyses produced models that provided a better fit to the data, as evident in the following characteristics:

- The regression coefficients were associated with broad credible intervals crossing 0.
- In fixed-effects analyses, measures of goodness of fit were inferior for models including a covariate than for unadjusted models.
- In random-effects analyses, the heterogeneity term was not materially reduced.

For all these reasons, the approach was judged not to be informative, and results have not been reported here.

Although this was the case for the relative effect estimates presented here, it was not true of the absolute HbA1c effect estimates – to which relative effects are then applied – that are necessary for the health economic model (see Appendix F3.5.1 for a description of the adjustment of these analyses for baseline level).

3.6.2.10 Inconsistency between direct and indirect evidence

This section was updated in 2015

As suggested in NICE DSU TSD 4 [Dias et al. 2012c], an 'inconsistency' model was fitted to each dataset on which NMA was undertaken. The outputs of these models were compared with the relevant NMA ('consistency' model) to identify any discrepancies between direct and indirect evidence. In particular, the posterior mean of the residual deviance contribution of each data point in each of the 2 models were plotted against each other and visually inspected to see if any inconsistency was suggested (any absolute discrepancy of greater than 0.5 was highlighted and investigated). In practice, few such inconsistencies were seen, and any that occurred were invariably easily explained (in particular, dichotomous syntheses in which zero events were observed in 1 or more trial-arm resulted in high and variable residual deviance estimates). For these reasons (and to avoid unnecessary multiplication of already-numerous results), outputs of the inconsistency models have not been reported. The posterior estimates of effect have, however, been used to show direct evidence in the pairwise relative effect plots relating to dichotomous data (which relied on cloglog or hybrid models that do not lend themselves to simple pairwise frequentist meta-analysis).

3.6.2.11 Presentation of results for network meta-analyses

This section was updated in 2015

The results of the meta-analyses were presented in a number of ways.

- Network diagram, showing availability of evidence. These diagrams have the following features:
    - The size of each node is proportional to total number of participants randomised to receive the treatment in question across the evidence-base.
    - The width of connecting lines is proportional to number of trial-level comparisons available.
    - Where possible, arrowheads are added to the connecting lines to indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior ($p<0.05$); outlined arrowheads show direction of trend where effect does not reach statistical significance. It has not been possible to add these for some analyses, as it is not straightforward to estimate direction of effect with more complex models.

- Plot of the relative effectiveness, including the results of the NMA of each regimen compared with the reference treatment (for example, see Figure 28) and any direct estimate available for the same comparison.
- Tabulated rank probabilities, giving the probability of each treatment being best (that is, ranked #1) and its median rank with 95% credible interval (CrI). In these outputs, higher ranking always reflect what is best for the patient (for example: higher rates of disease eradication, lower rates of adverse events, lower blood glucose levels, and so on).

More detailed model outputs and a summary of input data for each analysis are available in Appendix J.

3.7 Quality assessment

This section was updated in 2015

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'The guidelines manual (2012)'.

3.7.1 GRADE for pairwise meta-analyses

The quality of the evidence base was downgraded for the reasons outlined in Table 1.

Table 1: Rationale for downgrading quality of evidence in pairwise meta-analyses for intervention questions

GRADE criteria	Example reasons for downgrading quality
Risk of bias	This includes limitations in the design or execution of the study, including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating)
Inconsistency	Inconsistency of effects across studies: occurs when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the statistic, I^2 where ; $I^2 < 30$ was categorised as no inconsistency, I^2 between 30% and 60% was categorised as serious inconsistency and $I^2 > 60\%$ was categorised as very serious inconsistency (this can reduce the quality rating)
Indirectness	The extent to which the available evidence fails to address the specific review question (this can reduce the quality rating)
Imprecision	Present when there is uncertainty around the estimate of effect, for example when the confidence intervals are wide and cross the 'imaginary' lines of clinically significant effect that is minimal important difference. This reflects the confidence in the estimate of effect. Minimal important differences are selected *a priori* by GDG consensus or from published estimates. For dichotomous outcomes, imprecision was assessed by use of minimal important difference of 0.25 (this can reduce the quality rating)
Other considerations	Large magnitude of effect, evidence of a dose-response relationship, or confounding variables likely to have reduced the magnitude of an effect; these can increase the quality ratings in observational studies, provided no downgrading for other features has occurred

3.7.2 Modified GRADE for network meta-analyses

The use of GRADE to assess the quality of studies addressing a particular review question for pairwise comparisons of interventions is relatively established. However, the use of GRADE to assess the quality of evidence across a NMA is still a developing methodology. While most criteria for pairwise meta-analyses still apply, it is important to adapt some of the criteria to take into consideration additional factors, such as how each 'link' or pairwise comparison within the network applies to the others. As a result, the following was used when applying modified GRADE to a NMA.

Table 2: Rationale for downgrading quality of evidence in network meta-analyses

GRADE criteria	Example reasons for downgrading quality
Risk of bias	Trials with large reductions in outcome measures were associated with high risk of bias for example if: • There was a tendency for higher baseline HbA1c which may have had an undue effect (such as large trials with high baseline HbA1c levels of more than 69 mmol/mol (8.5%) for initial therapy may have had an impact on the overall rankings)
Inconsistency	Evidence of any inconsistency between the direct and indirect estimates of effect was assessed using the residual deviance, deviance information criterion and the statistic tau. Downgrade if tau > 0.5
Indirectness	Trials were conducted in countries where dietary habits may differ and may not be representative of people with type 2 diabetes living in the UK (for example Japan and China). Evidence was only downgraded if this was likely to have a large impact on the overall rankings (that is, within smaller networks where there is a lack of evidence or within larger networks in large trials which show large reductions in outcomes)
Imprecision	This was assessed based on the overall distribution of the rankings, such that evidence was downgraded if no interventions had rank credible intervals ≤33% of total distribution of comparators

3.7.3 Modified GRADE for prognostic evidence

GRADE has not been developed for use with prognostic studies; therefore a modified approach was applied using the framework provided for GRADE in diagnostic studies. This assessment was used for evidence in the review question on optimal target values (see section 8.1).

This section was updated in 2015.

Cohort studies within the non-modified GRADE approach start at the low-quality level because of accepted inherent study design limitations. Within a modified approach it is acceptable to initially indicate a high-quality level to this study type and to assess the quality of evidence from this point. The same criteria (risk of bias, inconsistency, imprecision and indirectness) were used to downgrade the quality of evidence. Quality ratings were downgraded further for risk of bias if there was evidence of selection bias. Indirectness was assessed by examining any important differences in population, prognostic factor or outcome of the included evidence compared with those for whom the recommendation is intended. Imprecision was assessed by examining the sample size or the 95% confidence intervals around the estimate of effect. GRADE provides a guide when assessing imprecision in intervention questions (that is, where the total sample size is less than 400, the event rate is less than 300, or the 95% confidence intervals cross the thresholds for appreciable benefit or harm or the minimal important difference). The evidence was downgraded for imprecision where the 95% confidence intervals were wide or the sample size was less than 400.

4 Education

4.1 Structured education

4.1.1 Clinical introduction

This section was updated in 2015

Type 2 diabetes mellitus is a progressive long-term medical condition that is predominantly managed by the person with diabetes and/or their carer as part of their daily life. Accordingly, understanding of diabetes, informed choice of management opportunities, and the acquisition of relevant skills for successful self-management play an important role in achieving optimal outcomes. Delivery of these needs is not always assured by conventional clinical consultations. Structured programmes have been designed not only to improve people's knowledge and skills, but also to help motivate and sustain people with diabetes in taking control of their condition and in delivering effective self-management.

Information from the Health Commission survey in 2007 suggests that only 11% of people with type 2 diabetes report being offered structured education.[8] This suggests that the majority of healthcare providers have found it difficult to implement and resource quality education programmes that meet these standards. There appears to be an urgent need to ensure that all people with type 2 diabetes are offered high-quality structured education. The aims of structured education and self-management programmes are to improve outcomes through addressing the individual's health beliefs, optimising metabolic control, addressing cardiovascular risk factors (helping to reduce the risk of complications), facilitating behaviour change (such as increased physical activity), improving quality of life and reducing depression. An effective programme will also enhance the relationship between the person with diabetes and their healthcare professionals, thereby providing the basis of true partnership in diabetes management.

The clinical question that has been addressed is how to deliver such education, including what approaches deliver the intended benefits, and what components of the education process best deliver the surrogate, self-care, and quality of life outcomes.

4.1.2 Methodological introduction and evidence statements

Please refer to the Technology Assessment Report 'The clinical effectiveness of diabetes education models for type 2 diabetes: a systematic review' commissioned by the NHS R&D Health Technology Assessment (HTA) programme on behalf of the NCC-CC. Available at www.ncchta.org/project/1550.asp

4.1.3 Health economic methodological introduction

Two papers were identified in the search for health economics. Neither study was conducted in the UK and the results were not generalisable to the UK setting so both were excluded.[9,10]

4.1.4 Evidence to recommendations

The GDG noted that the last review of this area by a HTA on behalf of NICE in 2003 looked at the evidence for structured education. Little robust evidence of the effectiveness of any particular educational approach for people with type 2 diabetes was found. One conclusion was that further research was required, but meanwhile that educational programmes with a theoretical basis demonstrated improved outcomes, and that group education was a more effective use of resources and may have additional benefits.

Educational interventions are not only complex in themselves, but they also exist in a complex environment with other aspects of managing a chronic disease. Such interventions will interact with, and support medical management directed at vascular risk factors and that of diabetes complications which have already developed. Their success is likely to depend on the individual's personal and cultural beliefs, the overall healthcare setting, their lifestyles, and perhaps their educational background.

It was noted that to address some of the difficulties in describing and implementing effective structured education and self-management programmes, a Patient Education Working Group (PEWG) had been convened by the Department of Health and Diabetes UK, and had laid out in detail the necessary requirements for developing high-quality patient education programmes. The key criteria had been endorsed by the recent HTA review. The 5 standards were as follows.

1. Any programme should have an underpinning philosophy, should be evidence-based, and suit the needs of the individual. The programme should have specific aims and learning objectives, and should support development of self-management attitudes, beliefs, knowledge and skills for the learner, their family and carers.
2. The programme should have a structured curriculum which is theory-driven, evidence-based, resource-effective, have supporting materials, and be written down.
3. It should be delivered by trained educators who should have an understanding of the educational theory appropriate to the age and needs of the programme learners, and be trained and competent in delivery of the principles and content of the specific programme they are offering.
4. The programme itself should be quality assured, be reviewed by trained, competent, independent assessors and be assessed against key criteria to ensure sustained consistency.
5. The outcomes from the programme should be regularly audited.

The GDG found no reason to diverge from these principles. The GDG noted and endorsed the importance of quality assurance and audit in this complex area.

As the intervention is complex, the measured outcomes of any particular programme are by nature multifaceted and will vary with such factors as the timing in relation to diagnosis, critical changes of therapy, or other critical clinical findings. Even then, appropriate study outcomes are for the most part interim surrogate measures; no studies included late complications. However, psychological outcomes as well as biomedical outcomes can be appropriately assessed, to include quality of life and change in healthcare behaviours, and aspects of depressed mood. More directly cognitive measures, knowledge, acquisition of skills, and changing health beliefs were found to be useful indicators of a programme's effectiveness.

The HTA commissioned for this review included 14 studies, of which 8 appeared to have been conducted since 2003, and most were for people with established (rather than newly diagnosed) type 2 diabetes. The GDG noted that, as expected, some studies showed effects on HbA1c, others improved body weight and other lifestyle changes, some improved quality of life or knowledge, and yet others changed health beliefs or reduced depression. This diversity was often a reflection of study aims and design. The HTA review acknowledged that health psychology approaches and some methods of health promotion have a good evidence base, but little is incorporated into studies of structured education, even though addressing health beliefs and motivating individuals to change behaviour is a cornerstone of any educational programme. Reported training for diabetes educators was poorly detailed in most studies.

The GDG was concerned that only 3 studies were UK-based. As cultural issues, patient health beliefs and attitudes are likely to differ from 1 country to another, applicability of the others may be limited. The GDG noted that the UK Diabetes Education and Self

Management for Ongoing and Newly Diagnosed (DESMOND study) found changes in health beliefs, reduction in depression, and increases in self-reported physical activity, reduction in weight and improvement in smoking status. In people with established diabetes there was useful evidence from the X-PERT programme with improvements in HbA1c, reduced diabetes medication, body weight, waist circumference, total serum cholesterol, diabetes knowledge and increase in self-reported physical activity and treatment satisfaction.

Overall the GDG then felt that well-designed and well-implemented programmes were likely to be effective and cost-effective interventions for people with type 2 diabetes, in line with the NICE TA. For those people in whom education delivered in a group setting is appropriate, it is evidently likely to be more cost effective.

4.1.5 Recommendations and research recommendations

4.1.5.1 Individualised care

The current recommendations can be found at www.nice.org.uk/guidance/ng28

5 Lifestyle and non-pharmacological management

5.1 Dietary advice

5.1.1 Clinical introduction

All people with type 2 diabetes should be supported to:

- try to achieve and maintain blood glucose levels and blood pressure in the normal range or as close to normal as is safely possible
- maintain a lipid and lipoprotein profile that reduces the risk of vascular disease.

Optimal dietary behaviours can contribute to all of these.

Dietary intervention should address the individual's nutritional needs, taking into account personal choices, cultural preferences and willingness to change, and to ensure that quality of life is optimised. It is usual that a registered dietician plays a key role in providing nutritional care advice within the multidisciplinary diabetes team. It is also recognised that all team members need to be knowledgeable about nutritional therapy, and give emphasis to consistent dietary and lifestyle advice.[11]

The management of obesity is not specifically addressed in the current guideline. Readers are referred to the NICE obesity guideline which addresses the area in some detail.[12]

Smoking cessation is not addressed in the current guideline. Readers are referred to the NICE public health programme guidance on smoking cessation services, including the use of pharmacotherapies, in primary care, pharmacies, local authorities and workplaces, with particular reference to manual working groups, pregnant smokers and hard to reach communities.

Clinical questions arise around the optimal strategies to reduce calorie intake (and thus improve sensitivity to endogenous insulin), to control exogenous delivery of free sugars into the circulation, to control blood pressure, and to optimise the blood lipid profile. Issues specifically related to people with kidney disease or of medical use of fish oils are not considered in this this guideline.

5.1.2 Methodological introduction

The search attempted to identify RCTs and observational studies conducted in adults with type 2 diabetes which were assessing different forms of dietary advice targeting weight loss. A sample size threshold of N=50 and a follow-up of at least 3 months were established as cut-off points. Studies evaluating purely pharmacological interventions for weight reduction were excluded.

There were only 8 studies that addressed this question.[13–20] Two RCTs were excluded due to methodological limitations.[c] In all the studies, the intent was for participants to lose weight and thereby improve glycaemic, lipid and blood pressure control.[d] Among the remaining 6 studies there were 4 RCTs and 2 observational studies. No major methodological limitations were identified across these studies.

[c] One RCT comparing the effects of a high-protein with a low-protein diet[15] and another RCT comparing low-carbohydrate versus conventional weight loss diets in severely obese adults.[18]
[d] Four studies focused on the effects of diet in obese people with type 2 diabetes.

RCTs

One RCT[17] compared the effects of a combined intervention; low-calorie diet, sibutramine therapy and meal replacements with an individualised reduced calorie diet, and was the only study to include the use of weight-loss medication.

Two RCTs used the American Diabetes Association (ADA) guidelines as a comparison group to either a soy-based meal replacement intervention,[13] N=104 with a 1-year follow-up, or a low-fat vegan diet,[14] N=99 with a 22-week follow-up.

A further RCT compared a low-fat with a low-carbohydrate diet.[16]

Observational studies

A case series with a follow-up of 6.5 years investigated the onset of diabetic complications and adherence to ADA recommendations.[19] A prospective cohort study addressed the relationship between eating habits and long-term weight gain, following a group of patients being managed in primary care for a period of 4 years.[20]

It should be noted that the results of diet interventions aimed at patients with type 2 diabetes are difficult to interpret due to differences in the interventions, the populations, the study designs and the outcomes reported.

As is obvious, isolated diet interventions without adequate educational support and concomitant lifestyle changes are very unlikely to reduce risk factors and to improve clinical outcomes and quality of life for patients with type 2 diabetes.

5.1.3 Health economic methodological introduction

No health economic papers were identified.

5.1.4 Evidence statements

5.1.4.1 Weight reduction and glycaemic control outcomes

RCTs

Studies that compared a meal replacement intervention with a reduced calorie diet

A RCT comparing a soy-based meal replacement with an individualised diet based on ADA recommendations in obese people with type 2 diabetes[13] found that average weight reduction in the meal replacement group was greater than that in the individualised diet group. At 6 months, the meal replacement group had lost on average 5.24±0.60 kg, and the individualised diet group had lost an average of 2.85±0.67 kg (p=0.0031). At 1 year this difference was not significant with the meal replacement group losing on average 4.35±0.81 kg and the individualised diet group losing an average of 2.36±0.76 kg (p=0.0670). **Level 1+**

The same RCT reported that similar changes were observed in the body mass index (BMI) at 12 months with a reduction of 1.47±0.27 kg/m^2 in the meal replacement group and 0.77±0.25 kg/m^2 in the individualised diet group. Although these values were significantly different from their baseline values, none were significantly different from each other (p=0.0687). **Level 1+**

With respect to glycaemic control, the RCT found that mean HbA1c levels were significantly lower in the meal replacement than in the individualised diet group, 0.49±0.22% (p=0.0291), for the entire study period. Plasma glucose concentrations were significantly lower in the meal replacement group than in the individualised diet group at 3 (p=0.04) and 6 (p=0.002) months, but not at 12 months (p=0.595). **Level 1+**

The study by Redmon[17] reported on a combination intervention including sibutramine, an intermittent low-calorie diet with the use of meal replacements for 1 week every 2 months, and the use of meal replacements between the low-calorie diet weeks. The comparison group received an individualised diet plan with a 500–1000 kcal energy deficit per day.

The study reported that at 1 year of follow-up, the combination therapy group had a significantly greater weight loss of 7.3±1.3 kg than the standard therapy group 0.8±0.9 kg ($p<0.001$), with most weight loss occurring during the low-calorie weeks and some weight gain occurring in between the low-calorie weeks. **Level 1+**

In relation to glycaemic control, the study showed that at 1 year, HbA1c had declined from a baseline of 8.1±0.2% to 7.5±0.3% in the combination therapy group but had remained unchanged at 8.2±0.2% in the standard therapy group, and this difference was significant ($p=0.05$). After adjusting for medication changes, this difference remained significant. In an analysis of those participants whose medication had not changed, it was found that there was a significant positive linear association between change in weight at 1 year and change in HbA1c ($r=0.53$; $p=0.006$). A 5 kg decrease in weight at 1 year was associated with a 0.4% decrease in HbA1c. **Level 1+**

Studies comparing a low carbohydrate with a low fat diet

One RCT[16] examined the short-term effects, participants were followed up for 3 months, of a low-carbohydrate diet compared with a reduced portion low-fat diet in obese people with type 2 diabetes. There was a significantly larger mean weight reduction in the low-carbohydrate arm (N=51) of the RCT, 3.55±0.63 kg, than in the low-fat arm (N=51) which showed a mean reduction of 0.92±0.40 kg ($p=0.001$). **Level 1+**

The same RCT reported that glycaemic control improved in both arms of the trial. Improvements were greater in the low-carbohydrate arm, HbA1c decreased from a baseline of 9.00±0.20%, by 0.55±0.17%, but this did not reach statistical significance. In the low-fat arm HbA1c decreased from a baseline of 9.11±0.17% by 0.23±0.13% ($p=0.132$). **Level 1+**

Studies comparing low or modified fat diets with reduced calorie diets

Barnard et al.[14] investigated the effects of a low-fat vegan diet compared with a diet based on ADA guidelines, on body weight and glycaemic control in a RCT with 99 people with type 2 diabetes, followed up for 22 weeks. During the study period, 43% (21/49) of vegan participants and 26% (13/50) of ADA participants reduced their diabetic medications, mainly as a result of hypoglycaemia. Eight per cent in each group, 4/49 of the vegan group and 4/50 of the ADA group, increased their medications.

The study concluded that for the whole sample, body weight was reduced in both groups by 5.8 kg in the vegan group and 4.3 kg in the ADA group, but this difference was not statistically significant ($p=0.082$). In those whose medication was stable this difference was significant with a 6.5 kg reduction in the vegan group, and 3.1 kg in the ADA group, $p<0.001$. BMI declined by 2.1±1.5 kg/m^2 in the vegan group and by 1.5±1.5 kg/m^2 in the ADA group ($p=0.08$). The waist-to-hip ratio declined in the vegan group 0.02±0.01 but not in the ADA group ($p=0.003$). **Level 1+**

With respect to glycaemic control, the RCT stated that while the HbA1c decline in both groups was statistically significant from their baseline values with a decrease of 0.96% ($p<0.0001$) in the vegan group and 0.56% ($p=0.0009$) in the ADA group, there was no significant difference between the groups ($p=0.089$). Again the results were different in those participants whose medication was unchanged. The HbA1c decline was greater in the vegan group, 1.23±1.38%, than in the ADA group, 0.38±1.11%, ($p=0.01$). **Level 1+**

Table 3: Summarised results for body weight reduction and glycaemic control across RCTs

RCTs	Follow-up	Comparison	Comparison	Weight/BMI	Glycaemic control
Li (2005)[13]	1 year	Soy based meal replacement	Individualised diet	Weight and BMI=NS	HbA1c significantly lower in meal replacement arm
Redmon (2003)[17]	1 year	Sibutramine + low calorie diet + meal replacement	Individualised diet	Weight reduction significantly higher in combination arm	HbA1c significantly lower in combination arm*
Daly (2006)[16]	3 months	Low-carbohydrate diet	Reduced portion low-fat diet	Weight reduction significantly higher in combination arm	HbA1c=NS
Barnard (2006)[14]	22 weeks	Low-fat vegan diet	Diet based on ADA guidelines	Weight=NS	HbA1c=NS
*A 5 kg decrease in weight at 1 year was associated with a 0.4% decrease in HbA1c NS not significant					

Observational studies

In an observational study with 4 years of follow-up,[20] the authors investigated the association between eating behaviour and long-term weight gain. Ninety-seven people with type 2 diabetes were recruited at diagnosis and after initial nutrition advice were followed up for a period of 4 years.

The study found that at the end of follow-up, mean body weight change in men was a gain of 1.3±5.4 kg, whereas in women, there was a mean body weight reduction of –1.1±5.0 kg. These changes were not statistically significant (p values not given). Similarly, BMI increased in men by 0.42±1.76 kg/m^2 and decreased in women by 0.40±1.89 kg/m^2 (p values not given). Glycaemic outcomes were not reported. **Level 2+**

In the second observational study,[19] weight loss over the 6.5-year follow-up is not reported. However, metabolic control did improve in patients over the period, with the proportion of patients with HbA1c <7% increasing from 52.4% to 64.3% in men and from 43.9% to 50.9% in women. It was not reported whether or not this was significant. **Level 3**

5.1.4.2 Blood pressure and blood lipid control outcomes

RCTs

Studies that compared a meal replacement intervention with a reduced calorie diet

The RCT by Li et al.[13] reporting on the comparison of a soy-based meal replacement plan with an individualised diet plan, did not report on changes in blood pressure during the study.

For the blood lipid control outcomes, while there were no significant differences between groups during the study for lipid parameters, there were differences within the groups when compared to baseline values. In the meal replacement group, there were decreases in total cholesterol, triglycerol, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) at the end of the study, however these changes were only significant in the triglycerol group with an overall decrease from baseline of 28.00 mg/dl (p=0.038). Decreases in total cholesterol were significant at 3 (p<0.0001) and 6 (p=0.0037) months, but at 12 months with a reduction of 10.76 mg/dl from baseline, this was not significant (p=0.084). LDL decreased by 11.04 mg/dl at 3 months (p=0.024), but at 12 months the change from baseline had reduced to 6.10 mg/dl (p=0.255). HDL had decreased by 0.97 mg/dl at 12 months (p=0.345). In the individualised diet plan group, after initial decreases at 3 or 6 months, at 12 months there were increases in total cholesterol by 5.26 mg/dl (p=0.396), LDL by 8.76 mg/dl (p=0.129) and HDL by 2.26 mg/dl (p=0.012). Only in triglycerol levels was there a sustained decreased at 12 months with a reduction from baseline of 28.89 mg/dl (p=0.119). **Level 1+**

In the study by Redmon[17] which compared a combined intervention (described above) with an individualised diet plan, at 1 year there were reductions in systolic and diastolic blood pressure in both groups, although this did not differ between the groups. Systolic blood pressure reduced in the combination group by 6±3 mmHg and by 6±2 mmHg in the comparison group. Diastolic blood pressure reduced in the combination group by 3±1 mmHg and by 6±2 mmHg in the comparison group. **Level 1+**

At 1 year, changes in fasting cholesterol, HDL, LDL and fasting triglycerides did not differ between groups. There were reductions from baseline values in fasting cholesterol and LDL cholesterol in both groups, with a decrease in fasting cholesterol of 6±8 mg/dl in the combination therapy group and 17±9 mg/dl in the comparison group (p=0.90). LDL decreased by 12±5 mg/dl in the combination therapy group and 13±6 mg/dl in the comparison group (p=0.89). Fasting triglycerides decreased by 46±24 mg/dl in the combination group compared to an increase of 8±18 mg/dl in the comparison group, however this was not significant (p=0.07). **Level 1+**

Studies comparing a low-carbohydrate with low-fat diet

At 12 weeks of follow-up, in the low-carbohydrate arm of this RCT[16] there was a reduction in systolic blood pressure of 6.24±2.96 mmHg and a reduction of 0.39±2.64 mmHg in the low-fat arm, with no significant difference between the arms (p=0.147). **Level 1+**

With respect to lipid parameters, there was a greater reduction in the total cholesterol: HDL ratio in the low-carbohydrate arm, mean reduction of 0.48, than in the low-fat arm, mean reduction 0.10 (p=0.011). There were also reductions in triglycerides in both arms, 0.67 mmol/l in the low-carbohydrate arm and 0.25 in the low-fat arm, which did not approach statistical significance (p=0.223). **Level 1+**

Studies comparing low- or modified fat diets with reduced calorie diets

In the RCT comparing the low-fat vegan diet with the ADA diet,[14,20] there were non-significant reductions in systolic and diastolic blood pressure in both groups. In the vegan group systolic blood pressure decreased by 3.8±12.6 mmHg (p<0.05) compared with baseline and in the ADA group by 3.6±13.7 mmHg from baseline, with no significant difference between the groups (p=0.93). Similarly the reduction in diastolic blood pressure was greater in the vegan group, 5.1±8.3 mmHg (p<0.0001) than in the ADA group 3.3±8.8 mmHg (p<0.05) although this was not different between groups (p=0.30). **Level 1+**

For the entire sample, although lipid parameters decreased significantly from baseline values, there were no significant differences between groups. Among those whose lipid controlling medications remained constant (vegan N=39/49; ADA N=41/50), total cholesterol reduced in the vegan groups by 33.5±21.5 mg/dl (p<0.0001), in the ADA group by 19.0±28.5 mg/dl (p<0.0001) and this was a significantly different between groups (p=0.01). Reductions in HDL cholesterol were not significantly different between the groups.

Reductions in non-HDL cholesterol were significantly lower than baseline in the vegan groups 27.6±21.1 mg/dl (p<0.0001) and in the ADA group 16.3±30.1 mg/dl (p<0.05), but not significantly different between the groups (p=0.05).

LDL cholesterol reduced in the vegan group by 22.6±22.0 mg/dl (p<0.0001) and in the ADA group by 10.7±23.3 mg/dl (p<0.05), and was significantly different between the groups (p=0.02). The total-to-HDL cholesterol ratio and triglyceride concentrations fell for both groups, but there was no difference between the groups. **Level 1+**

Table 4: Summarised results for blood pressure and lipid levels across RCTs

RCTs	Follow-up	Comparison	Comparison	Blood pressure	Lipid levels
Li (2005)[13]	1 year	Soy-based meal replacement	Individualised diet	No changes	NS differences
Redmon (2003)[17]	1 year	Sibutramine + low calorie diet + meal replacement	Individualised diet	NS differences	NS differences
Daly (2006)[16]	3 months	Low carbohydrate diet	Reduced portion low-fat diet	NS differences	TC:HDL ratio significantly lower in carbohydrate arm
Barnard (2006)[14]	22 weeks	Low-fat vegan diet	Diet based on ADA guidelines	NS differences	NS differences
NS not significant					

Observational studies

In the observational study investigating the effect of eating behaviours on weight,[20] changes in blood pressure or lipid profiles were not reported.

In the diabetes nutrition and complications trial[19] changes in blood pressure were reported as the proportion of patients who had a systolic blood pressure <130 mmHg, which decreased from 28.6% at baseline to 11.9% at the end of the study. Similarly in women there was a decrease from 15.8% at baseline to 8.8% after 6.5 years. The proportion of patients with a diastolic blood pressure of <80 mmHg decreased from 26.2% to 21.4% and from 31.6% to 28.1% in men and women respectively.

In this study they reported the number of patients who were adherent to the ADA diet recommendations and were able to achieve the recommended intakes of various types of fats. They found that levels of adherence to the recommendations was low with only 26.6% of patients consuming the recommended amount of saturated fatty acids (SFAs), 13.0% consuming the recommended ≥10% of dietary energy from polyunsaturated fats, and 38.5% consuming the recommended ≥60% of dietary energy from carbohydrates and monounsaturated fats. They also estimated that 46.4% of patients consumed a ratio of polyunsaturated fatty acids (PUFAs)/SFAs >0.4 and 69% consumed a ratio of monounsaturated fats (MUFAs)/SFAs >1.5. Patients who consumed MUFAs/SFAs <1.5 had a 3.6–4.7 times greater risk of developing diabetic complications (confidence intervals (CIs) not presented). Patients who consumed PUFAs/SFAs <0.4 were 3.4–8.2 times more at risk of developing diabetic complications. **Level 3**

5.1.5 Evidence to recommendations

The GDG noted that there was little new evidence to warrant any change to previous views in this field. The major consensus-based recommendations from the UK and USA emphasise sensible practical implementation of nutritional advice for people with type 2 diabetes.. Management otherwise will concentrate on principles of healthy eating (essentially those for optimal cardiovascular risk protection), and reduction of high levels of free carbohydrate in foods that may cause hyperglycaemia in the presence of defective insulin secretory reserve.

If people are currently gaining weight, weight maintenance is advantageous.

The GDG noted that in some people with type 2 diabetes and weight problems it might be appropriate to consider pharmacotherapy, however this was not within the clinical questions addressed.

As with Patient Education delivery of dietary advice was noted to depend not only on specific skills, but also required all members of the diabetes care team to be familiar with local policy and thus delivering consistent advice.

Concerns continue to be noted over the promotion of ‘diabetic foods’ which may be low in classical sugars but high in calories and thus unsuitable as well as unnecessary for the overweight. While reduction in weight was clearly understood to be beneficial through improvements in insulin insensitivity (whether relying on endogenous or exogenous insulin), low-carbohydrate diets were noted to be of unproven safety in the long term and thus could not be endorsed. Similarly high-protein diets are acknowledged as promoting short-term weight loss, but cannot be recommended as safe in the long term.

A dietary plan for people with diabetes would follow the principles of healthy eating in the general population, and thus include carbohydrate from fruits, vegetables, wholegrains, and pulses (and thus high fibre and low glycaemic index), reduction in salt intake, the inclusion of low-fat milk and oily fish, and control of saturated and trans fatty acid intake.

The importance of advice on alcohol to the overweight and to those prone to hypoglycaemia through use of insulin secretagogues or insulin was judged important.

5.1.6 Recommendations and research recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng28

Research recommendations

1. **What is the effectiveness of low carbohydrate diets in adults with type 2 diabetes?**

   Why this is important

   Type 2 diabetes is associated with obesity, and lifestyle interventions including diet and physical activity are thought to be useful in helping to control the condition and improve patient outcomes such as reducing the risk of long-term complications and increasing quality of life. Low carbohydrate diets have been a source of discussion over the past two decades and there is much debate regarding its effectiveness and safety in controlling blood glucose levels, particularly in the longer-term. Specifically, there is little consensus on the optimal intake of daily carbohydrates, where the risk of adverse effects such as hypoglycaemia is minimised. A randomised controlled trial addressing this clinical question would help to provide a better understanding of the effects of low carbohydrate diets on diabetes control and maintenance to inform appropriate management strategies.

6 Blood pressure therapy

This section was updated in 2019 by the NICE guideline on hypertension in adults.

6.1 Clinical introduction

People with type 2 diabetes are at high cardiovascular (CV) risk, high risk of diabetes eye damage, and high risk of renal disease. These adverse outcomes are known to be reduced by improved blood pressure (BP) control, which can be used to lower the risk of stroke, MI, blindness and renal failure.[226] Some other forms of diabetes associated microvascular damage, including peripheral nerve damage, are known to be associated with higher BP.[227] BP lowering is likely to be highly cost-effective in people with type 2 diabetes, more so than in the general population.

A number of clinical questions then face the person with diabetes and their advisors, these include:

- at what levels of BP to initiate therapy
- whether, and to what extent, those levels should be influenced by particular risk factors (in particular those involved in renal disease)
- what level of BP to aim for, and whether that should be modified by the presence of renal, eye, or macrovascular damage
- what lifestyle measures are effective and cost-effective in lowering BP
- what pharmacological interventions are effective and cost-effective in BP lowering
- how choice of agent might be modified by the presence of end organ damage.

Lifestyle measures (explored elsewhere) and monotherapy medication are known to have limited efficacy in lowering BP. Additional clinical questions arise over:

- the combinations of medications to be used after first-line therapy
- considerations including synergies of action, side effects of some combinations, and cost.

6.2 Blood pressure lowering – targets and intervention levels

6.2.1 Methodological introduction

There were 8 papers identified as relevant to this question. These included 4 papers which further analysed data from large RCTs; 2 papers analysed data from the Irbesartan in Diabetic Nephropathy Trial (IDNT), N=1590, median follow-up 2.6 years,[228] and median follow-up 2.9 years.[229] One study analysed data from the UKPDS study,[230] N=1148, and a further study considered data from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, N=1513, median follow-up 3.4 years.[231]

Two RCTs considered the effects of intensive compared with moderate treatment, 1 considered the effects of intensive treatment (valsartan) with moderate treatment (placebo) for BP control, mean follow-up <1–4 years (mean 1.9 years), N=129,[232] and the other, the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, considered an intensive treatment with either enalapril or nisoldipine compared with moderate treatment (placebo), follow-up 5 years, N=480.[233]

A systematic review of several RCTs investigated the effects of different BP-lowering regimens on serious CV events in patients with and without diabetes.[234]

The final study was a 10 year observational study which considered a BP cut-off level for renal failure but not macrovascular complications, N=385.[235]

As with the papers considered for hypertension, studies which consider BP control have flexibility in their design to allow for the introduction of further antihypertensive therapy during the course of the study if required.

6.2.2 Health economic methodological introduction

No health economic papers were identified.

6.2.3 Evidence statements

Overall, an association could be established between low BP values and a lower incidence of CV events across 3 of the 4 studies looking at the relationship between BP levels and CV outcomes.[229,232,233,235] However, no clear BP threshold was identified as a potential therapeutic target.

An RCT[233] with a follow-up of 5 years concluded that intensive BP control (mean BP=28±0.8/75±0.3) in normotensive type 2 diabetes patients was associated with a significantly lower incidence of CV events compared with those in the moderate BP control group (mean BP=137±0.7/81±0.3). **Level 1**

Another RCT conducted in normotensive type 2 diabetes patients[232] showed non-significant differences in the incidence of CV events between the intensive blood control group (mean BP=118±10.9/75±5.7) and the moderate group (mean BP=124±10.9/80±6.5). **Level 1+**

The analysis completed on the IDNT data[229] identified a decreased risk in CV mortality and congestive heart failure (CHF) where the systolic blood pressure (SBP) decreased from >170 to 120–130 mmHg, with a 20 mmHg lower SBP being associated with a 39% reduction in both. An achieved SBP □20 mmHg compared with >120 mmHg showed a greater risk of CV mortality and CHF (see Table 5). **Level 1+**

Table 5: Post hoc analysis of the IDNT study – Berl[229], N=1590

CV Outcome	Size effect
CV mortality	A decrease in risk was observed where achieved SBP decreased from >170 to 120–130 mmHg. In this range a 20 mmHg lower SBP was associated with a 39% reduction in CV mortality, p<0.002
	An achieved SBP ≤120 showed a significantly greater risk of CV mortality compared to those with an achieved SBP >120 mmHg, RR 4.06 (2.11 to 7.80), p<0.0001
CHF	A decrease in risk was observed where achieved SBP decreased from >170 to 120–130 mmHg. In this range a 20 mmHg lower SBP was associated with a 39% reduction in CHF, p=0.001
	Those with an achieved SBP ≤120 had a significantly greater risk of CHF than those with an achieved SBP >120 mmHg, RR 1.80 (1.17 to 2.86), p=0.008
MI	A 10 mmHg lower mean achieved DBP was associated with a significantly higher risk of MI, RR 1.61 (1.28 to 2.02), p<0.0001
Stroke	A 10 mmHg lower mean achieved DBP was associated with a significantly lower risk of stroke, RR 0.65 (0.48 to 0.88), p=0.005
DBP diastolic blood pressure	

A systematic review[234] identified 27 trials which included 33,395 individuals with diabetes and 125,314 without. Overall the analysis suggests that patients with diabetes achieved greater reductions in the risk of total major CV events and CV death with regimens targeting lower BP goals[e] than those without diabetes (see Table 6). **Level 1+**

Table 6: Systematic review – by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC)[234]

Stroke					
More vs less intensive	**More intensive**	**Less intensive**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	63/1731	86/1868	-6.0/-4.6	0.64 (0.64 to 0.89)	NS differences
No diabetes	103/6303	204/12,080	-3.7/-3.3	0.89 (0.70 to 1.13)	NS differences
Coronary heart disease					
More vs less intensive	**More intensive**	**Less intensive**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	63/1731	44/1868	-6.0/-4.6	0.69 (0.38 to 1.25)	NS differences
No diabetes	103/6303	31/12,080	-2.9/-3.0	1.10 (0.60 to 2.01)	NS differences
Heart failure					
More vs less intensive	**More intensive**	**Less intensive**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	63/1731	44/1868	-6.0/-4.6	0.69 (0.38 to 1.25)	NS differences
No diabetes	103/6303	31/12,080	-3.7/-3.3	1.10 (0.60 to 2.01)	NS differences

The observational study[235] identified that baseline SBP was lower (141±19 mmHg) for those with no complications compared with those who had an MI (154±20 mmHg), $p<0.01$. SBP was also lower during the observation period for those with no complications (145±16 mmHg) compared with those who had an MI (152±15 mmHg), $p<0.05$ and also those who had a stroke (153±15 mmHg), $p<0.001$. This study also noted that DBP was lower at baseline for those with no complications (84±9) compared with those who developed an MI (87±9 mmHg), $p<0.05$. **Level 2+**

6.2.3.1 Renal outcomes

Five studies[228,231–233,235] were identified looking at several renal outcomes and their relation with BP control. On the whole, it could be ascertained that high BP levels (SBP and/or DBP) in patients with type 2 diabetes were associated with a more rapid decline in renal function than in those with lower BP values.

6.2.3.2 RENAAL study

The RENAAL study[231] demonstrated that for SBP the baseline level of 160–179 mmHg or ≥180 mmHg compared with less than 130 mmHg had a significantly greater risk of reaching the primary end point (time to doubling of serum creatinine, end stage renal disease (ESRD) or death), risk of ESRD or death and risk of ESRD alone. Kaplan-Meier curve also showed that for those with a baseline SBP ≥140 compared with <140 mmHg there was a significantly higher risk of reaching the primary end point and risk of ESRD alone. For achieved SBP

e There were 5 studies comparing more intensive and less intensive regimes. The target BP levels (mmHg) for these studies were as follows: MAP £92 vs 102–107; DBP £75 vs £90; DBP 10 mmHg below baseline vs 80–89; DBP £80 vs £85 OR £90 and DBP <85 vs <105.

those who had a SBP of 140 to ≥180 mmHg compared with less than 130 mmHg had a significantly greater risk of reaching the primary end point; for those with an achieved SBP of 140–159 mmHg compared with less than 130 mmHg there was a significantly greater risk of ESRD or death and ESRD alone.

For achieved DBP those with a DBP from 90 to ≥100 mmHg compared with those with an achieved DBP of <70 mmHg had a significantly greater risk of reaching the primary end point (time to doubling of serum creatinine, ESRD or death), risk of ESRD or death and risk of ESRD alone[231] (see Table 7 and Table 8). **Level 1+**

Table 7: RENAAL study – systolic blood pressure in baseline

SBP at baseline (mmHg)	Risk of doubling of SCr, ESRD or death (primary end point)	Risk of ESRD or death	Risk of ESRD alone
160–179 vs <130	HR 1.28 (0.97 to 1.69) p<0.001	HR 1.96 (1.40 to 2.74) p<0.001	HR 2.13 (1.39 to 3.27) p<0.001
≥180 vs <130	HR 1.85 (1.33 TO 2.57) p<0.01*	HR 2.10 (1.44 to 3.06) p<0.01**	HR 2.02 (1.24 to 3.29) p=0.005***
* Kaplan-Meier curve for baseline SBP <140 vs ≥140 mmHg, a significantly higher risk for those ≥140 mmHg (HR 1.66, p<0.001) ** Every 10 mmHg rise in baseline SBP increased the risk for ESRD or death by 6.7%, p=0.007 (multivariate model adjusted for urinary ACR (log scale), creatinine, albumin, haemoglobin) *** Kaplan-Meier curve for baseline SBP <140 vs ≥140 mmHg, a significantly higher risk for those ≥140 mmHg (HR 1.72, p<0.001) SCr serum creatinine ratio			

Table 8: RENAAL study – systolic blood pressure achieved

SBP achieved (mmHg)	Risk of doubling of SCr, ESRD or death (primary end point)	Risk of ESRD or death	Risk of ESRD alone
140–159 vs <130	HR 1.49 (1.18 to 1.90) p<0.001	HR 1.33 (1.02 to 1.72) p=0.03	HR 1.52 (1.07 to 2.15) p=0.02
90–99 vs <70	HR 1.72 (1.32 to 2.23) p<0.001	HR 1.55 (1.16 to 2.08) p=0.003	HR 1.67 (1.15 to 2.44) p=0.008
≥100 vs <70	HR 2.54 (1.70 to 3.80) p<0.001	HR 2.74 (1.78 to 4.24) p<0.001	HR 3.26 (1.90 to 5.58) p<0.001
* Every 10 mmHg rise in baseline DBP decreased the risk for ESRD or death by 10.9% (p=0.01) (multivariate model adjusted for urinary ACR (log scale), creatinine, albumin, haemoglobin)			

Other studies reporting renal outcomes

The 2 studies which used intensive and moderate control groups showed significant differences between the groups only for adjusted log urinary albumin excretion rate (UAER) findings.[232,233] **Level 1+**

The further analysis from the IDNT study identified that baseline BP correlated significantly with doubling SCr or ESRD and that 36% of those with baseline SBP >170 mmHg compared with 18% for those with baseline SBP <145 mmHg reached renal end point. Following correction for estimated glomerular filtration rate (eGFR) and albumin:creatinine ratio (ACR) each 20 mmHg decrease in SBP was associated with a 30% reduction in the risk of a renal event. Though it should be noted that while there was an increasing risk for reaching a renal end point with seated SBP, those with SBP <120 mmHg were not substantially better than those between 120–130 mmHg.[228] **Level 1+**

The 10 year observational study identified that baseline SBP and DBP were significantly lower for those with no complications than those who developed renal failure, SBP was also lower for this during the observation period. A BP cut-off of >140 mmHg showed a NSx38.5 increase in the risk of renal failure.[235] **Level 2+**

6.2.3.3 Retinopathy outcomes

The intensive (118±10.9/75±5.7) and moderate (124±10.9/80±6.5) groups found NS difference between the groups for progression or regression of retinopathy.[232] **Level 1+**

The other study which considered intensive (128±0.8/75±0.3) and moderate (137±0.7/81±0.3) groups identified less progression of retinopathy with the intensive group compared with the moderate group at both 2 years (13 vs 21%, p=0.046) and 5 years (34 vs 46%, p=0.019).[233] **Level 1+**

The analysis completed on the data from the UKPDS study on retinopathy is detailed in the Table 9.[230] This considered the impact of tight blood pressure control (TBP) aiming for a BP less than 150/85 and less tight blood pressure control (LTBP) aiming for a BP of 180/105 or less. The TBP group had significantly lower microaneurysms, hard exudates and cotton wool spots than the LTBP group. This TBP group also had less retinopathy grading by the Early Treatment of Diabetic Retinopathy Study (ETDRS) grading and lower absolute risk events per 1000 patient years for photocoagulation and blindness in 1 eye. **Level 1+**

Table 9: Retinopathy outcomes – Matthews study[230]

Progression of retinopathy assessed by specific lesions	
MA % with ≥5 MA	• at 4.5 years; TBP vs LTBP (23.3% vs 33.5%) RR 0.7 (99% CI 0.51 to 0.95), p=0.003 • at 7.5 years; TBP vs LTBP (29.3% vs 44.8%) RR 0.66 (99% CI 0.48 to 0.90), p<0.001
Hard exudates	Overall increase 11.2% to 18.3% • at 4.5 years; TBP vs LTBP (12.5% vs 21.2%) RR 0.59 (99% CI 0.38 to 0.92), p=0.002 • at 7.5 years; TBP vs LTBP (14.1% vs 26.6%) RR 0.53 (99% CI 0.33 to 0.85), p<0.001
Cotton wool spots	Overall increase 14.0% to 22.4% • at 4.5 years; TBP vs LTBP (16.6% vs 17.4%) RR 0.69 (99% CI 0.47 to 1.02), p=0.02 • at 7.5 years; TBP vs LTBP (17.4% vs 32.5%) RR 0.53 (99% CI 0.35 to 0.81), p<0.001
Ocular end points	
Photocoagulation	• TBP vs LTBP had lower absolute risk events per 1000 patient years (11.0 vs 17.0) RR 0.63 (99% CI 0.39 to 1.07), p=0.03 • due to maculopathy, 7.6 vs 13.0 (TBP vs LTBP) RR 0.58 (99% CI 0.32 to 1.04), p=0.02
Vision loss	
Blindness in 1 eye	• TBP group had lower absolute risk events per 1000 patient years than the LTBP group (3.1 vs 4.1) RR 0.76 (98% CI 0.29 to 1.99), p=0.046
Retinopathy progression by ETDRS grading	• at 4.5 years 2-step or more deterioration; TBP vs LTBP (27.5% vs 36.7%) RR 0.75 (99% CI 0.50 to 0.89), p=0.02 • at 7.5 years 2-step or more deterioration; TBP vs LTBP (34.0% vs 51.3%) RR 0.66 (99% CI 0.50 to 0.89), p=0.001 • more than 1/3 (TBP) did not change compare with 1/5 (LTBP)
MA microaneurysams	

6.2.3.4 Nephropathy outcome

The intensive (118±10.9/75±5.7) and moderate (124±10.9/80±6.5) groups found NS difference between the groups for progression or regression of nephropathy.[232] **Level 1+**

The other study which considered intensive (128±0.8/75±0.3) and moderate (137±0.7/81±0.3) groups identified NS difference between the groups for progression of nephropathy.[233] **Level 1+**

6.2.4 Evidence to recommendations

The GDG noted the problems in assigning BP lowering targets in this area, and in particular the:

- problem setting a cut-off where the evidence suggests the lower the blood pressure the better (without adverse effects)'
- difficulties of achieving any reasonable target in some people
- individual targets that should logically vary with individual risk
- arbitrary dichotomy that arises immediately above and below any target level.

The results of some RCTs suggested that SBP well into the normal range (below usual target values) was both achievable and associated with benefit in people with type 2 diabetes, consistent with epidemiological evidence from other studies. In some other studies tight BP control seemed difficult to achieve, consistent with the group's clinical experience. This led the group to take a simple risk approach centered on a target level of <140/80 mmHg for most people with type 2 diabetes, and <130/80 mmHg for those at more particular risk. The latter group included people with raised albumin excretion rate (AER) (microalbuminuria or worse), eGFR<60 ml/min/1.73 m^2, those with retinopathy, and those with prior stroke or transient ischaemic attack (TIA). The concern that more active prevention was being targeted at those who had already developed end-organ damage was recognised, but it was noted that for both microalbuminuria and early retinopathy the recommendations on annual surveillance meant that markers of damage would be detected many years before ill health ensued.

6.3 Blood pressure lowering medications

6.3.1 Methodological introduction

The search identified a systematic review of several RCTs investigating the effects of different BP lowering therapies (that is, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor (A2RB) antagonists, calcium channel blockers (CCB), beta-blockers and diuretics) on serious CV events in patients with and without diabetes.[234]

6.3.1.1 ACEI

There were 14 papers identified for this question, these included 2 Cochrane reviews, considering antihypertensive agents for preventing diabetic kidney disease[236] and ACEI and A2RB antagonists for preventing the progression of diabetic kidney disease.[237] There was also a meta-analysis which considered the effect of inhibitors of the renin-angiotensin system (RAS) and other antihypertensive drugs on renal outcomes.[238]

ACEI vs placebo

Three studies compared ramipril with a placebo, they were sub-analysis of the 5-year Heart Outcomes and Prevention Evaluation (HOPE) study, considering the diabetic subgroup, N=3577 (total study population, N=9297)[239,240] and an extension phase of 2.6 years, N=4528.[241]

ACEI vs A2RB

The DETAIL (Diabetics Exposed to Telmisartan and Enalapril) study considered telmisartan compared with enalapril over 5 years, N=250.[242] An open-label study considered lisinopril compared with telmisartan and compared with a combination of the 2 treatments over 52 weeks, N=219.[243]

ACEI vs CCB

Three studies considered ACEI and CCB. One study considered lercanidipine compared with ramipril for 36–52 weeks, N=180.[244] An open-label study considered amlodipine compared with fosinopril and compared the combination of both drugs for 4 years, N=309.[245] A post hoc analysis of the Bergamo Nephrologic Diabetic Complications Trial (BENDICT) study was performed, this considered verapamil compared with trandopril compared with a combination of both drugs for 3.6 years, N=1204.[246]

ACEI vs CCB vs diuretic

One study considered lisinopril compared with amlodipine and chlorthalidone[f] with a type 2 diabetes group analysis, mean follow-up 4.9 years, N=12,063 (total study population N=31,512); the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT).[247]

ACEI + CCB vs ACEI + diuretic

One study considered verapamil + trandopril compared with enalapril + hydrochlorothiazide over 6 months, N=103.[248]

ACEI + CCB vs beta blocker + diuretic

Another study considered N=463 participants who were dosed with verapamil SR + ACE trandopril compared with atenolol + chlorthalidone for 20 weeks.[249]

All studies were either RCTs or subgroup analysis of RCTs, the majority of which were double- blinded (2 open-label studies).[243,245] All studies involved participants with type 2 diabetes or considered a diabetic subgroup from a larger study. Many of the studies used BP target levels, if these were not achieved with the initial dose of the drug then either dose escalation or the introduction of other antihypertensive medication was allowed to ensure that target BP was maintained accordingly.

6.3.1.2 A2RB

A total of 10 studies were found relevant to the question.[237,250–258]

The studies selected were RCTs with a follow-up of at least 6 months and with a sample size of more than 100. All studies involved participants with type 2 diabetes or considered a diabetic subgroup from a larger study. Many of the studies used BP target levels, if these were not achieved with the initial dose of the drug then either dose escalation or the

f The ALLHAT study randomised patients to chlorthalidone 12.5–25.0 mg/day, amlodipine 2.5–10 mg/day or lisinopril 10–40 mg/day. The doses of these drugs were increased until a BP goal of <140/90 mmHg was achieved. In addition, other drugs could be added to the baseline treatments such as atenolol (25–100 mg/day), reserpine (0.1–0.2 mg/day) or clonidine (0.1–0.3 mg bid) at the discretion of the investigator. Also, hydralazine 25–100 mg bid could be added as a step three drug.

introduction of other antihypertensive medication was allowed to ensure that target BP was maintained according.

These 10 RCTs reviewed the evidence on the effectiveness and safety of A2RB blockers across several comparisons.

A2RB vs placebo

One Cochrane review[237] was identified analysing data from 5 studies placebo-controlled trials that is Brenner et al. 2001 (RENAAL), Lewis et al. 2001 (Renal data – IDNT), Parving et al. 2001 (IRMA), Tan et al. 2002 and, Berl et al. 2003 (CV data – IDNT).

Three post hoc analyses of large placebo-controlled trials were also identified: 2 post hoc studies of the RENAAL trial [253,254] and 1 post hoc study[255] of the IRMA study.

One post hoc analysis[254] analysed the impact of renal function at baseline on disease progression and response to treatment in 1513 patients who were enrolled in the RENAAL study.

Another post hoc analysis of the 1513 patients enrolled in the RENAAL study[253] analysed the effect of losartan versus placebo on long-term glycaemic control and serum potassium, uric acid, and lipid levels, as well as the relationship between these baseline metabolic factors and the composite end point (doubling of serum creatinine, ESRD, or death) or ESRD alone.

One post hoc analysis of the IRMA study[255] assessed the reversibility of kidney function changes after withdrawal of 2 years antihypertensive therapy with irbesartan on 133 type 2 diabetes patients.

A2RB vs CCB

Four studies looked at the comparison of an A2RB with a CCB. Irbesartan vs amlodipine,[257] valsartan vs amlodipine [252,258] and telmisartan vs nifedipine.[251] It should be noted that the study by Lewis[257] was included in the Cochrane review but no data on the head comparison between A2RB and CCB was reported.

A2RB vs sympatholytic agents

One study[256] considered A2RB (losartan) compared with a beta-blocker agent (atenolol) and another study[250] compared A2RB (irbesartan) with an alpha-blocker drug (doxazosin).

Studies comparing ACEI with A2RB have been analysed under the ACEI section.

It should be noted that differing dosing and titration regimens and the differing populations included in the studies, may limit direct comparisons between studies.

6.3.1.3 Beta blockers

One paper was identified which considered carvedilol and metoprolol in N=1235 participants for 5 months.[260]

Beta-blockers vs CCB

There were 3 papers identified for this. One paper was a sub-analysis of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial, which considered control-onset extended-release (COER) verapamil with atenolol or hydrochlorothiazide in N=16,476 (N=3239 type 2 diabetes) for 3 years.[261] A further paper considered a subgroup of the Anglo-Scandinavian Cardiac Outcomes Trial: Blood Pressure Lowering Arm (ASCOT: BPLA) trial, with N=19,257 (N=5145 with diabetes), which was stopped prematurely at 5.5 years.[262] The third paper reported on the International Verapamil-

Trandolapril Study (INVEST) trial which considered verapamil SR with atenolol for N=22,576 (N=6400 type 2 diabetes) participants over 24 months.[259]

6.3.2 Health economic methodological introduction

6.3.2.1 ACEI

Three studies were identified, 2 based in the UK and 1 in Germany.

Beard et al. (2001)[263] and Schadlich et al. (2004)[264] used data from the HOPE and micro-HOPE studies, which compared an ACEI, ramipril, to placebo. In both analyses the treatment effects were not continued beyond the trial period of 5 years and the continued survival of patients was considered.

Gray et al. (2001)[265] was based on UKPDS data, comparing an ACEI, captopril, to a beta-blocker, atenolol. In this study a tight BP target of <150/<85 mmHg was set and other antihypertensive treatments could be added on to achieve this target. After the trial period it was assumed that beyond the trial period the 2 groups had identical hazard rates.

In all 3 studies the outcomes of interest were CV events.

6.3.2.2 A2RB

The studies identified looked at the renal protection effect of angiotensin II receptor antagonists (A2RB).

Three studies were based on the IDNT. Irbesartan 300 mg to amlodipine 10 mg and to a control. All participants could take standard antihypertensive therapies which exclude ACEI, A2RB, and CCBs. This study included type 2 diabetes patients with proteinuria. No significant difference was found between irbesartan and amlodipine in reducing BP. The control had an average of 3.3 mmHg increased BP.

The combined end point of the study was doubling of serum creatinine concentration, ESRD or death from any cause. Irbesartan reduced this end point by 23% compared to amlodipine and 20% compared to control.

Palmer et al. (2004)[266] was set in the UK, Rodby et al. (2003)[267] was set in the US, and Coyle et al. (2004)[268] was set in Canada. In these studies various time horizons were used, where a 10-year time horizon was the base case, 25 years was tested in the sensitivity analysis.

Vora et al. (2005)[269] was based on the RENAAL study which compared losartan 50–100 mg with a regimen of conventional antihypertensive treatment (CCBs, diuretics, alpha-blockers, beta-blockers, and centrally acting agents). Patients had type 2 diabetes and nephropathy. The same combined end point as the IDNT was used. Losartan was found to reduce this by 25% compared with control. This analysis was set in the UK and a lifetime time horizon was used.

Smith et al. (2004)[270] was based on the Microalbuminuria Reduction with Valsartan (MARVAL) study comparing the A2RB, to the CCB amlodipine. Patients with type 2 diabetes and microalbuminuria were included. The study found that valsartan significantly reduced urinary excretion rate compared to amlodipine. Similar reductions in BP were found. This analysis was set in the US. An 8-year time horizon was used.

6.3.3 Evidence statements

A systematic review showed that for the outcome stroke, there was no evidence of differences in the effects of the treatment regimens between patients with and without diabetes except in the comparison that included A2RB-based regimens. In this comparison, A2RB provided lesser protection to patients with diabetes compared with those without diabetes (see Table 10).[234]

For the outcomes coronary heart disease (CHD) and heart failure, the review did not show differences between patients with and without diabetes for any comparison, again except for the comparison that included A2RB. Diabetic patients treated with A2RB experienced a significantly greater protection compared to those without diabetes for the outcome heart failure.[234]

According to their review, there was also some evidence of a difference between the 2 patient groups in protection against CV death and total mortality favouring patients with diabetes in the comparison of ACEI-based regimens vs placebo (see Table 13).[234]

Table 10: Stroke – systematic review by the BPLTTC[234]

ACEI	ACE	Placebo	⊗ BP mmHg	RR 95% CI	Diabetes vs no diabetes
Diabetes	125/2378	174/2336	–3.6/–1.9	0.69 (0.55 to 0.86)	NS differences
No diabetes	347/6733	485/6782	–5.8/–2.7	0.73 (0.62 to 0.85)	
CCB	**CCB**	**Placebo**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	21/911	45/900	–6.3/–3.0	0.47 (0.28 to 0.78)	NS differences
No diabetes	52/2883	72/2788	–9.2/–3.7	0.70 (0.49 to 0.99)	
A2RB	**ARB-based regimen**	**Control regimen**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	143/2226	173/2793	–2.1/–0.9	0.96 (0.77 to 1.19)	p=0.05 by X2 test of homogeneity
No diabetes	253/6186	342/6153	–1.4/–0.6	0.74 (0.63 to 0.86)	

Table 11: Coronary heart disease – systematic review by the BPLTTC[234]

ACEI	ACE	Placebo	⊗ BP mmHg	RR 95% CI	Diabetes vs no diabetes
Diabetes	96/2378	105/2336	–3.6/–1.9	0.88 (0.67 to 1.16)	NS differences
No diabetes	123/6733	164/6782	–5.8/–2.7	0.78 (0.62 to 0.98)	
CCB	**CCB**	**Placebo**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	94/868	75/858	–6.3/–3.0	1.29 (0.97 to 1.72)	NS differences
No diabetes	10/2514	13/2416	–9.2/–3.7	1.07 (0.43 to 2.62)	
ARB	**ARB-based regimen**	**Control regimen**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	150/2226	208/2793	–2.1/–0.9	0.92 (072 to 1.17)	NS differences

ACEI	ACE	Placebo	⊗ BP mmHg	RR 95% CI	Diabetes vs no diabetes
No diabetes	285/6186	269/6153	–1.4/–0.6	1.05 (0.89 to 1.24)	

Table 12: Heart failure – systematic review by the BPLTTC[234]

ACEI	ACE	Placebo	⊗ BP mmHg	RR 95% CI	Diabetes vs no diabetes
Diabetes	96/2378	105/2336	–3.6/–1.9	0.88 (0.67 to 1.16)	NS differences
No diabetes	123/6733	164/6782	–5.8/–2.7	0.78 (0.62 to 0.98)	
CCB	**CCB**	**Placebo**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	94/868	75/858	–6.3/–3.0	1.29 (0.97 to 1.72)	NS differences
No diabetes	10/2514	13/2416	–9.2/–3.7	1.07 (0.43 to 2.62)	
ARB	**ARB-based regimen**	**Control regimen**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	150/2226	208/2793	–2.1/–0.9	0.92 (072 to 1.17)	NS differences
No diabetes	285/6186	269/6153	–1.4/–0.6	1.05 (0.89 to 1.24)	

Table 13: CV Deaths – systematic review by the BPLTTC[234]

ACEI	ACE	Placebo	⊗ BP mmHg	RR 95% CI	Diabetes vs no diabetes
Diabetes	145/2378	211/2336	–3.6/–1.9	0.67 (0.55 to 0.82)	p=0.05 X^2 test of homogeneity
No diabetes	330/6733	389/6782	–5.8/–2.7	0.86 (0.75 to 0.99)	
CCB	**CCB**	**Placebo**	**⊗ BP mmHg**	**RR 95% CI**	**Diabetes vs no diabetes**
Diabetes	42/868	62/858	–5.9/–3.1	0.54 (0.21 to 1.42)	NS differences
No diabetes	61/2514	73/2416	–9.3/–3.9	0.64 (0.24 to 1.68)	

Finally, the review did not report significant differences between different BP lowering regimens (that is, head-to-head comparisons) in terms of stroke, CHD, heart failure in patients with diabetes. The exception being CCBs, which were associated with a higher risk of heart failure when they were compared with diuretics or beta-blockers,[234] (see Table 14, Table 15 and Table 16). In the same way, no differences were seen in the head-to-head comparisons for total major CV events, CV deaths, and total mortality in patients with diabetes.

Table 14: Head-to-head comparisons. Stroke – systematic review by the BPLTTC[234]

ACE vs D/BB	ACE	D/BB	⊗ BP mmHg	RR 95% CI
5 studies	282/4385	405/6614	2.2/0.3	1.02 (0.88 to 1.19)
CCB vs D/BB	**CCB**	**D/BB**	**⊗ BP mmHg**	**RR 95% CI**
8 studies	279/6276	427/8550	0.7/–0.8	0.94 (0.81 to 1.09)
ACE vs CCB	**ACE**	**CCB**	**⊗ BP mmHg**	**RR 95% CI**
5 studies	246/4101	227/4222	1.6/1.2	1.09 (0.88 to 1.36)
BB, beta-blocker, D, diuretics				

Table 15: Head-to-head comparisons. CHD – systematic review by the BPLTTC[234]

ACE vs D/BB	ACE	D/BB	⊗ BP mmHg	RR 95% CI
5 studies	402/4385	623/6614	2.2/0	3 0.83 (0.62 to 1.12)
CCB vs D/BB	**CCB**	**D/BB**	**⊗ BP mmHg**	**RR 95% CI**
8 studies	431/6276	638/8550	0.7/–0.8	1.00 (0.89 to 1.13)
ACE vs CCB	**ACE**	**CCB**	**⊗ BP mmHg**	**RR 95% CI**
5 studies	358/4101	407/4222	1.6/1.2	0.76 (0.51 to 1.12)

Table 16: Head-to-head comparisons. Heart failure – systematic review by the BPLTTC[234]

ACE vs D/BB	ACE	D/BB	⊗ BP mmHg	RR 95% CI
4 studies	251/4076	384/6351	2.5/0.4	0.94 (0.55 to 1.59)
CCB vs D/BB	**CCB**	**D/BB**	**⊗ BP mmHg**	**RR 95% CI**
6 studies	337/5276	399/7521	0.5/–0.8	1.27 (1.01 to 1.61)
ACE vs CCB	**ACE**	**CCB**	**⊗ BP mmHg**	**RR 95% CI**
5 studies	263/4101	325/4222	1.6/1.2	0.92 (0.67 to 1.27)

6.3.3.1 ACEI

Overall, the evidence appraised showed no significant differences in terms of CV outcomes when treatment with ACEI was compared with other antihypertensive therapies or with placebo. ACEI also failed to demonstrate superiority over other agents on the basis of BP lowering power (unless combination therapy is compared with monotherapy). However, the evidence suggested that treatment with ACEI is related to greater benefits in terms of renal outcomes in patients with type 2 diabetes as compared with other BP lowering agents.

6.3.3.1.1 Cardiovascular outcomes

All-cause mortality

The Cochrane review on antihypertensives for preventing diabetic kidney disease found NS difference for ACEI vs placebo (3 trials, N=2683) and for ACEI vs CCBs (6 trials, N=1286).[236] These findings were supported by the Cochrane review on ACEI and A2RB for preventing the progression of diabetic kidney disease for ACEI vs placebo (21 trials, N=7295)*[g] and ACEI vs A2RB (5 studies, N=3409).[237] **Level 1++**

ACEI vs CCB vs diuretic

The diabetes ALLHAT analysis showed NS difference between the treatments for the incidence of total mortality.[247] **Level 1+**

6.3.3.1.2 *Major cardiovascular events*

ACEI/placebo

The extension phase of the HOPE study showed a NS trend towards reduction in major CV events and risk of MI, with ramipril, stroke and CV death as NS. At follow-up of the study and extension there was a significant risk reduction with ramipril for the outcomes of MI, stroke and CV death.[241] **Level 1+**

ACEI vs CCB vs diuretic

The diabetes analysis of ALLHAT identified NS difference in the incidence of fatal CHD and non-fatal MI for lisinopril vs chlorthiadone in any of the 3 glycaemic strata that were analysed diabetes mellitus, impaired fasting glucose and normoglycaemia. This was also evident for diabetes mellitus and normoglycaemia for amlodipine vs chlorthalidone.[247] **Level 1+**

6.3.3.1.3 *Blood pressure*

BP reduction with all hypertensive treatments was a consistent feature of the studies and therefore only studies where there were significant differences between the treatments will be highlighted.

ACEI/A2RB

At the 52-week follow-up point, the combination of lisinopril and telmisartan showed significantly greater reductions in both SBP and DBP than the individual monotherapies (p=0.003 for both SBP and DBP).[243] **Level 1+**

ACEI/CCB + diuretic

Similarly, the combination of amlodipine and fosinopril showed a reduction in sitting BP of 28.7/17.1 compared with 17.2/11.8 (fosinopril, p<0.01) and 19.9/12.8 (amlodipine, p<0.01).[245] **Level 1+**

ACEI + CCB/beta-blocker + diuretic

The study which compared verapamil + trandopril with atenolol + chlorthalidone identified that while both treatments significantly reduced BP that comparison between the groups showed a difference of 4.85 mmHg SBP (1.94 to 7.76, p=0.0011) and 1.79 mmHg DBP (0.26 to 3.32, p=0.0222) favouring atenolol + chlorthalidone.[249] **Level 1++**

ACEI/CCB

A post hoc analysis of the BENEDICT[246] study considered the impact on BP control and ACEI therapy on new-onset microalbumuniuria. Baseline SBP, DBP, mean arterial pressure (MAP) and pulse pressure did not predict the onset of microalbuminuria. Participants who

g Though a subgroup analysis which used ACE at maximum tolerable dose did find a significant decrease vs placebo (5 trials; N=2034, RR 0.78, 0.61 to 0.98).

developed microalbuminuria had significantly lower reductions in SBP than those who did not develop microalbuminuria (7.9±11.5 vs 10.6±11.9, p<0.05). This study also identified that those with follow- up BP below the medians or with BP reduction above the medians were more frequently on ACE therapy (particularly trandopirl + verapamil) and less frequently on concomitant treatment with diuretics, beta-blockers or CCBs.[246] **Level 1+**

6.3.3.1.4 Renal outcomes

The Cochrane review, ACEI and A2RB antagonists for preventing the progression of diabetic kidney disease, identified ACE compared with placebo reduced the progression from micro- to macroalbuminuria, increased the regression from micro- to normoalbuminuria, and reduced the risk of ESRD.[237]

The Cochrane review, antihypertensive agents for preventing diabetic kidney disease, identified that ACEI compared with placebo/no treatment reduced the development of microalbuminuria, and ACEI compared with CCB reduced the risk of developing kidney disease.[236]

The meta-analysis identified that an ACEI or A2RB compared with other treatments only showed significant reduction in UAER.[238]

The HOPE study identified that ramipril compared with placebo reduced the risk of new microalbuminuria and that both new microalbuminuria and progression of proteinuria was higher for the diabetic group than the non-diabetic group.[240]

Combination compared with monotherapy

The combination of lisinopril and telmisartan identified higher reduction with AER compared with the monotherapies.[243]

The combination of fosinopril + amlodipine reduced UAE compared with amlodipine monotherapy (all time points) and with fosinopril monotherapy (after 18 months).[245]

Renal outcomes are detailed in the Table 17, including study results which identified NS difference between treatments.

Table 17: ACEI – renal outcomes

Progression of proteinuria	
HOPE study[240] ACEI/placebo Level 1+	ACEI/placebo Progression higher with non-diabetic participants than diabetic (34% vs 17%, p<0.01) Diabetes was the factor most strongly associated with the progression of proteinuria (OR 2.45, 2.148 to 2.75, p<0.05)* Ramipril vs placebo NS (adjustment for baseline reduced proteinuria by 22%, p=0.0495)
New microalbuminuria/risk of developing microalbuminuria	
Cochrane review[236] Level 1++	ACEI vs placebo/no treatment, reduced development of microalbuminuria (6 trials, N=3480, RR 0.58, 0.40 to 0.84) ACEI vs CCB reduced the risk of developing kidney disease (micro- or macroalbuminuria) (4 trials, N=1210, RR 0.58, 0.40 to 0.84) ACEI vs beta-blockers NS difference
Cochrane review[237] Level 1++	ACE vs placebo/no treatment significantly reduced the progression from micro- to macroalbuminuria (17 trials, N=2036, RR 0.49, 0.29 to 0.69) ACEI vs A2RB NS difference
HOPE study[240] Level 1+	ACEI/placebo New microalbuminuria was higher in diabetic than in non-diabetic participants (38.2% vs 18.1%)

Progression of proteinuria	
	Ramipril reduced the risk of new microalbuminuria by 10% p=0.046 vs placebo, in those with diabetes
Regression from micro- to normoalbuminuria	
Cochrane review[237] Level 1++	ACEI vs placebo/no treatment ACEI significantly increased regression (16 studies, N=1910, RR 3.06, 1.76 to 5.35) ACEI vs A2RB NS difference
Dalla (2004) [244] Level 1+	ACEI/CCB Ramipril vs lercanidipine NS for those who reverted to normoalbuminuria
Fogari (2002) [245] Level 1+	At 48 months 46% (fosinopril), 33% (amlodipine) and 67% (combination fosinopril + amlodipine) had moved to non-microalbuminuric status
Doubling of creatinine	
Cochrane review[236] Level 1++	ACEI vs placebo NS difference
Meta-analysis[238] Level 1+	ACEI or A2RB vs other active interventions NS, those with diabetes (6 trials, N=3044) and NS those without diabetes
Serum creatinine	
Meta-analysis[238] Level 1+	ACEI or A2RB vs other treatments NS, those with diabetes (18 trials, N=4615), those without diabetes, small reduction
HOPE study[240] Level 1+	ACEI/placebo No evidence of effect on ramipril on serum creatinine levels
Barnett (2004)[242] Level 1+	ACEI/A2RB Enalapril vs telmisartan NS difference
GFR	
Meta-analysis[238] Level 1+	ACEI or A2RB vs other treatments NS, those with diabetes (37 studies, N=15,742), NS those without diabetes
HOPE study[240] Level 1+	ACEI/placebo Ramipril vs placebo NS difference
Barnett (2004)[242] Level 1+	ACEI/A2RB Mean change in GFR: the lower treatment boundary in favour of enalapril was –7.6, greater than the pre-defined level of –10.0 indicating no difference between the treatments Enalapril vs telmisartan NS difference in annual decreases in GFR
AER	
Dalla (2004)[244] Level 1+	ACEI/CCB Ramipril vs lercanidipine NS difference Proportion of participants with reduction >50% was 22.2% with ramipril and 34.2% lercanidipine
Sengul (2006)[243] Level 1	ACEI/A2RB Lisinopril vs telmisartan NS difference Combination of lisinopril + telmisartan vs monotherapies AER reduction was significantly higher (p<0.001)
ESRD	
Cochrane review[237] Level 1++	ACEI vs placebo/no treatment reduction in the risk of ESRD (10 studies, N=6819, RR 0.68, 0.39 to 0.93)
Meta-analysis[238] Level 1+	ACEI or ARB vs other treatments, NS reduction in ESRD occurrence, those with diabetes (4 trials, N=14,437), those without diabetes there was a reduction with ACE or A2RB
Meta-analysis[238] Level 1+	ACEI or A2RB vs other treatments showed a reduction in UAER for those with diabetes, (34 trials, N=4772, RR –12.21, –21.68 to –2.74), for those without diabetes (44 trials, N=5266, RR –15.73, –24.75 to –6.74, p=0.001)

Progression of proteinuria	
Fogari (2002)[245] Level 1+	ACEI/CCB Combination of fosinopril + amlodipine showed significantly greater reduction vs amlodipine monotherapy at any time and vs fosinopril from 18 months onwards
Barnett (2004)[242] Level 1+	ACEI/A2RB Enalapril vs telmisartan, annual changes were small with large CI in both groups. % changes were NS difference
* The association with smoking, hypertension, male gender and peripheral vascular disease was less strong GFR, glomerular filtration rate	

6.3.3.1.5 *Metabolic outcomes*

Risk of diabetes

The extended HOPE trial identified that at the end of the extension phase there was a significant further reduction in risk for diabetes for ramipril vs placebo (2.7% vs 4.0%, RR 0.66, 0.46 to 0.95).[241] **Level 1+**

HbA1c and glycaemic control

The study which considered fosinopril and amlodipine monotherapy, and in combination, found that HbA1c was NS changed by any treatments and body weight remained unchanged.[245] **Level 1+**

The study which compared verapamil SR + trandopril and atenolol + chlorthalidone found that HbA1c remained stable with verapamil SR + trandopril but increased with atenolol + chlorthalidone 7.8 (1.26) at baseline and 8.6 (1.77) at last visit, treatment difference, p=0.0001; fasting glucose and fructosamine treatment difference, p=0.0001.[249]

Similarly, fasting glucose and fructosamine remained stable with verapamil SR + trandopril but increased with atenolol + chlorthalidone, treatment difference p=0.0001.[249] **Level 1++**

The study which considered verapamil + trandopril vs enalapril + hydrochlorothiazide identified that HbA1c remained stable with verapamil + trandopril but increased with enalapril + hydrochlorothiazide (baseline 5.96±1.25% to final 6.41±1.51%), difference between groups, p=0.040.[248] Crude blood glucose changes were 23±69 mg/dl for verapamil + trandopril (16.8% reduction) and 1±32 mg/dl (0.8% reduction) with enalapril + hydrochlorothiazide. The percentage of participants with glycaemic control (<126 mg/dl) increased from 50% to 72% with verapamil + trandopril, but did not change with enalapril + hydrochlorothiazide.[248] **Level 1++**

6.3.3.1.6 *Adverse events*

Both Cochrane reviews identified an increased risk of cough with ACE vs placebo/no treatment (4 trials, N=3725, RR 1.79, 1.19 to 2.69),[236] (10 trials, N=7087, RR 3.17, 2.29 to 4.38).[237]**Level 1++**

Throughout the other studies the incidence of discontinuation due to AEs was small and the AEs reported were mainly; progression of diabetes, unsatisfactory therapeutic response, hypotension, ankle oedema, tachycardia, headache, cough, nausea, stomach upset, respiratory infection, and dizziness. **Level 1+**

6.3.3.2 A2RB

In summary, A2RB therapy was associated with greater benefits for type 2 diabetes patients in terms of renal outcomes (e.g. progression to ESRD, doubling of serum creatinine, proteinuria) than treatment with placebo, CCB or sympatholytic agents. In addition, treatment with A2RB was also associated with a better metabolic and BP profile than sympatholytic therapy but non- significant differences were observed over those treated with CCB.

A2RB vs placebo

6.3.3.2.1 Cardiovascular outcomes

All-cause mortality

A Cochrane review[237] did not find a statistically significant reduction in the risk of all-cause mortality in the 5 studies (3409 patients) of A2RB vs placebo/no treatment. RR 0.99, 95% CI 0.85 to 1.17. **Level 1++**

Hospitalisations for heart failure

A post hoc analysis[254] compared the incidence of hospitalisation for heart failure within 3 tertiles of baseline serum creatinine concentration (highest, 2.1 to 3.6 mg/dl; middle, 1.6 to 2.0 mg/dl; lowest, 0.9 to 1.6 mg/dl). The study reported that the crude incidence of first hospitalisations for heart failure was higher in the highest (16.4%) and middle (15.0%) tertiles than in the lowest (11.1%) tertile (trend test across tertiles, p=0.02).

The study concluded that losartan decreased the hospitalisations for heart failure by 50.2 and 45.1, in the highest and middle tertile, respectively but was associated with a non-significant increased risk (42.5%) of hospitalisations in the lowest tertile. **Level 1+**

6.3.3.2.2 Renal outcomes

Progression to ESRD

A Cochrane review[237] found a significant reduction in the risk of ESRD with A2RB compared to placebo/no treatment (3 studies, N=3251): RR 0.78, 95% CI 0.67 to 0.91. **Level 1++**

A post hoc analysis[254] compared the incidence of ESRD within 3 tertiles of baseline serum creatinine concentration (highest, 2.1 to 3.6 mg/dl; middle, 1.6 to 2.0 mg/dl; lowest, 0.9 to 1.6 mg/dl). The study reported that the observed crude incidence of ESRD was significantly higher in the highest (40.5%) and middle (19.3%) tertiles as compared with the lowest (7.3%) tertile (trend test across tertiles, p<0.0001).

The study concluded that losartan decreased the risk of ESRD by 24.6, 26.3, and 35.3% in highest, middle, and lowest tertiles respectively. **Level 1+**

Doubling of serum creatinine

A Cochrane review[237] found a significant reduction in the risk of doubling of serum creatinine concentration with A2RB compared to placebo/no treatment (3 studies, 3251 patients): RR 0.79, 95% CI 0.67 to 0.93. **Level 1++**

Progression from micro- to macroalbuminuria

A Cochrane review[237] showed that the use of A2RB versus placebo/no treatment was also associated with a significant reduction in the risk of progression from micro- to macroalbuminuria (3 studies, 761 patients); RR 0.45, 95% CI 0.32 to 0.75. **Level 1++**

Regression from micro- to normoalbuminuria

A Cochrane review[237] found a significant increase in regression from micro- to normo-albuminuria with A2RB versus placebo/no treatment (16 studies, 1910 patients) RR 1.42, 95% CI 1.05 to 1.93. **Level 1++**

Proteinuria

A post hoc analysis[254] compared the median proteinuria reduction (%) within 3 tertiles of baseline serum creatinine concentration (highest, 2.1 to 3.6 mg/dl; middle, 1.6 to 2.0 mg/dl; lowest, 0.9 to 1.6 mg/dl). The study showed a significantly (p<0.0001) greater median percentage proteinuria reduction (versus baseline) on losartan than on placebo in the highest (24 vs –8%), middle (16 vs –8%), and lowest (15 vs –10%) tertiles respectively. **Level 1+**

A post hoc analysis of the IRMA study[255] reported that after 2 years of follow-up UAER decreased by 34% (95% CI 8 to 53), and 60% (95% CI 46 to 70) in the irbesartan 150 mg and irbesartan 300 mg groups respectively (p<0.05 vs baseline). No significant reductions in UAER were found in patients receiving placebo.

One month after withdrawal of irbesartan therapy, the same post hoc analysis[255] found no significant increases in UAER in patients receiving placebo or irbesartan 150 mg when compared with baseline values. However, the study reported that UAER remained persistently reduced by 47% (95% CI 24 to 63) in the irbesartan 300 mg group (p<0.05 vs baseline). This persistent reduction in the irbesartan 300 mg group, as compared with baseline, was highly significantly different from irbesartan 150 mg (p<0.01). This difference occurred although the regain in GFR between the 2 irbesartan groups were nearly identical. **Level 1+**

6.3.3.2.3 Blood pressure

A post hoc analysis of the IRMA study[255] found that after 2 years of treatment there were no significant differences in mean arterial blood pressure between patients treated with placebo or irbesartan (150 or 300 mg). However, 1 month after withdrawal of irbesartan therapy mean arterial blood pressure was unchanged in the placebo group, but increased significantly in the irbesartan groups to 109±2 and 108±2 in the 150 mg and 300 mg groups respectively (p<0.01). **Level 1+**

6.3.3.2.4 Metabolic outcomes

A post hoc analysis of the RENAAL study[253] found no significant differences between patients treated with losartan or placebo in terms of glycaemic levels, lipid profile or serum uric acid after 3.4 years of follow-up. **Level 1+**

6.3.3.2.5 Adverse events

A Cochrane review[237] found a significant increase in the risk of hyperkalaemia with A2RB compared to placebo/no treatment (2 studies, 194 patients); RR 4.93, 95% CI 1.87 to 15.65. A2RB were not found to be associated with an increased risk of cough compared to placebo/no treatment. **Level 1++**

6.3.3.3 A2RB vs CCB

6.3.3.3.1 Cardiovascular and renal outcomes

One RCT[257] with a follow-up of 2.6 years, found that treatment with irbesartan significantly reduced the risk of doubling serum creatinine concentration, development of ESRD, or death from any cause, by 23% compared to the amlodipine therapy (p=0.006). **Level 1++**

When individual end points were analysed the RCT[257] reported:

- A significantly lower risk of a doubling in the serum creatinine concentration in patients receiving irbesartan compared to amlodipine-treated patients (37% lower in the irbesartan group than in the amlodipine group, p< 0.001).
- Non-significant differences in terms of progression to ESRD between irbesartan-treated patients and those receiving amlodipine (risk 23% lower in the irbesartan group p=0.07).
- Non-significant difference in the rates of death from any cause between patients treated with irbesartan and those treated with amlodipine. **Level 1++**

The same study[257] did not find a significant benefit associated with irbesartan as compared with amlodipine in reducing the secondary composite end point of death from CV causes, non-fatal MI, heart failure resulting in hospitalisation, a permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle. **Level 1++**

An RCT[258] comparing therapy with valsartan and amlodipine reported results for a pre-specified subgroup of type 2 diabetes patients and found non-significant differences between the 2 treatment arms for the primary composite cardiac outcome which looked at cardiac mortality and morbidity.*[h] **Level 1+**

Another RCT[252] which also compared treatment with valsartan and amlodipine, found that after 24 weeks there was a significant reduction in UAER in patients receiving valsartan as compared with those treated with amlodipine (p<0.001; 95% CI for ratio, 0.520 to 0.710). The UAER at 24 weeks with valsartan was 56% (95% CI, 49.6 to 63.0) of baseline, equivalent to a 44% reduction. The UAER for amlodipine at week 24 was 92% (95% CI, 81.7 to 103.7) of baseline, a reduction of only 8%. **Level 1++**

The same RCT[252] showed a significantly greater percentage of patients returning to normo-albuminuria status by week 24 with valsartan (29.9%) than with amlodipine (14.5%). Treatment difference 15.4%, 95% CI, 5.6 to 25.8, p<0.001. **Level 1++**

6.3.3.3.2 *Blood pressure*

One RCT[257] did not find significant differences in mean arterial pressure in patients treated with irbesartan and amlodipine after 2.6 years of follow-up. **Level 1++**

6.3.3.3.3 *Metabolic outcomes*

One RCT[251] reported that at 12 months there were no significant changes from baseline in HbA1c, FPG, BMI, triglycerides and high-density lipoprotein cholesterol (HDL-C) in patients treated with telmisartan or nifedipine gastrointestinal therapeutic system (nifedipine GITS) and there were no significant differences in any of these parameters between treatments. **Level 1+**

The same RCT[251] showed that reduction in total cholesterol and low-density lipoprotein with telmisartan were significantly greater than those with nifedipine GITS (p<0.05). **Level 1+**

6.3.3.3.4 *Adverse events*

One RCT[257] reported that the incidence of hyperkalaemia (necessitating discontinuation of the study medication) was significantly higher in patients receiving irbesartan as compared to those receiving amlodipine. **Level 1++**

One RCT[252] found that ankle oedema occurred significantly less frequently in valsartan-treated patients compared to those treated with amlodipine (1.2% vs 7.4%, difference –6.2%, 95% CI –12.9% to –0.4%, p<0.006). **Level 1+**

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h The primary end point was time to first cardiac event (a composite of sudden cardiac death, fatal MI, death during or after percutaneous coronary intervention or coronary artery bypass graft, death as result of heart failure, and death associated with recent MI at autopsy, heart failure requiring hospital management, non-fatal MI, or emergency procedures to prevent MI).

6.3.3.4 A2RB vs sympatholytic agents

6.3.3.4.1 Cardiovascular outcomes

One RCT[256] with a follow-up of 4.7 years found that treatment with losartan significantly reduced the risk of CV death, stroke, or MI compared to atenolol therapy. RR 0.76 (95% CI 0.58 to 0.98), p=0.031. **Level 1++**

When individual end points were analysed the RCT[256] reported:

- a statistically significant reduction in the risk of all-cause mortality in losartan-treated patients compared to those receiving atenolol. RR 0.61 (95% CI 0.45 to 0.84), p=0.002
- a statistically significant reduction in the risk of CV death favouring the losartan group. RR 0.63 (95% CI 0.42 to 0.95), p=0.028
- a non-significant difference in the incidence of stroke or MI between patients treated with losartan and those treated with atenolol.

6.3.3.4.2 Blood pressure[i]

One RCT[250] found that after 12 months, patients treated with irbesartan had significantly lower SBP and DBP levels as compared to those receiving doxazosin, (p<0.05). **Level 1+**

6.3.3.4.3 Metabolic outcomes

One RCT[250] found significantly lower HbA1c levels in doxazosin-treated patients as compared to patients receiving irbesartan after 12 months of follow-up. **Level 1+**

The same RCT[250] found that patients treated with doxazosin had significantly higher levels of HDL-C as compared to those treated with irbesartan (p<0.05). **Level 1+**

6.3.3.4.4 Adverse events

One RCT[256] showed that albuminuria was reported less frequently (p=0.002) as an AE in the losartan than in the atenolol group (losartan 7% vs atenolol 13%). **Level 1++**

The same RCT[256] found that chest pain was more frequently reported in the losartan arm (p=0.036) (losartan 2% vs atenolol 8%). **Level 1++**

6.3.3.5 Beta-blockers

The evidence appraised suggested that treatment with beta-blockers in patients with type 2 diabetes failed to demonstrate a better CV profile when compared with CCB therapy. Furthermore a landmark RCT showed a significant reduction in the incidence of CV outcomes in patients receiving CCB as compared with those treated with beta-blockers. In terms of BP control, the evidence did not demonstrate differences between beta-blocker therapy and other antihypertensives.

6.3.3.5.1 Cardiovascular outcomes

All reported CV outcomes were for beta-blockers vs CCBs.

For the study considering COER verapamil and atenolol or hydrochlorothiazide there was NS difference between the groups for both the composite of acute MI, stroke or CV related death and also for the incidence of any component of the composite in the diabetes subgroup.[261] **Level 1+**

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i BP reduction with all hypertensive treatments was a consistent feature of the studies and therefore only studies where there were significant differences between the treatments will be highlighted.

The ASCOT-BPLA study found that for the diabetes subgroup for total CV events and procedures there was significantly lower occurrence with the amlodipine based group vs the atenolol based group (HR 0.87, 0.76 to 0.99, p=0.0283), this was also found for the participants who did not have diabetes.[262] **Level 1++**

The INVEST study found NS difference in the treatments (verapamil SR and atenolol) for death or first occurrence of non-fatal MI or non-fatal stroke in both groups of patients with and without diabetes.[259] **Level 1+**

6.3.3.5.2 Blood pressure

Within all the papers included that reported BP outcomes the treatments reduced BP and there was NS difference found between the treatment groups.[260–262]

6.3.3.5.3 Renal outcomes

Only the study comparing 2 beta-blockers reported on renal outcomes.

The study considering carvedilol and metoprolol found that carvedilol reduced the albumin:creatinine ratio vs metoprolol (relative reduction 16%, p=0.003).[260] This study also identified those with albuminuria of 30 mg or less at baseline, fewer in the carvedilol group vs the metoprolol group progressed to microalbuminuria (6.4%, 25/388 vs 10.3%, 56/542), or from carvedilol vs metoprolol, 0.60, 0.36 to 0.97, p=0.04).[260] **Level 1++**

6.3.3.5.4 Metabolic outcomes

Only the study comparing 2 beta-blockers reported on metabolic outcomes.

The study considering carvedilol and metoprolol found that carvedilol treatment had no HbA1c changes from baseline while metoprolol increased HbA1c. The mean difference was 0.12%, p=0.006. More participants withdrew due to worsening glycaemic control with metoprolol (2.2%, 16/737) than with carvedilol (0.6%, 3/498), p=0.04.[260] **Level 1++**

6.3.3.5.5 Adverse events

The study comparing COER verapamil with atenolol or hydrochlorothiazide[261] reported that participants assigned COER verapamil withdrew more often due to adverse signs or symptoms compared with those assigned atenolol of hydrochlorothiazide (p=0.02); the most common reason was constipation (216 in the COER verapamil compared with 28 in the atenolol of hydrochlorothiazide group). However, fewer participants assigned COER verapamil (N=115) atenolol of hydrochlorothiazide withdrew because of poor BP control compared with those assigned atenolol of hydrochlorothiazide (N=207) (p<0.001 by log-rank). **Level 1+**

The INVEST study[259] showed that verapamil and atenolol were generally well tolerated in each treatment group. Patients in the verapamil group reported constipation and coughs more frequently than patients in the atenolol group, while atenolol-treated patients had more dyspnoea, light-headedness, symptomatic bradycardia, and wheezing. **Level 1+**

The RCT comparing carvedilol with metoprolol did not report significant differences between groups in overall safety profile. However, the study stated that no participant taking carvedilol had a respiratory event in contrast with 7 events in 6 participants taking metoprolol. **Level 1+**

The ASCOT-BPLA study concluded that the most frequent AEs found in the amlodipine based group were peripheral oedema 23%; cough 19%; joint swelling 14%; dizziness 12%; chest pain 8%; fatigue 8%. In the atenolol based group the most frequent AEs were dizziness 16%; fatigue 16%; dyspnoea 9%; cough 8%; erectile dysfunction 7%. **Level 1+**

6.3.4 Health economic evidence statements

6.3.4.1 ACEI

Ramipril was found to be cost-effective compared to placebo, £2971/LYG[263] and €2486/LYG[264] (£1699/LYG, exchange rate 0.68, 13 March 2007).[271]

No statistically significant difference was found between captopril and atenolol. Atenolol had significantly lower mean costs.[265]

6.3.4.2 A2RB

Irbesartan was found to be both more effective and cost saving than amlodipine and standard antihypertensive treatment.[266-268]

Losartan was found to be both more effective and cost saving than standard antihypertensive treatment.[269]

Valsartan was found to be both more effective and cost saving compared to amlodipine.[270]

6.3.5 Evidence to recommendations

The GDG used as its starting point the 2006 update of the NICE hypertension guidelines and the NICE type 2 diabetes hypertension guideline from 2002, available at www.nice.org.uk. The group noted that the health economic model for the former did not include renal or retinopathy outcomes, both of particular importance when considering choice of therapies for use in people with type 2 diabetes. Thus 25% of people with type 2 diabetes develop diabetic nephropathy within 20 years of diagnosis, while the drugs studied in the UKPDS hypertension study had strong effects on retinopathy progression. Therefore, the GDG was particularly interested in reviewing the evidence as to whether there were any differential effects in terms of different classes of antihypertensive agent on microvascular as well as cardiovascular outcomes in people with type 2 diabetes.

The GDG noted a wealth of new evidence in this area since the hypertension guideline 2002 was published, and were cognisant of the early revision of the NICE hypertension guidelines 2006, albeit these applying to people without diabetes. Much of the new evidence seemed to be driven by studies in people with diabetes with increased AER (microalbuminuria or worse). The high known prevalence of renal damage in people with type 2 diabetes and the need to prevent this and its progression were noted to emphasise the importance of BP control. Little evidence on retinopathy prevention was available to the GDG, but it was aware of the positive data previously assessed for ACEI and a beta-adrenergic blocker. Published CV outcome data was noted to be of limited quality in some studies due to under powering in studies with other primary end points, even when combined for meta-analysis.

The GDG noted that the evidence did not distinguish between medications on the basis of degree of BP lowering. The issues of importance revolved around differences of evidence of effectiveness in renal related outcomes and metabolic worsening. Some classes of medications, notably A2RB and alpha-adrenergic blockers, were only available in more expensive proprietary form, and thus without added evidence of efficacy would not be cost-effective compared to older drugs.

Overall it was felt that the best evidence for prevention of renal disease and limitation of metabolic worsening related to the renin angiotensin system-blockers (RAS-blockers) (ACEI and A2RB) as a class.

With regard to non-renal outcomes, no evidence was identified that caused the GDG to reach any different conclusions from the review of the evidence carried out for the NICE hypertension guideline 2006. The GDG recognised there was good evidence of efficacy for thiazide diuretics and CCBs, including when used in combination with RAS-blockers.

Given the benefits in terms of reno-protection and retinopathy of RAS blockade, it was felt appropriate to recommend RAS-blockers as first-line medication in the treatment of hypertension in type 2 diabetes. This was the only change in sequencing that the GDG felt was appropriate to make to the NICE hypertension guidelines 2006. On the grounds of cost a generic 24-hour ACEI should be used first line. A2RB (also selected on grounds of cost) should only be substituted in the event of significant ACEI intolerance, usually troublesome chronic cough (and not if hyperkalaemia or decreased renal function is the problem). An exception was highlighted in the NICE hypertension guideline 2006, where people of African-Caribbean descent are noted to respond less well to RAS- blockers, and for someone in this group either combination ACEI + diuretic therapy or CCB was thought appropriate first line therapy. Little specific information was available for other ethnic groups.

Thiazide diuretics and CCBs are recommended as second-line medications, though it was noted that it would be usual to need at least 2 drugs or more, so these would be added to a RAS-blocker and each other for the most part. There was some concern about the adverse metabolic effects of thiazides (in contrast to the positive effects of RAS-blockers and neutral effects of CCB), though the standard dose of bendroflumethiazide was thought not to be a problem in this regard.

Many people with diabetes do require 4 or even 5 antihypertensive agents to approach target levels. After 3 classes of medication had been used the GDG felt that reasons for distinguishing between other drug classes were poor. It was felt that any alpha-blocker, beta-blocker, or potassium-sparing diuretic could be added at this stage. If an RAS-blocker is used with a potassium-sparing diuretic, the potassium levels should be carefully monitored, the clinician being alert to the possibility of hyperkalaemia.

While in general this was felt to be the appropriate positioning of the beta-blockers, particularly because of their metabolic effects when used in combination with thiazides, it was recognised that some people would have a clearer indication for these drugs through having angina, heart failure, or previous heart attack. In these circumstances the drugs would already be being prescribed. One study suggested that carvedilol was superior to metoprolol both in metabolic terms and for renal protection. The GDG found the evidence interesting but incomplete in regard of target groups and active comparisons with the RAS-blockers; accordingly no out-of-class recommendations are made.

There is a need to emphasise caution over the use of some drug classes in the increasing numbers of women with type 2 diabetes who might become pregnant. The GDG felt comfortable that the decision to use, or not use such drugs should be one of informed agreement between each woman and their professional advisor.

Issues of adherence and the use of fixed-dose combination therapy were considered. The evidence was not formally available to the GDG, but clinical experience over the combined burden of medications faced by many people with type 2 diabetes led to an overall view that combination tablets could be appropriate in reducing that burden, and possibly improving outcomes through better adherence. No formal recommendations could be made.

The GDG were aware of the issues that arose from the burden of use of multiple therapies. In this area in particular it was therefore felt appropriate to further emphasise communication, discussion and agreement about medication use.

An issue considered of importance, but not covered in the evidence review was that of BP monitoring, including the role of self-monitoring and of ambulatory BP monitoring. The GDG was happy to defer to the NICE hypertension guideline 2006 (now update by the NICE hypertension guideline 2011) on these issues.

6.3.6 Recommendations

These recommendations have been updated and replaced the NICE guideline on hypertension in adults.

7 Antiplatelet therapy for primary prevention of cardiovascular disease

7.1 Clinical introduction

This section was updated in 2015

Antiplatelet therapy has an established role in the management of people with cardiovascular disease. However, its role in primary prevention for people without existing cardiovascular disease is less clear. This review question addressed whether aspirin or clopidogrel (either alone or in combination) should be used for the prevention of cardiovascular events in people with type 2 diabetes who do not have existing cardiovascular disease, that is for primary prevention. This question also covered whether their use should be restricted to specific subgroups of the population, when these treatments should be used and what adverse events are associated with their use.

7.1.1 Antiplatelet therapy in Clinical Guideline 66

This section was updated in 2015

Antiplatelet therapy was originally covered as part of CG66. The original searches were conducted from 2001 to 2007 (see Appendix G for search strategies from CG66). Update searches have been carried out for this topic with a date restriction of 2007 to June 2014 (see Appendix C for updates search strategies). Although the focus in CG66 was primary prevention of cardiovascular disease, the evidence also included studies on secondary prevention. In total, 8 RCTs were originally included for this review question.

7.1.2 Antiplatelet therapy in the update (2015)

This section was updated in 2015

Although aspirin and clopidogrel are not licensed for primary prevention of cardiovascular disease, the GDG considered that an updated evidence review was important as such off-label use of these particular drugs is common in current clinical practice. The Group agreed that only studies on adults with type 2 diabetes who did not have established cardiovascular disease should be included, to ensure that the findings of the review are specific to primary prevention. The GDG considered that people with type 2 diabetes and established cardiovascular disease are inherently different in terms of risk factors, and therefore findings from secondary prevention studies could not credibly be extrapolated to those without cardiovascular disease. In addition, the GDG recognised that the evidence supporting the role of antiplatelet therapy in secondary prevention is established, whereas there is debate surrounding its use in primary prevention, and changes in the evidence base would likely impact on clinical practice.

7.1.3 Evidence review

7.1.3.1 Review question

This section was updated in 2015 Should aspirin and/or clopidogrel be used for primary prevention of cardiovascular disease in people with type 2 diabetes?

Table 18: PICO table

Population	Adults (18 years and over) with type 2 diabetes without established cardiovascular disease

Interventions	Aspirin, clopidogrel, aspirin plus clopidogrel
Comparators	Placebo, listed interventions
Outcomes	Development of cardiovascular disease (myocardial infarction, heart failure, ischaemic stroke, acute coronary syndrome, transient ischaemic attack, revascularisation and stenting) Adverse events such as any bleeding including gastrointestinal bleeding, haemorrhagic stroke Mortality Health-related quality of life

Randomised controlled trials (RCTs) examining the use of aspirin or clopidogrel in people with type 2 diabetes were included. Papers were excluded if they:

- were non-randomised studies (such as observational studies, narrative reviews and conference abstracts)
- included a mixed population of people with type 1 and 2 diabetes and either did not report subgroup analyses, or less than 85% of the study population had type 2 diabetes
- focused on the use of aspirin or clopidogrel after acute cardiological events, cardiac interventions or cerebrovascular events (that is, secondary prevention)
- focused on the use of antiplatelet drugs other than aspirin or clopidogrel (such as dipyridamole, prasugrel, ticagrelor as these are generally used for secondary prevention). For the full excluded list, see Appendix L.

The main outcomes for this review question were the development of cardiovascular disease and adverse events specifically any bleeding including gastrointestinal bleeding. The detailed protocol is available in Appendix C.

7.1.3.2 Clinical evidence

The evidence that was originally included as part of CG66 was re-reviewed as part of the update. Six trials examining clopidogrel (either alone or in combination with aspirin) were excluded as they were conducted in people with established cardiovascular disease (Bhatt et al. 2002; Diener et al. 2004; Mehta et al. 2001; Steinhubl et al. 2002; Yusuf et al. 2001) or did not provide separate results for primary prevention (Bhatt et al. 2006). Another trial from CG66 (Khajehdehi et al. 2002) was also excluded as it reported data on kidney damage but no cardiovascular outcomes, and was limited to only 2 months of treatment. The final study, the Primary Prevention Project (PPP) trial (Sacco et al 2003) met the revised inclusion criteria for this update.

In total, 1204 references were found in the update searches and 1 RCT was included (Ogawa et al. 2008). The GDG was also aware of a post hoc analysis of cardiovascular outcomes that was being undertaken on the Early Treatment Diabetic Retinopathy Study (ETDRS Investigators 1992), and requested unpublished data from the authors on adults with type 2 diabetes without a history of cardiovascular disease.

Data from all 3 trials focused on the use of aspirin therapy compared with no aspirin. No trials were identified that examined the use of clopidogrel (alone or in combination with aspirin) in people with type 2 diabetes without existing cardiovascular disease.

Pooling of studies using meta-analysis was not possible because the definitions of cardiovascular outcomes varied across the studies and different estimates of effect were used that is, hazard ratios and risk ratios.

7.1.3.3 Description of included studies

This section was updated in 2015

The 3 RCTs including a total of 7281 participants were carried out in the USA (ETDRS: unpublished data 2013), Italy (Sacco et al. 2003) and Japan (Ogawa et al. 2008). All trials randomised participants to aspirin or no aspirin (placebo or vitamin E), with doses of aspirin ranging from 81 (Ogawa et al. 2008) to 650 mg (ETDRS: unpublished data 2013). The mean age of participants in 2 trials ranged from 64 to 65 years, while the last study did not provide this information (ETDRS: unpublished data 2013). Mean HbA1c at baseline ranged from 53 to 54 mmol/mol (7.0% to 7.1%) in 2 trials, with 1 study reporting that about 33% of the participants had baseline HbA1c greater than 86 mmol/mol (10%) (ETDRS: unpublished data 2013). The median follow-up ranged from 3.7 to 5 years. Details of the included studies are found in the evidence tables (see Appendix E).

A summary GRADE table is presented for this review question (see Appendix D for full GRADE tables).

Table 19: Summary GRADE profile for aspirin therapy for primary prevention of cardiovascular disease

Number of RCTs	Number of people		Relative effect (95% CI)	Quality
	Aspirin	Control		
All-cause mortality; follow-up for up to 5 years				
1 (ETDRS)†	587	565	HR 0.99 (0.83 to 1.17)	Moderate
1 (Sacco 2003)-PPP	25/519	20/512	RR 1.23 (0.69 to 2.19)	Very low
Cardiovascular mortality; follow-up for up to 5 years				
1 (ETDRS)†	587	565	CV death: HR 0.97 (0.79 to 1.19)	Moderate
1 (Sacco 2003)-PPP	10/519	8/512	CV mortality: RR 1.23 (0.49 to 3.10)	Very low
1 (Ogawa 2008)-JPAD	0/1262	5/1277	Fatal MI: HR not estimable because of no events in aspirin group	Low
Cerebrovascular mortality; follow-up for median 4.4 years				
1 (Ogawa 2008)-JPAD	1/1262	5/1277	Fatal stroke: HR 0.20 (0.024 to 1.74)	Low
Coronary and cerebrovascular mortality; follow-up for median 4.4 years				
1 (Ogawa 2008)-JPAD	1/1262	10/1277	HR 0.10 (0.01 to 0.79)	Low
Non-cardiovascular mortality; follow-up to median 3.7 years				
1 (Sacco 2003)-PPP	15/519	12/512	RR 1.23 (0.58 to 2.61)	Very low
Any atherosclerotic event[a]; follow-up from median 3.7 to 4.4 years				
1 (Sacco 2003)-PPP	20/519	22/512	RR 0.90 (0.50 to 1.62)	Very low

Number of RCTs	Number of people		Relative effect (95% CI)	Quality
	Aspirin	Control		
1 (Ogawa 2008)-JPAD	68/1262	86/1277	HR 0.80 (0.58 to 1.10) Subgroup: age ≥ 65 years: HR 0.68 (0.46 to 0.99 < 65 years: HR 1.00 (0.57 to 1.70) Subgroup: sex Male: HR 0.74 (0.49 to 1.12) Female: HR 0.88 (0.53 to 1.44) Subgroup: cardiovascular risk factors Hypertensive: HR 0.88 (0.60 to 1.30) Normotensive: HR 0.64 (0.36 to 1.13) Dyslipidaemia: HR 0.88 (0.57 to 1.37) Normolipidaemia: HR 0.71 (0.45 to 1.14) Current/past smoking: HR 0.73 (0.47 to 1.14) Non-smoker: HR 0.83 (0.53 to 1.31) Subgroup: renal function eGFR ≥ 90: HR 0.87 (0.36 to 2.12)[d] eGFR 60-89: HR 0.53 (0.34 to 0.83)[d] eGFR < 60: HR 1.24 (0.69 to 2.23)[d] Subgroup: existing therapies Insulin: HR 1.00 (0.50 to 2.00)[d] OHA: HR 0.77 (0.52 to 1.14)[d] Diet alone: HR 0.20 (0.06 to 0.68)[d]	Low
Coronary heart disease events; follow-up from median 3.7 to 5 years				
1 (ETDRS)†	587	565	MI: HR 0.85 (0.70 to 1.05) CV event[b]: HR 0.97 (0.82 to 1.15)	Moderate
1 (Sacco 2003)-PPP	53/519	59/512	Total CV events: RR 0.89 (0.62 to 1.26)	Very low

Number of RCTs	Number of people		Relative effect (95% CI)	Quality
	Aspirin	Control		
	5/519	10/512	All MI: RR 0.49 (0.17 to 1.40)	
	13/519	16/512	Angina: RR 0.80 (0.39 to 1.64)	
1 (Ogawa 2008)-JPAD	28/1262	35/1277	Any fatal or nonfatal event: HR 0.81 (0.49 to 1.33)	Low
	12/1262	9/1277	Nonfatal MI: HR 1.34 (0.57 to 3.19)	
	12/1262	11/1277	Stable angina: HR 1.10 (0.49 to 2.50)	
	4/1262	10/1277	Unstable angina: HR 0.40 (0.13 to 1.29)	
			Cardiovascular events subgrouped by cardiovascular risk: In low risk group: HR 0.53 (0.23 to 1.21) In high risk group: HR 0.78 (0.55 to 1.11)	
Cerebrovascular events; follow-up from median 3.7 to 5 years				
1 (ETDRS)†	587	565	Stroke: HR 1.09 (0.78 to 1.53)	Low
1 (Sacco 2003)-PPP	9/519	10/512	All stroke: RR 0.89 (0.36 to 2.17)	Very low
	7/519	10/512	Transient ischaemic attack: RR 0.69 (0.27 to 1.79)	
1 (Ogawa 2008)-JPAD	28/1262	32/1277	Any fatal or nonfatal event: HR 0.84 (0.53 to 1.32)	Low
	22/1262	24/1277	Nonfatal ischaemic stroke: HR 0.93 (0.52 to 1.66)	
	5/1262	3/1277	Nonfatal haemorrhagic stroke: HR 1.68 (0.40 to 7.04)	
	5/1262	8/1277	Transient ischaemic attack: HR 0.63 (0.21 to 1.93)	
			Cerebrovascular events subgrouped by blood pressure control[c]: In non-aspirin group: HR 2.84 (1.52 to 5.52) indicating higher incidence in unattained group In aspirin group: HR 1.64 (0.83 to 3.29) indicating no difference in incidence in unattained vs. attained No HR reported for aspirin vs. non-aspirin but reported as not significant	
Peripheral artery disease; follow-up from median 3.7 to 4.4 years				
1 (Sacco 2003)-PPP	11/519	13/512	RR 0.83 (0.38 to 1.84)	Very low
1 (Ogawa 2008)-JPAD	7/1262	11/1277	HR 0.64 (0.25 to 1.65)	Low
Revascularisation; follow-up to median 3.7 years				
1 (Sacco 2003)-PPP	8/519	10/512	RR 0.79 (0.31 to 1.97)	Very low
			Creatinine clearance: MD -2.30 (-5.42 to 0.82)	

Number of RCTs	Number of people		Relative effect (95% CI)	Quality
	Aspirin	Control		
			Urine protein:creatinine ratio: MD -0.30 (-0.53 to -0.07)	
			% proteinuria change: MD -17.80 (-22.95 to -12.65)	
Adverse events: Any bleeding; follow-up for median 4.4 years				
1 (ETDRS 1992)	587	565	Only a few patients (2%) in both groups had some indication of bleeding[‡]	Low
1 (Ogawa 2008)-JPAD	1251	1272	Haemorrhagic events subgrouped by renal function: eGFR ≥ 90: HR not estimable eGFR 60-89: HR 1.03 (0.24 to 4.35) eGFR < 60: HR: 0.87 (0.10 to 7.27)	Low
	21/1262	6/1277	Other bleeding: RR 3.54 (1.43 to 8.75)	
	12/1262	4/1277	Gastrointestinal bleeding: RR 3.04 (0.98 to 9.39)	
Non-bleeding gastrointestinal event; follow-up for median 4.4 years				
1 (Ogawa 2008)-JPAD	47/1262	4/1277	RR 11.89 (4.30 to 32.90)	Moderate
Other adverse event[e]; follow-up for median 4.4 years				
1 (Ogawa 2008)-JPAD	5/1262	0/1277	RR 11.13 (0.62 to 201.08)	Low

Abbreviations: BP blood pressure; CV cardiovascular; eGFR estimated glomerular filtration rate; HR hazard ratio; MD mean difference; MI myocardial infarction; OHA Oral hypoglycaemic agents; RCT randomised controlled trial; RR relative risk

NB: data from ETDRS (unpublished 2013) are from multivariate analysis; data from the JPAD trial (Ogawa et al. 2008) are from Cox proportional hazards model (not specified as multivariate) in multiple publications; data from the PPP trial (Sacco et al. 2003) are relative risks as multivariate analyses using Cox regression are not reported for people with diabetes

[a] any atherosclerotic event was defined as a composite of sudden death, death from coronary, cerebrovascular and aortic causes, nonfatal acute MI, unstable angina, newly developed exertional angina, nonfatal ischaemic and haemorrhagic stroke, transient ischaemic attack or nonfatal aortic and peripheral vascular disease

[b] CV event was defined as CV death, myocardial infarction or stroke

[c] unattained group had systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and the attained group had systolic BP < 140mmHg and/or diastolic BP < 90mmHg

[d] adjusted for age, hypertension, dyslipidaemia and history of smoking

[e] Anaemia and asthma

[†] Unpublished subgroup analysis for people with type 2 diabetes without a history of cardiovascular disease from the ETDRS trial was provided by the authors

[‡] haemoglobin < 100 g/L or haematocrit < 0.30, haematuria, or blood in the stool

7.1.3.4 Health economic evidence

This section was updated in 2015

Literature searches were undertaken to find any existing cost–utility analyses (CUAs) of using clopidogrel or aspirin for the primary prevention of cardiovascular disease in people with type 2 diabetes (see appendix C for details of the search strategies). In total, 537 articles were found and 2 CUAs were returned that met the NICE reference case (National Institute for Health and Social Care, 2012).

One CUA (Li et al. 2010) used an existing diabetes health economic model (CDC-RTI model] [CDC Diabetes Cost-Effectiveness Group 2002) to compare daily aspirin use with no aspirin in a population of people with newly diagnosed type 2 diabetes. The treatment effect was taken from a non-diabetes-specific meta-analysis but other parameters (including costs and utilities) were specific to people with type 2 diabetes.

Another CUA (Lamotte et al. 2006) created a Markov model to assess the impact of daily aspirin use to no aspirin over 10 years in 4 countries (including UK). This model was not diabetes specific but used varying prespecified annual risks of CVD events. Costs were taken from UK reference costs and the UKPDS trial; utility sources were unclear.

One CUA (Lamotte et al. 2006) found that for the UK, daily aspirin use dominated no aspirin at baseline risks of CVD greater than 0.24% per year, whilst the other CUA (Li et al. 2010) found that, for America, daily aspirin use was cost effective compared to no aspirin (ICER $8800 per QALY). Both results were unchanged under both deterministic and probabilistic sensitivity analyses.

No CUAs were found that assessed the use of clopidogrel for primary prevention of cardiovascular disease in people with type 2 diabetes.

This question was not prioritised by the GDG for de novo economic modelling.

Table 20: Economic evidence for aspirin use to prevent cardiovascular events

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental Cost	Incremental Effect	Incremental ICER	Conclusions	Uncertainty
Lamotte et al. (2006) People without CHD history, annual baseline risk 1.5% per annum 4 countries (UK, Italy, Germany, Spain) Aspirin 75mg daily **Partly applicable**[a,b] **Potentially serious limitations**[c,h]	Effects: 2 meta-analyses (same trials), reasons for selection not given. Not UK specific Costs: Country specific. UK reference costs and UKPDS for complications (€, 2003, country specific discounting) Utilities: from literature. Not UK, limited detail	Markov model with 10 year time horizon Baseline annual CHD risk 1.5% 5 states – no CVD, MI, stroke, CVD, death. TIA, PAD and stable angina not considered. Only 2/5 trials contain women Funded by industry	UK -€201 Germany -€281 Spain -€797 Italy -€427	UK 0.04 QALYs Germany 0.02 QALYs Spain 0.03 QALYs Italy 0.03	UK: dominant Germany: dominant Spain: dominant Italy: dominant	In the UK, aspirin is likely to be cost saving given baseline annual CHD risk > 0.24%	Results over 10 years at baseline risk of 1.5% per annum ICER sensitive to risk GI bleeding and stroke risk in Italy In PSA, aspirin is dominant in 97% of replications Country cost comparisons differ because of the ratio between aspirin and complication costs Country utility comparisons differ because of country specific discount rates
Li et al. (2010) US residents aged 40-94 with newly diagnosed type 2 diabetes Aspirin 80mg daily **Partly applicable**[d,e] **Potentially serious limitations**[c,f,g]	Effects: US age-gender specific, non-diabetes specific meta-analysis Costs: other US studies, health system perspective ($, 2006, discount rate 3% for cost and utilities) Utilities: from literature. QWB scale from US type 2 diabetes attending hospital clinic	Existing Markov model with lifetime horizon Only RRs for major events and strokes statistically significant Diabetes specific meta-analysis found effect of aspirin in primary prevention unproven Base case models ischaemic and haemorrhagic strokes together People with newly diagnosed diabetes only but utilities from longstanding diabetes	$1700	0.19 QALYs	$8801/ QALY	Daily aspirin appears very cost effective for newly diagnosed people with type 2 diabetes aged 40+ years at $50,000/ QALY threshold	ICER sensitive to gender, primary and secondary effectiveness, but ICERs remain < $23,000/QALY In PSA, all iterations gave ICERs < $27,000/QALY (not all parameters varied) Cardiac events avoided offset the cost and risk of bleeding Probably not cost-saving because of aspirin extending life (and potential for complications)

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
a Not specific to type 2 diabetes b Source of utility value unclear c No evidence of systematic review for selection of clinical effects d Not 3.5% discount rate e Not UK based f May not include all relevant complications g Not all parameters varied in PSA h Potential conflict of interest							
CDC-RTI: Centre for Disease Control and Prevention Research Triangle Institute CHD: coronary heart disease CVD: cardiovascular disease ICER: incremental cost effectiveness ratio MI: myocardial infarction PAD: peripheral arterial disease PSA: probabilistic sensitivity analysis QALY: quality-adjusted life year QoL: quality of life RR: relative risks TIA: transient ischaemic attack UK: United Kingdom UKPDS: United Kingdom Prospective Diabetes Study US: United States							

7.1.4 Evidence statements

This section was updated in 2015

7.1.4.1 Clinical evidence

No trials were identified examining the use of clopidogrel alone or in combination with aspirin for primary prevention of cardiovascular disease in people with type 2 diabetes.

7.1.4.1.1 Mortality

One trial found a clinically important reduction in the rate of combined coronary and cerebrovascular mortality in people with type 2 diabetes who were assigned aspirin therapy compared with people who were assigned to no aspirin therapy. The quality of the evidence was low.

There was no clinically important difference in the risk of mortality by any other definition in the 3 trials. The evidence ranged from moderate to very low.

7.1.4.1.2 Atherosclerotic events with or without ischaemic events

Pre-specified subgroup analyses of 1 trial found a clinically important reduction in the incidence of atherosclerotic events in people aged 65 years and older who were assigned to aspirin therapy compared with those who were not.

Post hoc subgroup analyses from 1 trial found clinically important reductions in the rate of any atherosclerotic event in those who were assigned to aspirin therapy compared with those who did not receive aspirin in the following subgroups:

- people with mild renal dysfunction (eGFR between 60 and 89)
- people managed by diet alone.

The quality of the evidence was low.

There was no clinically important difference in the risk of overall atherosclerotic events in 2 trials. The evidence ranged from moderate to very low.

7.1.4.1.3 Coronary heart disease

Evidence from 2 trials found no clinically important differences between those who received aspirin and those who did not for the following conditions: myocardial infarction, angina (stable or unstable), transient ischaemic attack, peripheral artery disease, revascularisation and any cardiovascular event. The quality of the evidence ranged from moderate to very low.

7.1.4.1.4 Adverse events

Evidence from 1 trial found no clinically important differences in the rates of any bleeding between those who received aspirin therapy compared with people who did not. The quality of the evidence was low.

Evidence from 1 trial found no clinically important differences in the rates of gastrointestinal bleeding between people who received aspirin therapy and those who did not. The quality of the evidence was low. Evidence from the same trial found a clinically important difference in those receiving aspirin who were at greater risk of ‘other’ bleeding (non-gastrointestinal) compared with those who did not receive aspirin. The quality of the evidence was moderate.

Evidence from 1 trial found a clinically important difference in the rates of non-bleeding gastrointestinal events in those receiving aspirin who were at greater risk compared with those who did not receive aspirin. The quality of the evidence was moderate.

Evidence from 1 trial found no clinically important differences between the groups receiving aspirin or no aspirin, in terms of 'other adverse events' and haemorrhagic events. The quality of the evidence was low.

7.1.4.2 Health economic evidence

This section was updated in 2015

Two cost–utility analyses assessed the impact of taking aspirin compared with not taking aspirin for the primary prevention of cardiovascular events. While they were based on different assumptions and data, they found that aspirin was likely to be cost effective compared with not taking aspirin in both deterministic and probabilistic analyses.

7.2 Evidence to recommendations

This section was updated in 2015Table 21: Linking evidence to recommendations

Relative value of different outcomes	The GDG noted that, although reducing the risk of mortality or developing cardiovascular disease was important in improving life expectancy and quality of life, the relative impact of adverse events associated with the off-label use of aspirin and clopidogrel (such as bleeding) for primary prevention was also important in determining the safety and acceptability of treatment to the patient. Thus all outcomes were considered equally critical in decision-making.
Trade-off between benefits and harms	In clinical practice, the decision to offer aspirin or clopidogrel depends on the net benefit to the patient. Potential benefits must be balanced against the possible harms from adverse effects, such as bleeding and gastrointestinal symptoms. It is particularly important to know the risk of these adverse effects when aspirin is used as primary prevention in people as yet free of, but at risk of developing, cardiovascular disease. The GDG considered that, overall, there was limited evidence to indicate that aspirin was beneficial in reducing the incidence of mortality, with only 1 study showing a reduction in a specific combined outcome of coronary and cerebrovascular mortality. Overall, there was no benefit in reducing the risk of developing a cardiovascular event, except in certain subgroups, such as those aged 65 years or older, people with mild renal dysfunction and those managing their diabetes using dietary changes alone. The GDG agreed that there was evidence to support an increased risk of harm associated with the use of aspirin, in terms of an increased risk of non-gastrointestinal bleeding and non-bleeding related gastrointestinal events. The GDG discussed that any bleeding events would have a large negative impact on a patient's quality of life and anxiety levels. The GDG also agreed that the treatment of this adverse event may be costly. Non-bleeding gastrointestinal events can also have a negative impact on an person's quality of life.

	The GDG considered all the evidence and agreed that the increased risk of bleeding outweighed the potential benefits of taking aspirin.
Consideration of health benefits and resource use	The GDG considered that neither of the 2 cost–utility analyses (CUAs) reviewed accurately reflected the decision problem, and that both had serious limitations, but agreed that they both lent some value to the question. The GDG acknowledged that neither CUA used diabetes-specific treatment effects, but the UK-based study used a range of baseline cardiovascular event risks, the higher values of which could be seen as approximating the baseline cardiovascular event risks of people with type 2 diabetes. The GDG agreed that, if the clinical review had found aspirin use to be effective, then it would likely have been cost effective. However, the GDG noted that both the CUAs could be underestimating rates of adverse events compared with the clinical review. Underestimating adverse event rates would make the intervention appear more cost effective than it is.
Quality of evidence	The GDG noted that there was uncertainty about most of the outcome data, as indicated by confidence intervals that generally crossed the line of no effect. The GDG noted that all of the included studies examined aspirin and agreed that the overall quality of evidence was low to very low. The GDG expressed concern about some methodological and clinical issues with the evidence base. The baseline HbA1c levels (approximately 53 mmol/mol [7.0%]) of people in the included trials were relatively low compared to the UK, which encouraged the GDG to question the generalisability of these findings to clinical practice in the UK. None of the studies had a follow-up period longer than 10 years, which is the typical timeframe by which the risk of developing cardiovascular disease is defined. The GDG noted that the aspirin doses (81–650 mg) used in the studies were above the recommended UK maintenance dose of 75 mg. This cast further doubts on the generalisability of the findings to the UK clinical population. The GDG considered that higher doses could explain the increased risk of adverse effects found in the studies, but not the relative lack of benefit that one might expect to see. The GDG also noted that all of the studies included ‘any type of stroke’ in their composite outcomes of cerebrovascular and atherosclerotic events. However, the opinion of the GDG was that different types of stroke should be considered separately, with prevention of ischaemic stroke classified as a beneficial effect, but haemorrhagic stroke classified as an adverse event. The GDG recognised that the findings of trials which report both outcomes, that is, development of cardiovascular disease and adverse events, would not be affected by the combined reporting of all types of stroke events.

	The GDG recognised that the majority of data were derived from the JPAD trial, which was conducted in Japan, and questioned the generalisability of the findings to western countries. The GDG noted that the overall incidence of cardiovascular events was generally lower – possibly explained by different dietary habits, particularly fish consumption – in Japan, compared with western countries. The GDG noted that the significant findings for the 3 different subgroups in the post hoc analyses were from this trial and also commented on the overall significant difference observed in favour of aspirin for the composite outcome of coronary (fatal myocardial infarction) and cerebrovascular (fatal stroke) mortality. The GDG considered that because of the low event rate, this single significant finding was likely to be fragile and very small changes in the event numbers would have a large impact on the estimate of effect.
Other considerations	The GDG noted that there were 2 ongoing trials that should provide more direct and applicable evidence to answer this review question in the future. The GDG was aware of an ongoing trial (ASCEND), which is fully recruited, randomised and includes 15,480 people with either type 1 or type 2 diabetes without occlusive arterial disease. The trial is being conducted in the UK and is scheduled to continue until 2017. The purpose of this 2×2 factorial, double-dummy study is to determine whether 100 mg of aspirin daily, with or without supplementation of 1 g of omega-3 fatty acid daily, prevents serious vascular events compared with placebo or supplementation of 1 g of omega-3 fatty acid daily only. The primary outcome measure is the combination of non-fatal myocardial infarction, non-fatal stroke or vascular death, excluding confirmed cerebral haemorrhage. The study also aims to assess serious bleeding and other adverse events. Another ongoing trial (ACCEPT-D) aims to assess the effects of low-dose aspirin on the incidence of major vascular events in people with type 1 or type 2 diabetes with no clinical evidence of vascular disease. The trial is being conducted in Italy and is scheduled to end in 2015. The GDG discussed the use of antiplatelet therapy in people with microalbuminuria. Although the GDG recognised that microalbuminuria may be an indicator of cardiovascular risk because it may be an early signal of decline in kidney function, it also appears in people with type 2 diabetes and normal renal function. The GDG noted that there are other ways of assessing cardiovascular risk such as hypertension. The GDG noted that evidence from the STENO 2 trial showed a reduction in cardiovascular disease and progression of renal disease in people with type 2 diabetes and microalbuminuria. However, the GDG noted that this study assessed a multifactorial intervention which included components that could all influence cardiovascular outcomes (that is, the use of aspirin [75 mg], renin–angiotensin system blockers and lipid-lowering agents and tight glucose regulation) compared with conventional therapy. Therefore the GDG was not certain that the findings could be robustly

	extrapolated to reflect the true effects of aspirin alone and did not consider it was appropriate to make a specific recommendation for a microalbuminuria subgroup. The GDG agreed that it would be beneficial for large ongoing trials to consider the effects of antiplatelet therapy within this specific subgroup. When making recommendations for the use of antiplatelet therapy (aspirin and clopidogrel), the GDG considered the following points: • Although the evidence base is small, the included evidence supported an increased risk of harm (including bleeding events) associated with the use of aspirin. • There was uncertainty around whether aspirin reduced the incidence of cardiovascular events. A strong 'do not do' recommendation was made for this review question because, despite the small amount of evidence, the GDG was confident that aspirin would not be of sufficient benefit for the majority of patients with type 2 diabetes who had not previously experienced a cardiovascular event. A strong recommendation was considered to be justified because the potential harm associated with the off-label use of aspirin (such as bleeding) outweighed the benefits (such as reduction in cardiovascular events). Although it was acknowledged that the review only identified studies on aspirin, the GDG considered that the recommendation should be extended to include all off-label use of antiplatelet therapy, because it had seen no evidence of the effectiveness and safety of other drugs. The GDG agreed that the most appropriate thing to do, in this circumstance, was to assume that all options have similar benefits and harms. The GDG discussed the possibility of making no recommendation on the use of clopidogrel; however, the concern was expressed that, when set against the 'do not do' recommendation for aspirin, this might be read as tacit approval of clopidogrel, which the GDG wanted to avoid. The GDG discussed making a recommendation to advise on stopping antiplatelet therapy in people already on the medicines. The GDG noted that such recommendation may result in confusion in the case of secondary prevention and agreed that the strong 'do not do' recommendation should reasonably indicate to healthcare professionals to consider reviewing patients' existing therapies. The GDG noted that a cross-reference to other NICE guidance addressing the use of antiplatelet medicines for secondary prevention of cardiovascular disease was important to ensure healthcare professionals used these drugs as appropriate when caring for patients who have experienced a cardiovascular event.

7.3 Recommendations and research recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng28

Research recommendations

No research recommendations were made in relation to this review question.

8 Blood glucose management

This section was updated in 2015

The risks of arterial disease and microvascular complications in people with diabetes are thought to be related to the extent of hyperglycaemia over time. A comprehensive approach to blood glucose management incorporating education, assessment, self-monitoring and pharmacological strategies is required to facilitate optimal care. The chapter focuses on these key areas to provide guidance on optimal target values for blood glucose measures (sections 8.1 and 8.2), the use of self-monitoring to improve glycaemic control (section 8.3) and the effectiveness of different pharmacological interventions (section 8.4 and 8.5).

8.1 Optimal target values for blood glucose measures

8.1.1 Clinical introduction

This section addresses the clinical question of what blood glucose values should be targeted to reduce the risk of future vascular damage from diabetes. It also aims to explore the impact of different blood glucose lowering drug treatments on optimal target values and the nature of the relationship between target values and specific subgroups of the population.

8.1.1.1 Target values in Clinical Guideline 66

Target values for HbA1c were covered as part of CG66. However, fasting blood glucose and postprandial blood glucose target values were not included in CG66. The original searches were conducted from 2001 to 2007 to include systematic reviews, randomised controlled trials (RCTs) with sample sizes of at least 2000 and observational studies. CG66 included 1 meta-analysis (Selvin et al. 2004), 1 RCT (UK Prospective Diabetes Study, UKPDS; Adler et al. 1999) and 2 observational studies (Gerstein et al. 2005; Iribarren et al. 2001).

8.1.1.2 Target values in the update (2015)

For this update, several amendments were made to the review strategy. The sample size threshold applied in CG66 was removed as it was considered arbitrary and possibly inappropriate for specific population subgroups where participant numbers may be lower such as older people and different ethnic groups. As the question focused on elucidating the optimal blood glucose targets to reduce long-term macrovascular and microvascular complications in people with type 2 diabetes, studies which included rosiglitazone were excluded, as its association with cardiovascular mortality has the potential to confound the review findings. Similarly, studies with mixed populations of type 1 and type 2 diabetes patients were excluded as small numbers of people with type 1 diabetes may bias findings: the interventions used to manage diabetes are different and the long-term risk of cardiovascular disease may be different between type 1 and type 2 diabetes. Only prospective cohort studies that examined the development of long-term complications and its association with blood glucose measures were included.

The update review searches were completed in June 2014 with no date restriction for the following glycaemic measures: HbA1c, fasting blood glucose and postprandial blood glucose.

8.1.2 Evidence review

8.1.2.1 Review question

What are the optimal target values for HbA1c, fasting blood glucose and postprandial blood glucose in people with type 2 diabetes?

Table 22: PICO table

Population	Adults (18 years and over) with type 2 diabetes
Predictors	HbA1c, fasting blood glucose, postprandial blood glucose
Outcomes	Development of microvascular and macrovascular complications: • retinopathy (specific lesions or macular changes, referable retinopathy, blindness/loss of vision, visual acuity) • kidney damage (eGFR, serum creatinine, proteinuria, microalbuminuria, dialysis) • cardiovascular disease (myocardial infarction, heart failure, stroke, acute coronary syndrome, transient ischaemic attack, revascularisation and stenting) • foot complications (amputations, diabetic foot ulcers, Charcot osteoarthropathy, diabetic foot infection) Mortality

Prospective, longitudinal, cohort studies focusing on the development of microvascular or macrovascular complications and its association with blood glucose measures were included. Papers were excluded if they:

- were cross-sectional, case series and retrospective observational studies or conference abstracts, letters and editorials
- exploratory prognostic studies that examined blood glucose measures as one of many risk factors for diabetes-related complications
- focused on an association between blood glucose measures and microvascular or macrovascular complications without giving further information about the association
- focused only on an association between the variability of blood glucose measures (for example HbA1c-coefficient of variation, HbA1c-standard deviation) and long-term complications
- included a mixed population of people with type 1 and 2 diabetes, unless relevant subgroup analyses were reported
- included rosiglitazone as part of the drug treatment strategy.

For the full excluded list, see Appendix L. The detailed protocol is also available in Appendix C.

8.1.2.2 Clinical evidence

The evidence that was originally included in CG66 was re-reviewed as part of the update. All included studies in the meta-analysis (Selvin et al. 2004) were checked against the update protocol resulting in only 1 relevant study (Adler et al. 1999) which was also identified in the update search. Consequently, original publications of the UKPDS study were used and the meta-analysis was excluded. The 2 observational studies in CG66 were excluded as they included people with both type 1 and type 2 diabetes (Iribarren et al. 2001) or did not specify the type of diabetes (Gerstein et al. 2005).

In total, 14,660 references were found in the update searches and 14 studies were included (Adler et al. 1999; Drechsler et al. 2009; Eeg-Olofsson et al. 2010; Hsu et al. 2012; Hunt et al. 2013; Landman et al. 2010; Molyneaux et al. 1998; Morisaki et al. 1994; Nakagami et al.

1997; Salinero-Fort et al. 2013; Schulze et al. 2004; Torffvit and Agardh 2001; Zhao et al. 2013; Zoungas et al. 2012).

The evidence included studies that reported outcomes in specific subgroup populations:

- 4 studies provided data for older people (60 years and over [Morisaki et al. 1994; Zhao et al. 2013], 65 years and over [Zoungas et al. 2012] and over 75 years [Landman et al. 2010])
- 2 studies reported data based on sex (Zhao et al. 2013; Zoungas et al. 2012)
- 1 study reported data based on ethnicity (Hunt et al. 2013)
- 2 studies reported data based on duration of diabetes (7 years and over [Eeg-Olofsson et al. 2010; Zoungas et al. 2012])
- 2 studies reported data based on microvascular or macrovascular disease status (cardiovascular disease [Eeg-Olofsson et al. 2010]; microvascular and macrovascular disease [Zoungas et al. 2012])
- 1 study included people who were receiving dialysis (Drechsler et al. 2009)

The included studies all reported HbA1c as the main blood glucose measure or indicator. Outcomes were reported in relation to varying aspects of HbA1c including HbA1c at baseline and updated mean baseline HbA1c across the entire follow-up period. Where available, HbA1c at baseline was preferred. The associated risks of outcomes occurring depending on HbA1c were explored as a categorical variable, that is, at different threshold values of HbA1c. For example, Dreschler et al. (2009) and Zhao et al. (2013) reported results using reference HbA1c of 42 mmol/mol (6.0%) or less, Adler et al. (1999) used 45 mmol/mol (6.3%) or less, Eeg-Olofsson et al. (2010) used 42 to 52 mmol/mol (6.0 to 6.9%), Landman et al. (2010) used 48 to 53 mmol/mol (6.5 to 7.0%), Salinero-Fort et al. (2013) used 53 mmol/mol (7.0%) or less and Hunt et al. (2013) used 53 to 64 mmol/mol (7.0 to 8.0%). Other studies explored the association of risks of outcomes with a continuous variable (for example 11 mmol/mol (1%) increase or decrease in HbA1c). Owing to the different reference HbA1c values and analyses used to address confounding variables in the included studies, pooling of data was not possible and individual studies were assessed using the modified GRADE approach (see section 3.7.3).

Two studies also explored the identification of specific threshold values for HbA1c. Zoungas et al. (2012) examined the non-linear relationship between HbA1c and risk of the outcomes of all-cause mortality, microvascular and macrovascular events and identified HbA1c thresholds above which risk increased; this was considered to be 48 to 53 mmol/mol (6.5 to 7.0%) for macrovascular disease and for mortality, and 42 to 48 mmol/mol (6.0 to 6.5%) for microvascular disease. Analysis of the UKPDS trial (Adler et al. 1999) found no indication of a threshold for mortality or any complication below which risk no longer decreased or a level above which risk no longer increased.

One study (Adler et al. 1999) reported on fasting blood glucose but no studies reported on postprandial blood glucose.

8.1.2.2.1 *Description of included studies*

A total of 968,656 people (study size ranged from 114 to 892,223) were included from 14 prospective cohort studies, carried out in the UK (Adler et al. 1999; Zoungas et al. 2012), the Netherlands (Landman et al. 2010), Spain (Salinero-Fort et al. 2013), Germany (Drechsler et al. 2009), Sweden (Eeg-Olofsson et al. 2010; Torffvit and Agardh 2001), USA (Hunt et al. 2013; Schulze et al. 2004; Zhao et al. 2013), Australia (Molyneaux et al. 1998), Japan (Morisaki et al. 1994; Nakagami et al. 1997) and Taiwan (Hsu et al. 2012). The mean age in 13 studies ranged from 49.9 to 68.7 years, with 1 study not reporting this information (Adler et al. 1999). Mean HbA1c at baseline in 13 studies ranged from 50 to 81 mmol/mol (6.7% to 9.6%), with 1 study not reporting this information (Adler et al. 1999). The median follow-up in the studies ranged from 28 months to 10.4 years. Details of the included studies are found in the evidence tables (see Appendix E).

Summary GRADE tables for this review question are presented below (see Appendix D for full GRADE tables).

Table 23: Summary GRADE profile for optimal target values for HbA1c in relation to mortality

Number of cohort studies	Number of people	Relative effect (95% CI)	Quality
All-cause mortality			
1 (Landman 2010) – ZODIAC 5 to 10 year follow-up	1145	Categorical with 6.5-7.0% as a reference: < 6.5% HR 1.11 (0.71, 1.74) 7 to 8% HR 1.40 (0.99, 1.97) 8 to 9% HR 1.43 (0.97, 2.10) ≥ 9% HR 2.26 (1.39, 3.67) Per 1% HbA1c decrease: updated mean baseline HbA1c: HR 1.21 (1.07, 1.36) <u>Subgroup</u>: age >75 years (n=374) Per 1% HbA1c increase: < 5 years diabetes duration: HR 1.51 (1.17, 1.95) 5 to 11 years diabetes duration: HR 1.04 (0.84, 1.28) ≥ 11years diabetes duration: HR 1.05 (0.85, 1.30)	High
1 (Adler 1999) – UKPDS Median 10.4 year follow-up	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 6% (2, 10)	High
1 (Zoungas 2012) – ADVANCE Mean 4.5 year follow-up	11,086 (event rate not reported)	< 7%: HR 1.01 (0.85, 1.21) > 7%: HR 1.38 (1.29, 1.48) Per 1% HbA1c increase: 6.0%: HR 1.35 (1.27, 1.43) 6.5%: HR 1.38 (1.29, 1.46) 7.0%: HR 1.38 (1.29, 1.48) 7.5%: HR 1.38 (1.27, 1.49) Per 1% HbA1c decrease: 6.0%: HR 0.36 (.21, 0.62)	Moderate

Number of cohort studies	Number of people	Relative effect (95% CI)	Quality
		6.5%: HR 0.73 (0.55, 0.96) 7. 0%: HR 1.01 (0.85, 1.21) 7.5%: HR 1.16 (1.02, 1.32) Subgroup: age <65 years (*n* not reported) Per 1% HbA1c increase: > 7%: HR 1.33 (1.16, 1.53) Subgroup: age ≥65 years (*n* not reported) Per 1% HbA1c increase: > 7%: HR 1.40 (1.30, 1.52) Subgroup: male (n=6383) Per 1% HbA1c increase: > 7%: HR 1.32 (1.20, 1.44) Subgroup: female (n=4703) Per 1% HbA1c increase: > 7%: HR 1.45 (1.31, 1.61) Subgroup: duration of diabetes <7 years (*n* not reported) Per 1% HbA1c increase: > 7%: HR 1.51 (1.33, 1.71) Subgroup: duration of diabetes ≥7 years (*n* not reported) Per 1% HbA1c increase: > 7%: HR 1.33 (1.22, 1.45) Subgroup: no macrovascular disease (n~7514) Per 1% HbA1c increase: > 7%: HR 1.35 (1.24, 1.47)	

Number of cohort studies	Number of people	Relative effect (95% CI)	Quality
		Subgroup: macrovascular disease (n=3572) Per 1% HbA1c increase: > 7%: HR 1.42 (1.27, 1.59) Subgroup: no microvascular disease (n~9933) Per 1% HbA1c increase: > 7%: HR 1.37 (1.26, 1.49) Subgroup: microvascular disease (n=1153) Per 1% HbA1c increase: > 7%: HR 1.42 (1.25, 1.62)	
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	18,334	Categorical with 6.0-6.9% as a reference: 7.0 to 7.9% HR 1.08 (0.95 to 1.23) 8.0 to 8.9% HR 1.19 (1.03 to 1.38), p=0.02 Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.05, 1.14), p<0.001 Subgroup: duration of diabetes ≤7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.13 (1.05, 1.21) Subgroup: duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.07 (1.01, 1.13) Subgroup: previous cardiovascular disease (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.08 (1.01, 1.15)	Moderate

Number of cohort studies	Number of people	Relative effect (95% CI)	Quality
		Subgroup: no previous cardiovascular disease (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.04, 1.16)	
1 (Drechsler 2009) - 4D study Median 4 year follow-up	1255	Categorical with ≤6% as a reference: > 6 to ≤8% HR 1.34 (1.10, 1.63) > 8% HR 1.34 (1.02, 1.76) Per unit increase in HbA1c: HR 1.09 (1.02 to 1.17)	Moderate
1 (Hunt 2013) Mean 4.4 year follow-up	892,223	**Non-Hispanic White (n=548,808)** Categorical with 7.0 to 8.0% as a reference: < 7.0% HR 0.99 (0.97, 1.00) 8.0 to 9.0% HR 1.10 (1.08, 1.13) ≥ 9.0% HR 1.17 (1.14, 1.20) **Non-Hispanic Black (n=108,356)** Categorical with 7.0 to 8.0% as a reference: < 7.0% HR 1.07 (1.02, 1.12) 8.0-9.0% HR 1.00 (0.94, 1.06) ≥ 9.0% HR 1.09 (1.03, 1.15) **Hispanic (n=123,670)** Categorical with 7.0 to 8.0% as a reference: < 7.0% HR 1.02 (0.95, 1.09) 8.0-9.0% HR 1.09 (1.00, 1.19) ≥ 9.0% HR 1.15 (1.06, 1.25) **Other (n=111,389)** Categorical with 7.0 to 8.0% as a reference: < 7.0% HR 0.92 (0.87, 0.97) 8.0-9.0% HR 1.25 (1.16, 1.35)	Moderate

Number of cohort studies	Number of people	Relative effect (95% CI)	Quality
		≥ 9.0% HR 1.30 (1.20, 1.40)	
Mortality related to diabetes			
1 (Adler 1999) – UKPDS Median 10.4 year follow-up	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 9% (3, 14)	High
Sudden death			
1 (Drechsler 2009) - 4D study Median 4 year follow-up	1255	Categorical with ≤6% as a reference: > 6 to ≤8% HR 1.85 (1.22, 2.81) > 8% HR 2.26 (1.33, 3.85) Per unit increase in HbA1c: HR 1.21 (1.06 to 1.38)	Moderate
Mortality except for sudden death			
1 (Drechsler 2009) - 4D study Median 4 year follow-up	1255	Categorical with ≤6% as a reference: > 6 to ≤ 8% HR 1.19 (0.96, 1.50) > 8% HR 1.10 (0.80, 1.52) Per unit increase in HbA1c: HR 1.04 (0.96 to 1.13)	Moderate
Cardiovascular mortality			
1 (Landman 2010) – ZODIAC 5 to 10 year follow-up	1145	Categorical with 6.5 to 7.0% as a reference: < 6.5% HR 0.94 (0.47, 1.91) 7 to 8% HR 1.40 (0.84, 2.31) 8 to 9% HR 1.71 (0.99, 2.96) ≥ 9% HR 3.13 (1.62, 6.05) Subgroup: age >75 years (n=374) Per 1% HbA1c increase: < 5 years diabetes duration: HR 1.72 (1.19, 2.48) 5 to 11 years diabetes duration: HR 1.18 (0.87, 1.60) ≥ 11 years diabetes duration: HR 1.16 (0.86, 1.58)	Moderate

Number of cohort studies	Number of people	Relative effect (95% CI)	Quality
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	18,334	Categorical with 6.0 to 6.9% as a reference: 7.0 to 7.9% HR 1.11 (0.96 to 1.29) 8.0 to 8.9% HR 1.27 (1.07 to 1.50) Per 1% HbA1c increase: HR baseline HbA1c: 1.10 (1.05, 1.16) Subgroup: duration of diabetes ≤7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.14 (1.05, 1.24) Subgroup: duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.07 (1.01, 1.14) Subgroup: previous cardiovascular disease (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.01, 1.17) Subgroup: no previous cardiovascular disease (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.11 (1.04, 1.19)	Moderate
1 (Drechsler 2009) - 4D study Heart failure death Median 4 year follow-up	1255	Categorical with ≤6% as a reference: > 6 to ≤ 8% HR 1.53 (0.70, 3.33) > 8% HR 2.12 (0.75, 5.98) Per unit increase in HbA1c: HR 1.30 (1.00 to 1.68)	Low
Abbreviations: HR hazard ratio; n number of people			

Table 24: Summary GRADE profile for optimal target values for HbA1c in relation to macrovascular complications

Number of cohort studies	Number of people	Effect (95% CI)	Quality
Composite of combined cardiovascular events			
1 (Drechsler 2009) – 4D study Median 4 year follow-up	1255	Categorical with ≤6% as a reference: > 6 to ≤ 8% HR 1.31 (1.05, 1.65) > 8% HR 1.37 (1.00, 1.87) Per unit increase in HbA1c: HR 1.09 (1.01 to 1.18)	Moderate
Macrovascular events			
1 (Zoungas 2012) – ADVANCE Mean 4.5 year follow-up	11,086 (event rate not reported)	< 7%: HR 1.02 (0.86, 1.21) > 7%: HR 1.38 (1.30, 1.47) Per 1% HbA1c increase: 6.0%: HR 1.35 (1.27, 1.42) 6.5%: HR 1.37 (1.29, 1.45) 7.0%: HR 1.38 (1.30, 1.47) 7.5%: HR 1.39 (1.29, 1.50) Per 1% HbA1c decrease: 6.0%: HR 0.41 (0.25, 0.68) 6.5%: HR 0.77 (0.59, 1.00) 7.0%: HR 1.02 (0.86, 1.21) 7.5%: HR 1.13 (1.00, 1.28) <u>Subgroup</u>: age <65 years (*n* not reported) Per 1% HbA1c increase: > 7%: HR 1.34 (1.19, 1.50) <u>Subgroup</u>: age ≥65 years (*n* not reported) Per 1% HbA1c increase: > 7%: HR 1.40 (1.30, 1.51)	Moderate

Number of cohort studies	Number of people	Effect (95% CI)	Quality
		<u>Subgroup</u>: male (n=6383) Per 1% HbA1c increase: > 7%: HR 1.38 (1.27, 1.50) <u>Subgroup</u>: female (n=4703) Per 1% HbA1c increase: > 7%: HR 1.35 (1.23, 1.48) <u>Subgroup</u>: duration of diabetes <7 years (*n* not reported) Per 1% HbA1c increase: > 7%: HR 1.54 (1.38, 1.72) <u>Subgroup</u>: duration of diabetes ≥7 years (*n* not reported) Per 1% HbA1c increase: > 7%: HR 1.30 (1.21, 1.41) <u>Subgroup</u>: no macrovascular disease (n~7514) Per 1% HbA1c increase: > 7%: HR 1.37 (1.26, 1.49) <u>Subgroup</u>: macrovascular disease (n=3572) Per 1% HbA1c increase: > 7%: HR 1.38 (1.25, 1.52) <u>Subgroup</u>: no microvascular disease (n~9933) Per 1% HbA1c increase: > 7%: HR 1.37 (1.27, 1.48) <u>Subgroup</u>: microvascular disease (n=1153) Per 1% HbA1c increase:	

Number of cohort studies	Number of people	Effect (95% CI)	Quality
		> 7%: HR 1.44 (1.27, 1.62)	
Cardiovascular disease (fatal/non-fatal)			
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	18,334	Categorical with 6.0 to 6.9% as a reference: 7.0 to 7.9% HR 1.18 (1.08 to 1.29) 8.0 to 8.9% HR 1.31 (1.18 to 1.45) Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.07, 1.13) Subgroup: duration of diabetes ≤7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.08 (1.03, 1.13) Subgroup: duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.06, 1.14) Subgroup: previous cardiovascular disease (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.10 (1.05, 1.16) Subgroup: no previous cardiovascular disease (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.06, 1.13)	Moderate
Myocardial infarction (fatal and non-fatal)			
1 (Drechsler 2009) - 4D study Median 4 year follow-up	1255	Categorical with ≤6% as a reference: > 6 to ≤ 8% HR 0.94 (0.68, 1.30) > 8% HR 0.77 (0.47, 1.26) Per unit increase in HbA1c:	Moderate

Number of cohort studies	Number of people	Effect (95% CI)	Quality
		HR 0.94 (0.83 to 1.07)	
1 (Adler 1999) – UKPDS Median 10 to 10.4 year follow-up	3845	Categorical with ≤6.3% as a reference: > 6.3 to ≤ 7.6 HR 1.2 (0.9, 1.5) > 7.6 HR 1.5 (1.2, 1.8) Per 1% HbA1c decrease (n=3642): Risk reduction baseline HbA1c: 5% (0, 9)	High
Coronary heart disease (fatal/non-fatal)			
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	18,334	Categorical with 6.0 to 6.9% as a reference: 7.0 to 7.9% HR 1.25 (1.11 to 1.39) 8.0 to 8.9% HR 1.36 (1.20 to 1.55) Per 1% HbA1c increase: HR baseline HbA1c: 1.11 (1.07, 1.15) Subgroup: duration of diabetes ≤7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.09 (1.03, 1.15) Subgroup: duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.11 (1.06, 1.16) Subgroup: previous cardiovascular disease (n=3276) Per 1% HbA1c increase: Baseline HbA1c: HR 1.08 (1.02, 1.15) Subgroup: no previous cardiovascular disease (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.12 (1.07, 1.16)	Moderate

Number of cohort studies	Number of people	Effect (95% CI)	Quality
1 (Schulze 2004) Mean 7.4 year follow-up	921	Categorical into quartiles of median HbA1c with 5.21% as a reference: 5.80% RR 2.49 (1.19, 5.23) 6.90% RR 3.19 (1.56, 6.53) 8.97% RR 4.92 (2.46, 9.85)	Very low
Heart failure			
1 (Adler 1999) – UKPDS Median 10.4 years	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 0% (-12, 11)	High
Newly diagnosed angina			
1 (Adler 1999) – UKPDS Median 10 to 10.3 years	3836	Categorical with ≤6.3% as a reference: > 6.3 to ≤ 7.6 HR 1.5 (1.1, 2.0) > 7.6 HR 1.6 (1.1, 2.1)	High
Stroke (fatal and non-fatal)			
1 (Drechsler 2009) - 4D study Median 4 year follow-up	1255	Categorical with ≤6% as a reference: > 6 to ≤ 8% HR 1.56 (0.93, 2.62) > 8% HR 1.67 (0.84, 3.30) Per unit increase in HbA1c: HR 1.11 (0.93 to 1.32)	Low
1 (Eeg-Olofsson 2010) 5 to 6 year follow-up	18,334	Per 1% HbA1c increase: HR baseline HbA1c: 1.08 (1.03, 1.13) <u>Subgroup</u>: duration of diabetes ≤7 years (n=10,016) Per 1% HbA1c increase: Baseline HbA1c: HR 1.06 (0.98, 1.14) <u>Subgroup</u>: duration of diabetes >7 years (n=8318) Per 1% HbA1c increase: Baseline HbA1c: HR 1.07 (1.01, 1.14) <u>Subgroup</u>: previous cardiovascular disease (n=3276)	Moderate

Number of cohort studies	Number of people	Effect (95% CI)	Quality
		Per 1% HbA1c increase: Baseline HbA1c: HR 1.11 (1.03, 1.20) Subgroup: no previous cardiovascular disease (n=15,058) Per 1% HbA1c increase: Baseline HbA1c: HR 1.06 (1.00, 1.12)	
1 (Adler 1999) – UKPDS Median 10 to 10.3 years	3670	Categorical with ≤6.3% as a reference: > 6.3 to ≤ 7.6 HR 1.2 (0.8, 1.7) > 7.6 HR 1.1 (0.7, 1.6) Per 1% HbA1c decrease (n=3642): Risk reduction baseline HbA1c: -4% (-14, 6)	High
Peripheral vascular disease			
1 (Adler 1999) – UKPDS Median 10.4 years	2398	Per 1% HbA1c increase: OR 1.28 (1.12, 1.46) Amputation or peripheral vascular disease death (n=3642) : Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 28% (18, 37)	High
1 (Zhao 2013) – LSUHLS study Lower limb amputation Mean 6.83 year follow-up	35,368	African Americans (n=19,808) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.73 (1.07, 2.80) 7.0 to 7.9% HR 1.65 (0.99, 2.77) 8.0 to 8.9% HR 1.96 (1.14, 3.36) 9.0 to 9.9% HR 3.02 (1.81, 5.04) ≥ 10% HR 3.30 (2.10, 5.20) Per 1% HbA1c increase: Baseline HbA1c: HR 1.12 (1.08, 1.17)	Moderate

Number of cohort studies	Number of people	Effect (95% CI)	Quality
		Caucasians (n=15,560) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.16 (0.66, 2.02) 7.0 to 7.9% HR 2.28 (1.35, 3.85) 8.0 to 8.9% HR 2.38 (1.36, 4.18) 9.0 to 9.9% HR 2.99 (1.71, 5.22) ≥10% HR 3.25 (1.98, 5.33) Per 1% HbA1c increase: Baseline HbA1c: HR 1.15 (1.09, 1.21) Subgroup: male (n=13,363 at baseline) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.48 (0.95, 2.26) 7.0 to 7.9% HR 1.85 (1.20, 2.85) 8.0 to 8.9% HR 2.19 (1.40, 3.42) 9.0 to 9.9% HR 3.15 (2.04, 4.85) ≥ 10% HR 2.84 (1.93, 4.17) Subgroup: female (n=22,005 at baseline) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.63 (0.80, 3.32) 7.0 to 7.9% HR 2.37 (1.17, 4.80) 8.0 to 8.9% HR 2.26 (1.04, 4.91) 9.0 to 9.9% HR 3.43 (1.63, 7.24) ≥ 10% HR 4.96 (2.50, 9.71) Subgroup: age 60-94 years (*n* not reported) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 2.02 (0.94, 4.35) 7.0 to 7.9% HR 3.19 (1.42, 7.18)	

Number of cohort studies	Number of people	Effect (95% CI)	Quality
		8.0 to 8.9% HR 3.06 (1.18, 7.95) 9.0 to 9.9% HR 2.37 (0.80, 7.01) ≥ 10% HR 3.19 (1.27, 8.00) Subgroup: age 50-59 years (*n* not reported) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.13 (0.66, 1.94) 7.0 to 7.9% HR 1.50 (0.86, 2.63) 8.0 to 8.9% HR 2.26 (1.22, 4.18) 9.0 to 9.9% HR 3.69 (2.10, 6.47) ≥ 10% HR 2.89 (1.73, 4.82) Subgroup: age <50 years (*n* not reported) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.80 (0.95, 3.43) 7.0 to 7.9% HR 2.41 (1.27, 4.57) 8.0 to 8.9% HR 2.34 (1.25, 4.38) 9.0 to 9.9% HR 3.01 (1.63, 5.57) ≥ 10% HR 3.93 (2.26, 6.84) Subgroup: previous use of blood glucose lowering medication (n=12,788) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.30 (0.72, 2.33) 7.0 to 7.9% HR 2.24 (1.26, 3.98) 8.0 to 8.9% HR 1.94 (0.97, 3.88) 9.0 to 9.9% HR 2.81 (1.43, 5.51) ≥ 10% HR 2.73 (1.55, 4.82) Subgroup: no previous use of blood glucose lowering medication (n=22,580) Categorical with <6% as a reference and baseline HbA1c: 6.0 to 6.9% HR 1.62 (1.02, 2.59)	

Number of cohort studies	Number of people	Effect (95% CI)	Quality
		7.0 to 7.9% HR 1.93 (1.20, 3.12) 8.0 to 8.9% HR 2.20 (1.36, 3.58) 9.0 to 9.9% HR 3.41 (2.14, 5.45) ≥ 10% HR 3.50 (2.28, 5.36)	
Abbreviations: HR hazard ratio; n number of people; OR odds ratio; RR relative risk			

Table 25: Summary GRADE profile for optimal target values for HbA1c in relation to microvascular complications

Number of cohort studies	Number of people	Effect (95% CI)	Quality
Microvascular end points			
1 (Adler 1999) – UKPDS Median 10.4 years	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 23% (20, 27)	High
1 (Zoungas 2012) – ADVANCE Mean 4.5 year follow-up	11,086 (event rate not reported)	HR < 6.5%: 1.02 (0.76, 1.39) HR > 6.5%: 1.40 (1.33, 1.47) Per 1% HbA1c increase: 6.0%: HR 1.39 (1.32, 1.46) 6.5%: HR 1.40 (1.33, 1.47) 7.0%: HR 1.38 (1.30, 1.46) 7.5%: HR 1.33 (1.24, 1.42) Per 1% HbA1c decrease: 6.0%: HR 0.67 (0.36, 1.23) 6.5%: HR 1.02 (0.76, 1.02) 7.0%: HR 1.33 (1.10, 1.60) 7.5%: HR 1.51 (1.32, 1.72) <u>Subgroup</u>: age <65 years (*n* not reported) Per 1% HbA1c increase:	Moderate

Number of cohort studies	Number of people	Effect (95% CI)	Quality
		> 6.5%: HR 1.40 (1.30, 1.50) Subgroup: age ≥65 years (*n* not reported) Per 1% HbA1c increase: > 6.5%: HR 1.39 (1.29, 1.50) Subgroup: male (n=6383) Per 1% HbA1c increase: > 6.5%: HR 1.42 (1.33, 1.52) Subgroup: female (n=4703) Per 1% HbA1c increase: > 6.5%: HR 1.39 (1.29, 1.50) Subgroup: duration of diabetes <7 years (*n* not reported) Per 1% HbA1c increase: > 6.5%: HR 1.27 (1.14, 1.40) Subgroup: duration of diabetes ≥7 years (*n* not reported) Per 1% HbA1c increase: > 6.5%: HR 1.45 (1.36, 1.54) Subgroup: no macrovascular disease (n~7514) Per 1% HbA1c increase: > 6.5%: HR 1.44 (1.35, 1.53) Subgroup: macrovascular disease (n=3572) Per 1% HbA1c increase: > 6.5%: HR 1.30 (1.17, 1.43) Subgroup: no microvascular disease (n~9933)	

Number of cohort studies	Number of people	Effect (95% CI)	Quality
		Per 1% HbA1c increase: > 6.5%: HR 1.40 (1.32, 1.49) Subgroup: microvascular disease (n=1153) Per 1% HbA1c increase: > 6.5%: HR 1.36 (1.23, 1.50)	
Retinopathy			
1 (Molyneaux 1998) Median 28 month follow-up	963	Per 10% HbA1c decrease: Relative risk reduction: 24% (16, 32)	Moderate
1 (Morisaki 1994) 5 year follow-up	114	Multivariate logistic regression analysis showed that HbA1c was the only significant predictor of retinopathy Retinopathy prevalence at HbA1c: < 7%: 2% ≥ 7 to < 8%: 20% ≥ 8 to < 9%: 40% ≥ 9%: 61% With retinopathy HbA1c 8.8±1.1 Without retinopathy HbA1c 7.1±1.2	Very low
1 (Nakagami 1997) 10 year follow-up	137	Retinopathy prevalence at HbA1c: < 6%: 0% 6 to 6.9%: 17.2% 7 to 7.9%: 14.3% 8 to 8.9%: 41.9% ≥ 9%: 54.8% Multivariate logistic regression analysis showed that mean HbA1c over 10 year follow-up period was the only significant predictor of retinopathy	Very low
1 (Salinero-Fort 2013) – MADIABETES	2405	Categorical with <7% as a reference: 7 to 8% HR 1.39 (1.01, 1.92)	Moderate

Number of cohort studies	Number of people	Effect (95% CI)	Quality
4 year follow-up		> 8% HR 1.90 (1.30, 2.77)	
Cataract extraction			
1 (Adler 1999) – UKPDS Median 10.4 years	3642	Per 1% HbA1c decrease: Risk reduction baseline HbA1c: 9% (2, 16)	High
Nephropathy			
1 (Molyneaux 1998) Microalbuminuria Median 28 month follow-up	399	Per 10% HbA1c decrease: Relative risk reduction: 9% (-2, 19)	Very low
1 (Torffvit and Agardh 2001) Albuminuria Median 9 year follow-up	385	Cox regression analysis showed that HbA1c significantly predicted greater fractional albumin clearance (p<0.01) and development of renal failure (p<0.05) Normoalbuminuria mean HbA1c 7.8±1.5 Micro/macro-albuminuria HbA1c 8.5±1.6	Very low
1 (Hsu 2012) Microalbuminuria 5 to 7 year follow-up	821	Per 1% HbA1c decrease: Baseline HbA1c ≤ 8%: HR 1.13 (0.91, 1.39) Baseline HbA1c > 8%: HR 1.18 (1.04, 1.34)	Moderate
Abbreviations: HR hazard ratio; n number of people			

Table 26: Summary GRADE profile for optimal target values for fasting blood glucose in relation to macrovascular complications

Number of cohort studies	Number of people	Effect (95% CI)	Quality
Myocardial infarction (fatal and non-fatal)			
1 (Adler 1999, UKPDS)Ŧ Median 10 to 10.3 year follow-up up	5045	Categorical with ≤9.7 mmol/L as a reference: > 9.7 to ≤13.4 HR 1.1 (0.9, 1.4) > 13.4 HR 1.3 (1.1, 1.6)	High
Newly diagnosed angina			
1 (Adler 1999, UKPDS)Ŧ Median 10 to 10.3 year follow-up	5036	Categorical with ≤9.7 mmol/L as a reference: > 9.7 to ≤13.4 HR 1.3 (1.0, 1.7) > 13.4 HR 1.2 (0.9, 1.5)	High

Number of cohort studies	Number of people	Effect (95% CI)	Quality
Stroke (fatal and non-fatal)			
1 (Adler 1999, UKPDS)Ŧ Median 10 to 10.3 year follow-up	5040	Categorical with ≤9.7 mmol/L as a reference: > 9.7 to ≤13.4 HR 1.3 (0.9, 1.7) > 13.4 HR 1.3 (10, 1.8)	High
Abbreviations: HR hazard ratio *Ŧ Baseline data extracted at diagnosis only, not after dietary run-in. Model controlled for age at diabetes diagnosis, sex and ethnicity*			

8.1.2.3 Health economic evidence

This section was updated in 2015

Literature searches were undertaken to find any existing cost-utility analyses (CUAs) of intensive versus conventional blood glucose targets. Because of the similarity of the literature base, health economic evidence for review question 3 (target values) and review question 4 (intensive versus conventional regimens) are presented together. The GDG discussed and noted that, given the nature of the CUAs presented, it was difficult to categorise them to either review question. See section 8.2.2.3 for the health economic evidence for this review question and section 8.2.2.4 for the health economic evidence statement.

8.1.2.4 Evidence statements

8.1.2.4.1 Clinical evidence

Optimal target values

One study found that risk significantly increased above HbA1c levels of 48 mmol/mol (6.5%) for microvascular complications and 53 mmol/mol (7%) for mortality and macrovascular complications. The quality of the evidence was moderate. The second study did not find a specific threshold for which risk increased or decreased for mortality or any diabetes-related complication. The evidence was of high quality.

Mortality

Evidence from 6 studies found that all-cause mortality risk rose with increasing baseline levels of HbA1c. The quality of the evidence was moderate to high. Evidence from 3 studies found that an 11 mmol/mol (1%) decrease in HbA1c led to a lower risk of all-cause mortality, while an 11 mmol/mol (1%) increase was associated with an increased risk of all-cause mortality.

Macrovascular complications

Evidence from 6 studies found that the risk of macrovascular complications (defined as a composite of combined cardiovascular end points, macrovascular events, cardiovascular disease, myocardial infarction, coronary heart disease, heart failure, newly diagnosed angina, stroke and peripheral vascular disease) rose with increasing levels of baseline HbA1c. The quality of the evidence ranged from high to very low.

Evidence from 1 study found that in general, people aged 60 to 94 years were at greater risk of lower limb amputations at the same baseline HbA1c compared to people aged less than 59 years. The quality of the evidence was moderate.

Evidence from 1 study found that risk of myocardial infarction rose with increasing fastning blood glucose levels, but there was no difference in the risk of stroke and angina with increasing fasting blood glucose levels. The quality of the evidence was high.

Microvascular complications

Evidence from 8 studies found that the risk of microvascular complications (defined as a composite of microvascular end points, retinopathy, cataract extraction and renal outcomes) rose with increasing levels of baseline HbA1c, or that study participants who developed the specified end point had higher levels of HbA1c than those who did not. The quality of the evidence ranged from high to very low.

8.1.2.4.2 *Health economic evidence*

See section 8.2.2.4 for the health economic evidence statement.

8.1.3 Evidence to recommendations

Table 27: Linking evidence to recommendations

Relative value of different outcomes	The GDG agreed that the critical outcomes in determining the optimal target values for blood glucose measures are the risk of developing long-term diabetic complications (macrovascular and microvascular) and all-cause mortality. The GDG agreed that all outcomes should be weighted equally when deciding the optimal target values.
Trade-off between benefits and harms	The GDG recognised the trade-off between the increased benefits of setting target values for blood glucose to protect against long-term complications and the possible associated harms (for example hypoglycaemia). The GDG agreed that overall, the evidence showed that rising levels of HbA1c increase the risk of mortality and developing macrovascular and microvascular complications, with critical thresholds ranging from 42 to 53 mmol/mol (6.0 to 7.0%). The GDG agreed that it was not possible to provide guidance on HbA1c levels less than 42 mmol/mol (6.0%), as only 1 very-low-quality study reported data for values ranging from 33 to 38 mmol/mol (5.2 to 5.8%). The GDG discussed optimal target values for HbA1c, and agreed that a mid-range value of 48 mmol/mol (6.5%) would be achievable for most adults with type 2 diabetes that was managed by lifestyle and diet and/or 1 oral anti-diabetic drug not associated with hypoglycaemia. The GDG discussed specifying that the target of 48 mmol/mol (6.5%) may be most appropriate for newly diagnosed people, but agreed that because of the variable trajectory of diabetes, it would be inaccurate to focus only on this subgroup. The GDG agreed that the conditions set out in the recommendation that is 'people on diet/lifestyle interventions or in combination with 1 oral drug' provide adequate guidance on the clinical population that should be considered for setting an HbA1c target of 48 mmol/mol (6.5%). The GDG agreed that people who achieve this target HbA1c level using diet and exercise alone with no hypoglycaemic risk should be encouraged to safely attain lower levels if possible provided that there are no underlying pathological reasons for the low HbA1c levels. The GDG discussed the progressive nature of the condition, and agreed that drug treatment should be intensified if HbA1c levels rose to 58 mmol/mol (7.5%) and considering the risk of hypoglycaemia, a realistic target of 53 mmol/mol (7.0%) should be set to achieve glycaemic control. The GDG was confident that an HbA1c level of 58 mmol/mol (7.5%) was an adequate trigger to intensify drug treatment but considered that a lower threshold between 53 and 58 mmol/mol (7.0 and 7.5%) would be inappropriate given the natural fluctuating error of about 2 mmol/mol (0.2%) observed in HbA1c measurements. The GDG agreed that a drug intensification threshold of 53 mmol/mol (7.0%) with an associated target of 48 mmol/mol (6.5%) was too low and would be inappropriate for most patients as the condition progresses.

	The GDG also considered that, while guidance on target values was important particularly for generalists, the complexities of individual patient needs should predominate. In particular, the GDG agreed that special consideration of appropriate target values should be given to people at risk of hypoglycaemia, to achieve an acceptable balance between good glycaemic control and the likely negative impact on quality of life of this adverse event. The GDG also discussed groups for whom the target levels may not be appropriate, such as people with renal failure, people for whom the target level may require increased medication that may cause adverse events or decreased medication compliance, or people who would probably not benefit from the long-term impact on macrovascular and/or microvascular complications.
Consideration of health benefits and resource use	The GDG found the health economic evidence on optimal target values and intensive versus conventional control hard to distinguish. No cost–utility analyses (CUAs) gave direct evidence on whether one particular HbA1c target was more cost effective than another, but all the CUAs found intensive control at lower HbA1c targets to be more cost effective than less intensive control at higher HbA1c targets.
Quality of evidence	The GDG agreed that the evidence ranged from high to very low quality. The GDG discussed that in the majority of studies, HbA1c categorical levels started from 42 to 48 mmol/mol (6.0 to 6.5%), but that in routine clinical practice, target levels less than 42 mmol/mol (6.0%) would not be set. The GDG noted that one of the studies on HbA1c included patients who were on dialysis, which was a specified subgroup of interest. However, the GDG agreed that patients with advanced complications were not a true representation of the average type 2 diabetes population, and that dialysis may affect the accuracy of HbA1c measurements. The GDG discussed the findings of the clinical review and noted that there was little or no evidence on fasting and postprandial blood glucose measures, and therefore agreed that it was not possible to set target values for these tests. However, the GDG recognised the importance of these measures because they directly influence HbA1c levels.
Other considerations	The GDG noted that the mean age in the included studies ranged from 50 to 69 years and agreed that there was no evidence for younger adults with type 2 diabetes and limited evidence for those over the age of 70. The GDG discussed whether there were different considerations in reviewing target values for these groups. The GDG considered that when agreeing target values with adults with type 2 diabetes, it is more important to examine the nature of the person's current medical condition, that is, diabetes, its complications and any other comorbidities rather than age alone. The GDG agreed the importance of ensuring that all adults with type 2 diabetes are aware of the benefits associated with lowering HbA1c levels and achieving appropriate blood glucose targets with minimal fluctuation to maintain good glycaemic control. The GDG agreed that target values, appropriate to the person's situation, should be discussed and agreed with the patient to optimise care.

	The GDG also noted that the Quality and Outcomes Framework (QOF) refer to 3 levels of glucose control in people with type 2 diabetes: HbA1c of 75 mmol/mol (9.0%) or less, 64 mmol/mol (8.0%) or less and 59 mmol/mol (7.5%) or less.

8.1.4 Recommendations and research recommendations

8.1.4.1 HbA1c measurement and targets

8.1.4.1.1 Measurement

The current recommendations can be found at www.nice.org.uk/guidance/ng28

8.1.4.1.2 Targets

The current recommendations can be found at www.nice.org.uk/guidance/ng28

Research recommendations

2. **What is the natural history of individuals who are diagnosed with type 2 diabetes in childhood in terms of long-term complications/consequences in adulthood?**

   Why this is important

   Type 2 diabetes has historically been associated with adults, with research largely focused on this population. However, there is growing concern of the increasing incidence of type 2 diabetes in younger people, thought to be linked to the rising levels of obesity. In order to improve clinical management of people diagnosed in childhood, a better understanding of the early progression of the condition is needed, particularly in terms of its effects on the long-term risks of developing microvascular and macrovascular complications. A prospective longitudinal 10 year cohort study of children diagnosed with type 2 diabetes would help improve understanding of whether diabetes spanning the growth spurt would result in long-term complications occurring at a different rate compared to individuals who are diagnosed during adulthood.

8.2 Intensive and conventional blood glucose targets

8.2.1 Clinical introduction

This section was updated in 2015There has been a general acceptance that tight glycaemic control is beneficial in reducing the risk of cardiovascular disease. Evidence reported in the previous section (see section 8.1) identified an increased risk of long-term complications associated with higher baseline HbA1c levels. The risk increased with each 11 mmol/mol (1%) rise in HbA1c levels and correspondingly decreased with each 11 mmol/mol (1%) fall in HbA1c levels. However, the impact of intensive control at lower target values on other outcomes such as hypoglycaemia compared to conventional control at higher targets is unclear.

This section addresses the clinical question of whether intensive strategies to lower target values are more effective than conventional strategies to higher targets in reducing long-term complications. It also aims to explore situations in which intensive strategies should be used and whether the effect of intensive strategies differs in specific subgroups of the population.

8.2.1.1 Intensive and conventional blood glucose targets in Clinical Guideline 66

CG66 did not report on the effectiveness of intensive glycaemic control compared to conventional glycaemic control.

8.2.1.2 Intensive and conventional blood glucose targets in the update (2015)

This is a new question in this update and therefore searches have been carried out for this topic without any date restrictions.

This review compared the use of intensive glycaemic control against conventional glycaemic control. The strategies used to achieve intensive and conventional glycaemic control could include oral antidiabetic agents and/or insulin. Outcomes of interest to the GDG included hypoglycaemic episodes, development of macrovascular and microvascular complications (retinopathy, kidney damage, cardiovascular disease, foot complications), mortality and changes in body weight.

8.2.2 Evidence review

8.2.2.1 Review question

This section was updated in 2015

Should intensive or conventional target values be used to control blood glucose levels in people with type 2 diabetes?

Table 28: PICO table

Population	Adults (18 years and over) with type 2 diabetes
Intervention	Intensive blood glucose control (using pharmacological blood glucose lowering therapies) with target blood glucose levels lower than conventional values
Comparator	Conventional target values (targets that would be considered to be in the normal range for adults with type 2 diabetes)
Outcomes	Hypoglycaemic events Development of microvascular and macrovascular complications: • retinopathy (specific lesions or macular changes, referable retinopathy, blindness/loss of vision, visual acuity)

	• kidney damage (eGFR, serum creatinine, proteinuria, microalbuminuria, dialysis) • cardiovascular disease (myocardial infarction, heart failure, stroke, acute coronary syndrome, transient ischaemic attack, revascularisation and stenting) • foot complications (amputations, diabetic foot ulcers, Charcot osteoarthropathy, diabetic foot infection) Mortality Changes in body weight

Systematic reviews and randomised controlled trials (RCTs) focusing on the use of intensive blood glucose control compared to conventional strategies were included. Papers were excluded if they:

- were non-randomised studies (including cohort, case–control and case series) or narrative reviews, conference abstracts, letters and editorials
- included a mixed population of people with type 1 and 2 diabetes, unless relevant subgroup analyses were reported
- included rosiglitazone as part of the drug treatment strategy. For the full excluded list, see Appendix L.

The main outcomes for this review question were the development of microvascular and macrovascular complications and adverse events. The detailed protocol is available in Appendix C.

8.2.2.2 Clinical evidence

This topic was not covered in CG66 so no date restrictions were placed on the search strategy (see Appendix C for update search strategies). A total of 1782 references were identified for this question, including a number of systematic reviews and meta-analyses. A recent Cochrane systematic review (Hemmingsen et al. 2013) included all relevant RCTs and therefore was the primary source of evidence for this question.

For the purposes of this question, the studies in the Cochrane review were assessed for relevance. RCTs where intensive and conventional glycaemic control groups had significant baseline differences in adjunctive treatment for cardiovascular risk factors were excluded. This led to the exclusion of 8 RCTs included in the Cochrane systematic review: ACCORD (2008), ADDITION (2011), ADVANCE (2008), Araki (2012), Guo (2008), Steno-2 (2008), VADT (2009) and Yang (2007).

8.2.2.2.1 Description of included studies

Data from a Cochrane review was used to answer this question. This review included studies of adults (aged 18 years and older) with type 2 diabetes. The intensive control groups targeted HbA1c values ranging from 42 mmol/mol (6.0%) or less and up to 58 mmol/mol (7.5%) while the conventional control groups either had no target values or targeted HbA1c values above 42 mmol/mol (6.0%). The mean duration of the intervention period varied from 3 days to 12.5 years. Details of the included review are found in the evidence tables (see Appendix E).

A summary GRADE table is presented for this review question (see Appendix D for full GRADE tables).

Table 29: Summary GRADE profile for intensive versus conventional target values

Number of studies	Number of people		Measure of effect	Quality
	Intensive	Conventional		
All-cause mortality				
1 systematic review (Hemmingsen 2013) including 16 RCTs (Bagg 2001, Cao 2011, DIGAMI 2 2005, Fantin 2011, IDA 2009, Jaber 1996, Kumamoto 2000, Melidonis 2000, Natarajan 2012, REMBO 2008, Service 1983, Stefanidis 2003, UGDP 1975, UKPDS 1998, VA CSDM 1995, Zhang 2011)	762/4296	381/2208	RR 0.98 (0.88 to 1.09)	High
Cardiovascular mortality				
1 systematic review (Hemmingsen 2013) including 14 RCTs (Bagg 2001, Cao 2011, DIGAMI 2 2005, IDA 2009, Jaber 1996, Kumamoto 2000, Melidonis 2000, REMBO 2008, Service 1983, Stefanidis 2003, UGDP 1975, UKPDS 1998, VA CSDM 1995, Zhang 2011)	445/4225	195/2131	RR 1.15 (0.98 to 1.35)	Moderate
Macrovascular complications				
1 systematic review (Hemmingsen 2013) including 8 RCTs (Bagg 2001, Becker 2003, DIGAMI 2 2005, Fantin 2011, Kumamoto 2000, UKPDS 1998, VA CSDM 1995, Zhang 2011)	394/3543	235/1791	RR 0.98 (0.74 to 1.30)	Low
Non-fatal myocardial infarction				
1 systematic review (Hemmingsen 2013) including 9 RCTs (Bagg 2001, DIGAMI 2 2005, Fantin 2011, Kumamoto 2000, Melidonis 2000, Stefanidis 2003, UGDP 1975, UKPDS 1998, VA CSDM 1995)	342/3995	187/1907	RR 0.92 (0.78 to 1.09)	High
Congestive heart failure				

Number of studies	Number of people		Measure of effect	Quality
	Intensive	Conventional		
1 systematic review (Hemmingsen 2013) including 8 RCTs (Bagg 2001, DIGAMI 2 2005, Fantin 2011, Melidonis 2000, REMBO 2008, Stefanidis 2003, UKPDS 1998, VA CSDM 1995)	120/3777	75/1683	RR 0.82 (0.62 to 1.08)	Moderate
Non-fatal stroke				
1 systematic review (Hemmingsen 2013) including 8 RCTs (Bagg 2001, DIGAMI 2 2005, Fantin 2011, Kumamoto 2000, Melidonis 2000, Stefanidis 2003, UKPDS 1998, VA CSDM 1995)	156/3791	65/1697	RR 1.06 (0.80 to 1.41)	Moderate
Amputation of lower extremity				
1 systematic review (Hemmingsen 2013) including 7 RCTs (Fantin 2011, Kumamoto 2000, Melidonis 2000, Stefanidis 2003, UGDP 1975, UKPDS 1998, VA CSDM 1995)	36/3500	20/1579	RR 0.73 (0.42 to 1.25)	Moderate
Microvascular complications				
1 systematic review (Hemmingsen 2013) including 3 RCTs (Fantin 2011, UKPDS 1998, Zhang 2011)	253/3154	130/1222	RR 0.75 (0.61 to 0.92)	Moderate
Nephropathy				
1 systematic review (Hemmingsen 2013) including 7 RCTs (Bagg 2001, Fantin 2011, Kumamoto 2000, UGDP 1975, UKPDS 1998, VA CSDM 1995, Zhang 2011)	45/3167	66/1587	RR 0.64 (0.32 to 1.29)	Low
End-stage renal disease				
1 systematic review (Hemmingsen 2013) including 4 RCTs (Fantin 2011, Kumamoto 2000, UGDP 1975, UKPDS 1998)	28/3365	11/1438	RR 0.94 (0.47 to 1.89)	Low
Retinopathy				

Number of studies	Number of people		Measure of effect	Quality
	Intensive	Conventional		
1 systematic review (Hemmingsen 2013) including 5 RCTs (Fantin 2011, Kumamoto 2000, UGDP 1975, UKPDS 1998, VA CSDM 1995)	441/3098	273/1516	RR 0.79 (0.56 to 1.11)	Low
Severe hypoglycaemia				
1 systematic review (Hemmingsen 2013) including 13 RCTs (Bagg 2001, Blonde 2009, Cao 2011, Fantin 2011, IDA 2009, Jaber 1996, Kumamoto 2000, Melidonis 2000, Natarajan 2012, Stefanidis 2003, UKPDS 1998, VA CSDM 1995, Zhang 2011)	53/3688	11/1764	RR 2.23 (1.22 to 4.08)	Moderate
Mild hypoglycaemia				
1 systematic review (Hemmingsen 2013) including 12 RCTs (Bagg 2001, Blonde 2009, DIGAMI 2 2005, Fantin 2011, Kumamoto 2000, Melidonis 2000, Natarajan 2012, Stefanidis 2003, UGDP 1975, UKPDS 1998, VA CSDM 1995, Zhang 2011)	791/4200	263/2120	RR 1.85 (1.53 to 2.25)	Moderate
Changes in body weight				
No studies identified for this outcome				
Abbreviations: RR relative risk				

8.2.2.3 Health economic evidence

This section was updated in 2015

Literature searches were undertaken to find any existing cost–utility analyses (CUAs) of optimal target values for blood glucose measures. Because of the similarity of the literature base, health economic evidence for review question 3 (target values) and review question 4 (intensive versus conventional regimens) are presented together. The GDG discussed and noted that, given the nature of the CUAs presented, it was difficult to categorise them to either review question.

In total, 1680 references were returned for review question 3 and 421 references were returned for review question 4. Five CUAs were returned that met the NICE reference case (CDC Diabetes Cost-effectiveness Group 2002; Clarke et al. 2005; Eastman et al. 1997; Palmer et al. 2004; Valentine et al. 2006). Details of the 5 included studies are given in Table 30.

One CUA (Clarke et al. 2005) was a lifetime modelled analysis based on a UK RCT for newly diagnosed people with type 2 diabetes. The intensive arm received insulin and sulfonylureas; the conventional arm received dietary advice and pharmacological treatments if necessary. A further CUA (CDC Diabetes Cost-effectiveness Group 2002) used the same RCT but a different model to produce a lifetime analysis based on American costs and utilities.

One CUA (Eastman et al. 1997) gave a lifetime modelled analysis for newly diagnosed people with type 2 diabetes, using clinical data that was not specific to people with type 2 diabetes and that pre-dated the UKPDS RCT. The intensive arm received maximum doses of pharmacological agents (including insulin if necessary); the conventional arm received average doses of pharmacological agents (including insulin if necessary). This CUA only modelled microvascular and not macrovascular complications.

Two CUAs (Palmer et al. 2004; Valentine et al. 2006) used the CORE diabetes model to give lifetime modelled analyses for people with existing type 2 diabetes of unspecified interventions to achieve pre-specified reductions in HbA1c. These 2 CUAs did not include intervention costs or the costs of day-to-day diabetes management. Palmer et al. (2004) did not apply a discount rate to QALYs gained and Valentine et al. (2006) did not model adverse events.

Three of the CUAs (Eastman et al. 1997; Palmer et al. 2004; Valentine et al. 2006) assumed that treatment effects could be maintained for life. The GDG considered this assumption was unrealistic.

The CUAs used a range of baseline HbA1c values (between 48 and 86 mmol/mol [6.5% and 10%]) and a range of HbA1c improvements (between 10 and 31 mmol/mol [0.9% and 2.8%]). The highest quality and most applicable evidence was for people with newly diagnosed rather than with existing type 2 diabetes.

The CUA based on the UKPDS RCT was the most applicable and had the fewest limitations (Clarke et al. 2005). Other CUAs were limited by their use of non-UK (CDC Diabetes Cost-effectiveness Group 2002) and non-type-2-specific data (Eastman et al. 1997). CUAs that assumed a lifetime treatment effect and/or did not include the costs of the intervention were viewed to have very serious limitations (Eastman et al. 1997; Palmer et al. 2004; Valentine et al. 2006).

Most CUAs (CDC et al. 2002 (ICER $41,400 per QALY); Clarke et al. 2005 (ICER £6000 per QALY); Eastman et al. 1997 (ICER $16,000 per QALY)) found interventions that intensively reduce HbA1c to a given target to provide good value for money (at cost-effectiveness thresholds common in the relevant jurisdiction). The CUAs that did not include the cost of such treatment (Palmer et al. 2004; Valentine et al. 2006) found the intervention to be dominant. These 2 CUAs were also, at least in part, industry funded. Notably, no CUAs modelled the impact of differential rates of hypoglycaemia between treatment arms.

No health economic evidence was found to comment on the cost-effectiveness of different treatment regimens or target values. The most applicable and least limited CUAs (CDC et al. 2002; Clarke et al. 2005) were both based on the intervention used in the UKPDS RCT.

In sensitivity analysis, all CUAs noted the need for a long period of treatment (or young enough age at diagnosis) to enable costs of treatment to be recouped via complications avoided and utility to be accumulated.

It was noted that, whilst the clinical evidence was equivocal, the health economic evidence suggested intensive regimens to achieve lower HbA1c targets were cost effective. The GDG were presented with evidence on the uncertainty of the CUA results, as represented by probabilistic sensitivity analysis. Clarke et al. (2005) provided PSA details which showed the intervention to have a 74% probability of cost effectiveness, assuming QALYs are valued at £20,000 each.

Table 30: Economic evidence table for intensive control of blood glucose in people with type 2 diabetes

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Costs	Effects	ICER		
CDC Diabetes Cost Effectiveness Group (2002) People with newly diagnosed type 2 diabetes aged 25+ Intensive HbA1c, hypertension and cholesterol control USA **Partially applicable**[a,f,i] **Potentially serious limitations**[j,m,n]	Effects: UKPDS and other literature. Costs: various literature sources ($USA, 1997) Utilities: various USA sources (including type 1 RCTs)	CDC-RTI Markov model with lifetime horizon Intensive HbA1c UKPDS (insulin and/or SU) Baseline HBA1c: 6.8% Conventional HbA1c based on UKPDS at 7.9% Hypertension and cholesterol baselines taken from NHANES Discounted at 3% Also models intensive control of hypertension and cholesterol	$7927	0.1915 QALYs	$41,384/ QALY	Intensive blood glucose control seems cost effective compared with other interventions funded in the health care system. ICERs increase with age at diagnosis	ICERs for blood glucose and cholesterol increased with age at diagnosis whereas hypertension ICERs did not Blood glucose ICERs only less than $50,000/QALY for those aged under 55 at diagnosis and between 45-84 for cholesterol Reducing incremental HbA1c costs reduce ICERs No PSA reported, limited OSA
Clarke et al. (2005) People with newly diagnosed type 2 diabetes aged 25-65 Intensive control of blood glucose UK **Directly applicable** **Minor limitations**[p]	Effects: UKPDS RCT based Costs: UKPDS RCT based (£UK, 2004) Utilities: UKPDS RCT based	UKPDS model with lifetime horizon Intensive aimed for FPG < 6mmol/l (with insulin and/or SU), conventional FPG < 15mmol/l Intervention effect only lasts for RCT duration (11 years) – then all patients set to mean HbA1c UKPDS found no utility difference by regime Discounted at 3.5%	£884	0.15 QALYs	£6028/ QALY	Although point estimates of cost effectiveness fall within the acceptable range, cannot be confident that the interventions are cost effective	ICER sensitive to primary care costs and benefit duration, but remained cost-effective under wide range of assumptions In PSA, 10% chance of being cost-saving 74% change of being cost-effective at £20,000/ QALY Changes to standard care may mean benefits reported may no longer be achievable

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental Costs	Incremental Effects	Incremental ICER	Conclusions	Uncertainty
Eastman et al. (1997) People with newly diagnosed non-insulin type 2 diabetes Intensive versus conventional blood glucose control. USA **Partially applicable**[a,c,i] **Potentially serious limitations**[d,j,m,n]	Effects: USA WESDR study Some extrapolation from type 1 data Costs: Medicare rates ($USA, 1994) Utilities: literature (some type 1)	Eastman model with lifetime horizon (unspecified) Intensive HbA1c: 7.2% Conventional HbA1c aim: 10.0% Intervention HbA1c assumed to last for patient lifetime Only models impact on microvascular complications Discounted at 3%	$13,922	0.87 QALYs	$16,002/ QALY	Intensive HbA1c control appears cost effective compared to conventional control	ICERs sensitive to age at diagnosis and only remain cost effective up to around age 60 at diagnosis ICER sensitive to baseline HbA1c – cost effective to around 9% No PSA reported
Palmer et al. (2004) People with existing type 2 diabetes, treatment unspecified, aged 52 Compares 10 % improvement in HbA1c to no improvement USA **Partially applicable**[a,b,i] **Very serious limitations**[g,h,k,l,m,n,o]	Effects: 10% HbA1c decrease HbA1c assumed, no details of how achieved Costs: only complication costs included, daily management and intervention costs excluded ($USA, 2003) Utilities: no details given, assumed CDM standard	CDM with lifetime horizon (unspecified) Baseline HbA1c: 9.1% Assumes 10% improvement lasts for patient lifetime. Intensive HbA1c control not specified or costed Costs discounted at 3%; QALYs not discounted Also models intensive control of hypertension and cholesterol (10% improvement) individually and all 4 combined Funded by industry	HbA1c: -$10,800	HbA1c 0.81 QALYs	Improved HbA1c dominates no change	Improved blood glucose increase QALYs and reduce costs, meaning improved blood glucose dominates no change Cost savings driven by decreased end stage renal disease	Because of lack of intervention and day to day management costs, results may underestimate lifetime treatment costs Very limited OSA, no PSA Results insensitive to deterministic changes in discount rates or costs.

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Costs	Effects	ICER		
Valentine et al. (2006) People with poorly controlled type 2 diabetes USA **Partially applicable**[a,i] **Very serious limitations**[h,k,m,n,o]	Effects: assumed, to represent various targets, no details given of how achieved Costs: various sources for complications. Treatment costs not included Utilities: no details given, assumed CORE model standard	CDM with lifetime horizon 3 stepwise HbA1c reductions (all versus no reduction from that base) 9.5% to 8.0%, 8.0% to 7.0%, 7.0% to 6.5% Baseline characteristics from NHANES and RCT No adverse events modelled (hypos, weight gains) Discounted at 3% Funded by industry	9.5%-8.0% -$5209 8.0%-7.0% -$3099 7.0%-6.5% -$1637	9.5%-8.0% 0.58 QALYs 8.0%-7.0% 0.38 QALYs 7.0%-6.5% 0.18 QALYs	9.5%- 8.0% Treatment dominates 8.0%-7.0% Treatment dominates 7.0%-6.5% Treatment dominates	Improving HbA1c dominates no change in HbA1c in all cases	ICERs sensitive to time horizon – effect benefits only apparent after 2 years and cost savings after 10 years No other details given

a Not UK based
b Very limited details given of baseline population
c Clinical data predates UKPDS study
d Effectiveness data not type 2 diabetes specific
e Assumed effectiveness remains for patient lifetime
f Multifactorial intervention, impact not limited to impact on HbA1c
g Day to day diabetes care costs not included
h Costs of intervention not included
i Costs and outcomes not discounted at 3.5%
j Utilities not type 2 diabetes specific
k Utility values not detailed
l QALYs not discounted
m Limited or no deterministic sensitivity analyses
n Limited or no probabilistic sensitivity analyses
o Potential conflict of interest
p Changes to current day standard care may mean benefits reported may no longer be achievable

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Costs	Effects	ICER		
CDC: Centre for Disease Control CDC-RTI: Centre for Disease Control Research Triangle Institute CDM: Centre for Outcomes Research Diabetes Model FPG: fasting plasma glucose HbA1c: glycosylated haemoglobin ICER: incremental cost effectiveness ratio mmol/l: millimoles/litre NHANES: National Health and Nutrition Examination Survey OSA: one-way sensitivity analysis PSA: probabilistic sensitivity analysis QALY: quality-adjusted life year RCT: randomised controlled trial SU: sulfonylureas UK: United Kingdom UKPDS: United Kingdom Prospective Diabetes Study USA: United States of America WESDR: Wisconsin Epidemiologic Study of Diabetic Retinopathy							

8.2.2.4 Evidence statements

8.2.2.4.1 Clinical evidence

This section was updated in 2015 **Mortality**

Evidence from 16 RCTs showed a trend of decreased risk of all-cause mortality with intensive target levels compared with conventional target levels. The quality of the evidence was high. However, 14 RCTs of moderate quality showed a trend of increased risk of cardiovascular mortality with intensive compared to conventional target levels. There was uncertainty surrounding these findings as all of the associated 95% confidence intervals crossed the line of minimal important difference and/or no effect.

Macrovascular complications

Evidence from 9 RCTs showed trends of decreased risk of macrovascular complications (composite macrovascular end point, myocardial infarction, congestive heart failure, lower extremity amputation) with intensive compared to conventional target levels. However, 8 RCTs of moderate quality showed trends of increased risk of stroke with intensive compared to conventional target levels. There was uncertainty surrounding these findings as all of the associated 95% confidence intervals crossed the line of minimal important difference and/or no effect. The quality of the evidence ranged from high to low.

Microvascular complications

Evidence from 7 RCTs showed trends of decreased risk of microvascular complications (nephropathy, end-stage renal disease, retinopathy) with intensive compared to conventional target levels. The quality of the evidence was low. For the composite outcome of microvascular complications, 3 RCTs of moderate quality found a significant decrease in risk with intensive compared to conventional target levels. Generally, there was uncertainty surrounding these findings as all of the associated 95% confidence intervals crossed the line of minimal important difference and/or no effect.

Hypoglycaemia

Evidence from 15 RCTs showed significant increased risk of hypoglycaemic events (mild and severe) with intensive target levels compared to conventional target levels. The quality of the evidence was moderate.

Changes in body weight

No studies were identified for this outcome.

8.2.2.4.2 Health economic evidence

One directly applicable CUA with minor limitations found that, for people newly diagnosed with type 2 diabetes, intensive control at lower HbA1c targets was cost effective compared to conventional control at higher HbA1c targets. Four partially applicable CUAs with potentially or very serious limitations found intensive control to be cost effective or dominant compared to conventional control.

8.2.3 Evidence to recommendations

This section was updated in 2015

Table 31: Linking evidence to recommendations

Relative value of different outcomes	The development of macrovascular and microvascular complications, mortality and hypoglycaemic events were considered critical in decision-making. The GDG noted that when reducing the risk of developing diabetes-related complications to improve life expectancy and quality of life, the relatively high impact of hypoglycaemic events that are associated with tight glycaemic control was also important in determining the safety and acceptability of treatment to the patient. The GDG agreed that all outcomes were weighted equally in deciding the optimal target values.
Trade-off between benefits and harms	The GDG discussed the presented evidence relating to the intensive and conventional target values. The Group noted that there was a lack of consistency in the definition of intensive and conventional targets, because they differed considerably between the included studies, and they may have changed over time. However, the GDG agreed that there is tentative evidence to suggest that intensive target levels may be beneficial in improving risks associated with mortality, macrovascular and microvascular complications compared with conventional target levels. The GDG also recognised that intensive target levels are associated with increased risk of hypoglycaemia compared with conventional target levels. In addition, the Group acknowledged that there was a statistically non-significant trend for increased risk of cardiovascular mortality and non-fatal stroke for people receiving intensive treatment compared with conventional strategies, but agreed that the findings were uncertain. The GDG agreed overall that there was evidence to support the setting of target values, but considered it important to ensure that a person's risk of hypoglycaemia is evaluated when setting appropriate target levels.
Consideration of health benefits and resource use	The GDG found the health economic evidence on optimal target values and intensive versus conventional control hard to distinguish. No cost–utility analyses (CUAs) gave direct evidence on whether one particular HbA1c target was more cost effective than another, but all the CUAs found intensive control at lower HbA1c targets to be more cost effective than less intensive control at higher HbA1c targets.
Quality of evidence	The GDG agreed that, overall, the quality of the evidence ranged from high to low. The GDG noted that there was considerable heterogeneity in the target HbA1c levels used in the intensive control arms, because these ranged between 42 mmol/mol (6.0%) or lower and less than 58 mmol/mol (7.5%). There was also no restriction placed on which interventions could be used to achieve these targets. Both of these issues served to raise some doubt over the findings.
Other considerations	The GDG also discussed the differences in the strategies and target values used, and the potential for confusion for patients by the indeterminate nature of the intensive and conventional terminology.

	The GDG agreed that it would be better to provide recommendations on appropriate target values without classifying whether they are considered to be intensive or conventional.

8.2.4 Recommendations and research recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng28

8.3 Self-monitoring of blood glucose

8.3.1 Clinical introduction

This section was updated in 2015

Self-monitoring is a direct method by which a person with diabetes can be made aware of their level of blood glucose control. It is useful in people on drug treatments that require dose adjustments (such as insulin), have erratic effects or increase the risk of hypoglycaemia. There is debate surrounding the routine use of self-monitoring in people with type 2 diabetes as part of an overall educational package designed to enhance self-care and provide feedback on the impact of lifestyle measures on blood glucose control. Indirect monitoring using urine glucose tests is cheaper, but is less informative than blood glucose monitoring.

This section addresses the use of self-monitoring of blood glucose (SMBG) to manage glycaemic control in people with type 2 diabetes treated with diet alone or in combination with any blood glucose lowering therapies including insulin. In addition, the review looked at whether the use of self-monitoring should be restricted to specific subgroups of the population, how often and when people should self-monitor, and where on the body tests should be carried out. The review also looked at the comparative effects of different types of SMBG.

8.3.1.1 Self-monitoring in Clinical Guideline 66

This section was updated in 2015

Self-monitoring was originally covered as part of CG66. The original searches were conducted from 2001 to 2007 (see Appendix G for search strategies from CG66). Update searches have been carried out for this topic with a date restriction of 2007 to June 2014 (see Appendix C for update search strategies). The evidence considered in this review question in CG66 included 4 systematic reviews, 2 randomised controlled trials (RCTs), 4 cohort studies, 1 cross-sectional study, 1 case-series and 2 qualitative studies.

8.3.1.2 Self-monitoring in the update (2015)

For this review question, the GDG agreed that at this update, there was sufficient evidence from systematic reviews and RCTs to warrant excluding other study designs. In addition, the group expanded the scope of the review to include comparisons of different types of SMBG.

8.3.2 Evidence review

8.3.2.1 This section was updated in 2015Review question

Should self-monitoring be used to manage blood glucose levels in people with type 2 diabetes?

Table 32: PICO table

Population	Adults (aged 18 years and over) with type 2 diabetes
Intervention	Self-monitoring of blood glucose using lancets
Comparators	No self-monitoring of blood glucose, standard or usual care, self-monitoring of urine glucose, other types of self-monitoring of blood glucose (such as augmentation via education, telecare, continuous glucose monitoring; or different aspects of treatment for example frequency and location of testing)
Outcomes	Changes in blood glucose levels (HbA1c, fasting and postprandial blood glucose) Hypoglycaemic events

	Development of microvascular and macrovascular complications: • retinopathy (specific lesions or macular changes, referable retinopathy, blindness/loss of vision, visual acuity) • kidney damage (eGFR, serum creatinine, proteinuria, microalbuminuria, dialysis) • cardiovascular disease (myocardial infarction, heart failure, stroke, acute coronary syndrome, transient ischaemic attack, revascularisation and stenting) • foot complications (amputations, diabetic foot ulcers, Charcot osteoarthropathy, diabetic foot infection) Health-related quality of life

RCTs that focused on the use of SMBG in people with type 2 diabetes with a minimum follow-up of 4 weeks were included. Papers were excluded if they:

- were non-randomised (such as observational studies, narrative reviews and conference abstracts)
- included a mixed population of people with type 1 and 2 diabetes and either did not report subgroup analyses, or less than 85% of the study population had type 2 diabetes
- focused on testing of fructosamine
- did not provide adequate details of standard/usual care or sufficient data for extraction on relevant outcomes. For the full excluded list, see Appendix L.

The main outcomes for this review question were changes in blood glucose levels, hypoglycaemia, diabetes-related complications and adverse events. The detailed protocol is available in Appendix C.

In the comparison on the effectiveness of SMBG versus no SMBG (including usual care and self-monitoring of urine glucose, SMUG), any type of SMBG reported in the studies was included in the meta-analysis. However, studies were excluded if they did not clearly specify that usual or standard care in the control group did not involve SMBG. Subgroup analyses on 3 characteristics were undertaken:

- current diabetes treatment that is diet, oral antidiabetic and/or insulin medicines
- type of SMBG that is, standard or enhanced
- frequency of SMBG that is, less than once a day, 1 to 2 times a day or more than twice a day. Frequency was taken as the average number of tests per day and calculated based on the trial prescription described in the study methods, or if reported, the actual frequency of SMBG that was applied by the study participants.

For the comparison of different types of SMBG, SMBG was categorised according to the main defining feature such as enhanced education, use of telephone or web-based applications to transmit blood glucose readings with or without automated and/or personalised feedback (telecare) and use of continuous glucose monitoring.

8.3.2.2 Clinical evidence

This section was updated in 2015

The evidence that was originally included in CG66 was re-reviewed as part of the update. Eight studies that did not meet the updated study design inclusion criteria were excluded. In addition, 1 RCT in CG66 (Moreland et al. 2006) did not meet the revised population inclusion criteria for this update as only 65% of the study participants had type 2 diabetes. One of the systematic reviews (Welschen et al. 2005) in CG66 has since been updated (Malanda et al. 2012), so the more recent version was used in this question. This Cochrane review was restricted to comparisons involving SMBG and usual care (Malanda et al. 2012). However, all of the RCTs included in the Cochrane review were also identified in the update searches and where possible, the original papers were preferentially used.

In total, 1808 references were found for this review question and 29 unique trials were included (Allen et al. 1990; Barnett et al. 2008; Bonomo et al. 2010; Bosi et al. 2013; Cho et al. 2009; Davidson et al. 2005; Del Prato et al. 2012; Farmer et al. 2007; Fontbonne et al. 1989; Franciosi et al. 2011; Guerci et al. 2003; Ismail et al. 2013; Kleefstra et al. 2010; Knapp et al. 2009; Kwon et al. 2004; Lim et al. 2011; Lu et al. 2011; Muchmore et al. 1994; Nauck et al. 2014; O'Kane et al. 2008; Pimazoni-Netto et al. 2011; Polonsky et al. 2011; Quinn et al. 2011; Scherbaum et al. 2008; Schwedes et al. 2002; Tildesley et al. 2010; Vigersky et al. 2012; Wing et al. 1986; Yoo et al. 2008). There were 2 cluster RCTs (Polonsky et al. 2011; Quinn et al. 2011), 1 of which was a 4-armed study with 2 groups relevant to this review (Quinn et al. 2011); 1 RCT applied a 2x2 factorial design (Nauck et al. 2014); while 4 RCTs involved 3 treatment arms (Farmer et al. 2007; Fontbonne et al. 1989; Lim et al. 2011; Lu et al. 2011). The following comparisons were included as part of this review question:

- SMBG versus no SMBG (including standard/usual care and SMUG) – 17 trials (Allen et al. 1990; Barnett et al. 2008; Bosi et al. 2013; Davidson et al. 2005; Farmer et al. 2007; Fontbonne et al. 1989; Franciosi et al. 2011; Guerci et al. 2003; Ismail et al. 2013; Kleefstra et al. 2010; Lim et al. 2011; Lu et al. 2011; Muchmore et al. 1994; Nauck et al. 2014; O'Kane et al. 2008; Schwedes et al. 2002; Wing et al. 1986)
- SMBG plus education versus conventional SMBG – 3 trials (Farmer et al. 2007; Pimazoni-Netto et al. 2011; Polonsky et al. 2011)
- SMBG plus telecare via telephone or internet with tailored or automated feedback versus conventional SMBG – 5 trials (Del Prato et al. 2012; Kwon et al. 2004; Lim et al. 2011; Quinn et al. 2011; Tildesley et al. 2010)
- Different mechanisms of exporting glucose readings that is using an automated mobile telephone connected glucometer versus standard glucometer requiring web log in to enter data – 1 trial (Cho et al. 2009)
- SMBG plus continuous glucose monitoring (CGM) versus conventional SMBG – 2 trials (Vigersky et al. 2012; Yoo et al. 2008)
- Frequency of SMBG testing – 2 trials (Bonomo et al. 2010, Scherbaum et al. 2008)
- Location of SMBG testing – 1 trial (Knapp et al. 2009)

8.3.2.2.1 *Description of included studies*

Details of the included studies are found in the evidence tables (see Appendix E).

SMBG versus no SMBG

A total of 4710 people (study size ranged from 23 to 1024) were included from 17 RCTs, carried out in the UK (Farmer et al. 2007; O'Kane et al. 2008), the Netherlands (Kleefstra et al. 2010), France (Fontbonne et al. 1989; Guerci et al. 2003), Germany (Nauck et al. 2014), Italy (Bosi et al. 2013; Franciosi et al. 2011), USA (Allen et al. 1990; Davidson et al. 2005; Muchmore et al. 1994; Wing et al. 1986), Korea (Lim et al. 2011; Lu et al. 2011) and Malaysia (Ismail et al. 2013); the remaining 2 were multinational studies (Barnett et al. 2008; Schwedes et al. 2002). The mean age ranged from 48.9 to 67.5 years. The mean duration of diabetes in 15 studies ranged from 2.7 to 15.4 years; 2 trials did not report this information (O'Kane et al. 2008; Wing et al. 1986). Mean HbA1c at baseline ranged from 56 to 108 mmol/mol (7.3% to 12.0%). Mean BMI ranged from 25 to 34.2 kg/m^2, with 7 studies not reporting this information (Allen et al. 1990; Barnett et al. 2008; Davidson et al. 2005; Franciosi et al. 2011; Guerci et al. 2003; Schwedes et al. 2002; Wing et al. 1986). People taking insulin were included in 5 studies (Barnett et al. 2008; Ismail et al. 2013; Lim et al. 2011; Nauck et al. 2014; Wing et al. 1986), 1 study included people managed on diet alone

(O'Kane et al. 2008), while the participants in the remaining trials were managed on diet and/or oral antidiabetic medicines. Follow-up periods ranged from 24 to 208 weeks.

SMBG plus education versus conventional SMBG

A total of 1015 people (study size ranged from 63 to 499) were included from 3 RCTs, carried out in the UK (Farmer et al. 2007), USA (Polonsky et al. 2011) and Brazil (Pimazoni-Netto et al. 2011). The mean age ranged from 56 to 65.6 years. The mean duration of diabetes ranged from 3 to 12 years. Mean HbA1c at baseline ranged from 58 to 86 mmol/mol (7.5% to 10.0%). Mean BMI ranged from 31.3 to 35.1 kg/m^2, with 1 study not reporting this information (Pimazoni-Netto et al. 2011). One study included people taking insulin (Pimazoni-Netto et al. 2011), while the other 2 studies included participants managed on non-insulin based therapies. Follow-up periods ranged from 12 to 208 weeks.

SMBG plus telecare versus conventional SMBG

A total of 768 people (study size ranged from 50 to 291) were included from 5 RCTs, carried out in the USA (Quinn et al. 2011), Canada (Tildesley et al. 2010), Italy (Del Prato et al. 2012) and Korea (Kwon et al. 2004; Lim et al. 2011). The mean age ranged from 53 to 67.5 years. The mean duration of diabetes ranged from 6.8 to 18.8 years. Mean HbA1c at baseline ranged from 57 to 79 mmol/mol (7.4% to 9.4%). Mean BMI in 4 studies ranged from 24 to 35.6 kg/m^2, with 1 study not reporting this information (Del Prato et al. 2012). Three studies included people taking insulin (Del Prato et al. 2012; Lim et al. 2011; Tildesley et al. 2010), while the other 2 studies did not specify whether participants were on existing therapies (Kwon et al. 2004; Quinn et al. 2011). Follow-up periods ranged from 12 to 52 weeks.

Automated mobile telephone glucometer versus standard glucometer

One 12 week trial conducted in Korea including 75 people (mean age 48 years; mean duration of diabetes 6.8 years; mean HbA1c at baseline 64 mmol/mol [8.0%]; mean BMI 24.5 kg/m^2) with unspecified existing therapies was analysed in this comparison (Cho et al. 2009).

SMBG plus continuous glucose monitoring (CGM) versus conventional SMBG

A total of 165 people (study sizes 65 and 100) were included from 2 RCTs, carried out in the USA (Vigersky et al. 2012) and Korea (Yoo et al. 2008). The mean ages were 56 and 58 years. The mean duration of diabetes was reported in 1 study as 13 years (Yoo et al. 2008). Mean HbA1c levels at baseline were 67 mmol/mol (8.3%) and 74 mmol/mol (8.9%). Mean BMI was not reported in either study, while both studies included people taking insulin. Follow-up periods were 12 and 52 weeks.

Frequency of SMBG testing

A total of 475 people (study sizes 202 and 273) were included from 2 RCTs, carried out in Italy (Bonomo et al. 2010) and Germany (Scherbaum et al. 2008). The mean ages were 61 and 64 years. The mean duration of diabetes was 8 and 10.6 years. Mean HbA1c levels at baseline were 55 mmol/mol (7.2%) and 64 mmol/mol (8.0%). Mean BMI was reported in 1 study as 29 kg/m^2 (Bonomo et al. 2010). Both studies included people managed on diet and/or oral antidiabetic medicines. Follow-up periods were 26 and 52 weeks.

Location of SMBG testing

One 30 week trial conducted in the USA including 174 people (mean age 53 years; mean duration of diabetes 12 years; mean HbA1c at baseline 73 mmol/mol [8.8%]; mean BMI 36 kg/m^2), some of whom were managed on insulin was analysed in the comparison of SMBG administered on the fingertip or on the forearm (Knapp et al. 2009).

The summary GRADE tables are presented for this review question (see Appendix D for full GRADE tables).

Table 33: Summary GRADE profile for SMBG versus no SMBG

	Number of people			
Number of RCTs	**SMBG**	**no SMBG**	**Effect (95% CI)**	**Quality**
HbA1c (%) at 24 to 52 week follow-up				
17 (Allen 1990; Barnett 2008; Bosi 2013; Davidson 2005; Farmer 2007; Fontbonne 1989; Franciosi 2011; Guerci 2003; Ismail 2013; Kleefstra 2010; Lim 2011; Lu 2011; Muchmore 1994; Nauck 2014; O'Kane 2008; Schwedes 2002; Wing 1986)	2217	2084	MD -0.22 (-0.31 to -0.13) Subgroup analysis based on current medication: Diet alone: MD -0.2 (-0.8 to 0.4) Diet ± oral antidiabetic therapy: MD -0.21 (-0.29 to -0.13) Diet, oral antidiabetic therapy ± insulin: MD -0.38 (-0.86 to 0.10), I^2=84% Subgroup analysis based on type of SMBG: Standard SMBG: MD -0.21 (-0.31 to -0.11) Enhanced SMBG: MD -0.29 (-0.49 to -0.09) Subgroup analysis based on frequency of SMBG: <1 per day: MD -0.31 (-0.55 to -0.07), I^2=68% 1-2 times per day: MD -0.19 (-0.29 to -0.10) >2 per day: MD -0.20 (-0.73 to 0.32)	Low
Change in HbA1c (%) by prespecified subgroups at 1 year follow-up				
1 (Farmer 2007) – DiGEM	151†	152	Diet alone: MD -0.12 (-0.29 to 0.05) Oral antidiabetic therapy: MD -0.19 (-0.40 to 0.02) Diabetes duration <36 months: MD -0.17 (-0.37 to 0.03) >36 months: MD -0.17 (-0.37 to 0.03) No diabetic complications: MD -0.23 (-0.43 to -0.03) With complications: MD -0.36 (-0.55 to -0.17)	Moderate
Fasting blood glucose (mmol/L) at 24 to 52 week follow-up				

Number of RCTs	Number of people		Effect (95% CI)	Quality
	SMBG	no SMBG		
6 (Allen 1990; Barnett 2008; Guerci 2003; Lim 2011; Lu 2011; Wing 1986)	835	810	MD -0.38 (-0.68 to -0.07) <u>Subgroup analysis based on current medication:</u> Diet ± oral antidiabetic therapy: MD -0.26 (-0.59 to 0.07) Diet, oral antidiabetic therapy ± insulin: MD -1.33 (-2.27 to -0.38) <u>Subgroup analysis based on type of SMBG:</u> Standard SMBG: MD -0.31 (-0.63 to 0.00) Enhanced SMBG: MD -1.57 (-2.94 to -0.20) <u>Subgroup analysis based on frequency of SMBG:</u> <1 per day: MD -0.20 (-0.86 to 0.47) 1-2 times per day: MD -0.55 (-1.30 to 0.20), I^2=54% >2 per day: MD -0.51 (-2.01 to 0.99)	Low
Postprandial blood glucose (mg/dL) at 6 months in older adults with type 2 diabetes treated with diet, oral antidiabetic and/or insulin medicines				
1 (Lim 2011)	96	48	MD -71.78 (-96.62 to -46.94) <u>Subgroup analysis based on type of SMBG:</u> Standard SMBG: MD -61.30 (-97.61 to -24.99) Enhanced SMBG: MD -81.00 (-111.05 to -46.95)	Low
Any hypoglycaemia* at 6 to 12 month follow-up (measured as the number of patients experiencing 1 or more events)				

Number of RCTs	Number of people		Effect (95% CI)	Quality
	SMBG	no SMBG		
6 (Barnett 2008; Farmer 2007; Guerci 2003; Lim 2011; Lu 2011; O'Kane 2008;)	203/1354	88/1138	RR 1.62 (1.19 to 2.22), I^2=34% <u>Subgroup analysis based on current medication:</u> <u>Diet alone: RR 1.27 (0.66 to 2.44)</u> Diet ± oral antidiabetic therapy: RR 1.80 (1.16 to 2.79), I^2=47% Diet, oral antidiabetic therapy ± insulin: RR 1.30 (0.70 to 2.39) <u>Subgroup analysis based on frequency of SMBG:</u> <1 per day: RR 2.28 (1.61 to 3.23) 1-2 times per day: RR 1.26 (0.89 to 1.79) >2 per day: RR 0.51 (0.06 to 4.37)	Low
Severe hypoglycaemia at 6 to 12 month follow-up (measured as the number of patients experiencing 1 or more events)				
3 (Bosi 2013; Farmer 2007; Lim 2011)	1/853	4/727	RR 0.35 (0.07 to 1.77) <u>Subgroup analysis based on current medication:</u> Diet ± oral antidiabetic therapy: RR 0.17 (0.01 to 4.12) Diet, oral antidiabetic therapy ± insulin: RR 0.45 (0.07 to 2.99) <u>Subgroup analysis based on frequency of SMBG:</u> <1 per day: RR 0.17 (0.01 to 4.12) 1-2 times per day: RR 0.45 (0.07 to 2.99)	Low
Any adverse events[a] at 6 month follow-up in people treated with diet and/or oral antidiabetic medicines (majority of events were of mild or moderate severity)				
1 (Barnett 2008)	41/311	45/299	RR 0.88 (0.59 to 1.30)	Moderate

Abbreviations: CI confidence interval; MD mean difference; RR relative risk
**Definitions of hypoglycaemia differed across the included studies. Overall Barnett (2008) and Lu (2011) used grades of hypoglycaemia with grades 1 and 2 relating to mild or moderate episodes and grades 3 and 4 referring to more severe episodes that require medical assistance. Barnett (2008) did not refer to specific blood glucose values but reported that 11/51 events in 27 patients in the SMBG group were SMBG confirmed hypoglycaemia. In both studies no patients experienced more than grade 3. Guerci (2003) referred to symptomatic or asymptomatic hypoglycaemia with no further definition but it was noted that no serious episode of hypoglycaemia was reported. Lim (2011) defined minor symptomatic hypoglycaemia as symptoms with blood glucose levels <3.5 mmol/L, major symptomatic hypoglycaemia as blood glucose levels <2.8 mmol/L and an episode requiring medical intervention or markedly depressed levels of consciousness or seizure and nocturnal hypoglycaemia as events occurring while asleep*
† intervention group relates to more intensive SMBG (this has not been combined with less intensive monitoring)

Table 34: Summary GRADE profile for SMBG plus education versus conventional SMBG

Number of RCTs	Number of people: SMBG plus education	Number of people: Conventional SMBG	Effect (95% CI)	Quality
HbA1c (%) at 3 to 12 month follow-up				
3 (Farmer 2007; Pimazoni-Netto 2011; Polonsky 2011)	439	408	MD -0.31 (-0.67 to 0.05), I^2=79% Subgroup analysis based on current medication: Diet ± oral antidiabetic therapy: MD -0.15 (-0.42 to 0.11), I^2=69% Diet, oral antidiabetic therapy ± insulin: RR -0.97 (-1.62 to -0.32)	Low
Any hypoglycaemia at 12 month follow-up in people treated with diet and/or oral antidiabetic medicines				
2 (Farmer 2007; Polonsky 2011)	48/407	37/377	RR 1.28 (0.88 to 1.86)	Low
1 (Pimazoni-Netto 2011)	32	31	The frequency of events was not significantly higher in intervention (4.11± 0.96%) vs. control (2.24 ± 0.64%, p>0.05)	Low

Abbreviations: CI confidence interval; MD mean difference; RR relative risk

Table 35: Summary GRADE profile for SMBG plus telecare (telephone or internet with feedback) versus conventional SMBG

Number of RCTs	Number of people: SMBG plus telecare	Number of people: Conventional SMBG	Effect (95% CI)	Quality
HbA1c (%) at 12 to 52 week follow-up				
5 (Del Prato 2012; Kwon 2004; Lim 2011; Quinn 2011; Tildesley 2010)	260	295	MD -0.57 (-1.06 to -0.08), I^2=85% Subgroup analysis based on current medication: Insulin: MD -0.27 (-0.68 to 0.13), I^2=71% Not specified: MD -1.04 (-1.42 to -0.65)	Low
Fasting blood glucose (mmol/L) at 26 and 44 week follow-up in people treated with oral hypoglycaemic drugs and/or insulin				
2 (Del Prato 2012; Lim 2011)	164	171	MD -0.19 (-0.61 to 0.24), I^2=40%	Low
Postprandial blood glucose (mg/dL) at 26 week follow-up in older adults treated with oral hypoglycaemic drugs and/or insulin				
1 (Lim 2011)	49	47	MD -19.07 (-42.84 to 3.44)	Low
Any hypoglycaemia at 26 week follow-up in people treated with oral hypoglycaemic drugs and/or insulin				

Number of RCTs	Number of people: SMBG plus telecare	Number of people: Conventional SMBG	Effect (95% CI)	Quality
1 (Lim 2011)	16/51	12/51	RR 1.33 (0.70 to 2.53)	Low
Total symptomatic hypoglycaemia at 44 week follow-up in people treated with insulin therapy				
1 (Del Prato 2012) – ELEONER	1.89 events per patient year	1.76 events per patient year	Rate ratio[¥] 1.07 (0.89 to 1.29)	Very low
Severe nocturnal hypoglycaemia at 44 week follow-up in people treated with insulin therapy				
1 (Del Prato 2012) – ELEONER	0.04 events per patient year	0.02 events per patient year	Rate ratio 2.00 (0.44 to 9.06)	Very low

Abbreviations: CI confidence interval; MD mean difference; RR relative risk
¥ Estimated using likely patient years to calculate number of events as only rates reported in full paper

Table 36: Summary GRADE profile for Automated mobile telephone glucometer versus standard glucometer

Number of RCTs	Number of people: Mobile telephone glucometer	Number of people: Standard glucometer	Effect (95% CI)	Quality
HbA1c (%) at 3 month follow-up in people with unspecified current therapy				
1 (Cho 2011)	35	34	MD 0.29 (-0.25 to 0.83)	Low
Fasting blood glucose (mmol/L) at 3 month follow-up in people with unspecified current therapy				
1 (Cho 2011)	35	34	MD -0.33 (-1.64 to 0.99)	Low
Postprandial blood glucose (mg/dL) at 3 month follow-up in people with unspecified current therapy				
1 (Cho 2011)	35	34	MD -11.57 (-46.55 to 23.41)	Very low

Abbreviations: CI confidence interval; MD mean difference

Table 37: Summary GRADE profile for SMBG plus continuous glucose monitoring (CGM) versus conventional SMBG

Number of RCTs	Number of people: SMBG plus CGM	Number of people: SMBG	Effect (95% CI)	Quality
HbA1c (%) up to 52 week follow-up in people treated with oral antidiabetic and/or insulin medicines				

Number of RCTs	Number of people		Effect (95% CI)	Quality
	SMBG plus CGM	SMBG		
2 (Vigersky 2012; Yoo 2008)	79	78	MD -0.46 (-0.87 to -0.06)	Very low
Fasting blood glucose (mmol/L) at 12 week follow-up in people treated with oral antidiabetic and/or insulin medicines				
1 (Yoo 2008)	29	28	MD -0.70 (-1.62 to 0.22)	Low
Postprandial blood glucose (mmol/L) at 12 week follow-up in people treated with oral antidiabetic and/or insulin medicines				
1 (Yoo 2008)	29	28	MD -0.90 (-2.67 to 0.87)	Low
Abbreviations: CI confidence interval; MD mean difference				

Table 38: Summary GRADE profile for frequency of SMBG testing (monthly versus fortnightly and 4 times weekly versus once weekly)

Number of RCTs	Number of people		Effect (85% CI)	Quality
	SMBG more frequently	SMBG less frequently		
	SMBG fortnightly	**SMBG monthly**		
HbA1c (%) at 6 month follow-up in people not on insulin				
1 (Bonomo 2010)	177	96	MD 0.04 (-0.20 to 0.28) Subgroup: people compliant with SMBG MD -0.31 (-0.59 to -0.03)	Moderate
Hypoglycaemia at 6 month follow-up in people not on insulin (defined as blood glucose <3.3 mmol/L)				
1 (Bonomo 2010)	177	96	RR 0.30 (0.03 to 2.86)	Low
	SMBG 4 times weekly	**SMBG once weekly**		
HbA1c (%) at study end in people not treated with insulin				
1 (Scherbaum 2008)	95	93	3 months: MD 0.00 (-0.28 to 0.28) 6 months: MD 0.10 (-0.20 to 0.40) 12 months: MD 0.20 (-0.10 to 0.50)	Moderate
Hypoglycaemia at 12 month follow-up in people not treated with insulin (1 event of SMBG <3.2mmol/L or several events)				

Number of RCTs	Number of people		Effect (85% CI)	Quality
	SMBG more frequently	SMBG less frequently		
1 (Scherbaum 2008)	18/102	5/100	RR 3.53 (1.36 to 9.14)	Moderate
Adverse events at 12 month follow-up in people not treated with insulin (hyperglycaemia, deteriorating neuropathy, retinopathy or nephropathy, multiple events or other events)				
1 (Scherbaum 2008)	8/102	14/100	RR 0.56 (0.25 to 1.28)	Low
Serious adverse events at 12 month follow-up in people not treated with insulin (hypoglycaemic shock, hyperosmolar coma, inpatient stay or death)				
1 (Scherbaum 2008)	15/102	20/100	RR 0.74 (0.40 to 1.35)	Low
Abbreviations: CI confidence interval; MD mean difference; RR relative *risk*				

Table 39: Summary GRADE profile for location of SMBG testing (forearm versus fingertip)

Number of RCTs	Number of people		Effect (95% CI)	Quality
	SMBG at forearm	SMBG at fingertip		
Change in HbA1c (%) at 6 month follow-up in people treated with insulin				
1 (Knapp 2009)	89	85	MD 0.10 (-0.29 to 0.49) <u>Subgroup analysis based on baseline HbA1c levels:</u> ≤7%: MD 0.00 (-0.41 to 0.41) 7.0-8.5%: MD 0.00 (-0.52 to 0.52) >8.5%: MD 0.20 (-0.45 to 0.85)	High
Hypoglycaemia at 6 month follow-up in people treated with insulin (more than 1 episode per month)				
1 (Knapp 2009)	3/89	3/85	RR 0.96 (0.20 to 4.60)	Moderate
Severe hypoglycaemia at 6 month follow-up in people treated with insulin (requiring urgent medical attention)				
1 (Knapp 2009)	3/89	1/85	RR 2.87 (0.30 to 27.01)	Moderate
Abbreviations: CI confidence interval; MD mean difference; RR relative *risk*				

8.3.2.3 Health economic evidence

This section was updated in 2015

Literature searches were undertaken to find any existing cost–utility analyses (CUAs) of self-monitoring of blood glucose in people with type 2 diabetes (see appendix C for detail of the search strategies). In total, 838 articles were found and 8 CUAs were returned (Cameron et al. 2010; Farmer et al. 2009; Palmer et al. 2006; Pollock et al. 2010; Simon et al. 2008; Tunis et al. 2010; Tunis and Minshall 2008; Tunis and Minshall 2010) that met the NICE reference case (National Institute for Health and Care Excellence 2012).

In addition, 1 recent UK health technology assessment report (HTA) was found (Clar et al. 2010). The HTA report did not undertake de novo modelling but reviewed the existing health economic evidence. Four of the CUAs included for this guideline (Farmer et al. 2009; Palmer et al. 2006; Simon et al. 2008; Tunis and Minshall 2008b) were included in the HTA report, with 4 CUAs (Cameron et al. 2010; Pollock et al. 2010; Tunis et al. 2010; Tunis and Minshall 2010) published after the HTA report.

With the exception of 1 CUA (Simon et al. 2008), all the CUAs were lifetime-modelled analyses using either the CDM (Centre for Outcomes Research Diabetes Model) (Palmer et al. 2004) or the UKPDS Outcomes Model (Clarke et al. 2004). One CUA (Simon et al. 2008) was an RCT-based economic evaluation that was later extended to a lifetime-modelled analysis (Farmer et al. 2009).

Three CUAs (Farmer et al. 2009; Palmer et al. 2006; Simon et al. 2008) were based on mainly UK data, 3 CUAs (Cameron et al. 2010; Tunis and Minshall 2008; Tunis and Minshall 2010) were based on mainly American or Canadian data and 2 CUAs (Pollock et al. 2010; Tunis et al. 2010) were based on data mainly from European countries.

The CUAs all compared self-monitoring of blood glucose to no monitoring, but contained different self-monitoring comparisons. Two CUAs (Farmer et al. 2009; Simon et al. 2008) incrementally compared more and less intensive testing regimes to no self-monitoring. One CUA (Cameron et al. 2010) compared self-monitoring at 9 tests per week to no self-monitoring. Five CUAs (Palmer et al. 2006; Pollock et al. 2010; Tunis et al. 2010; Tunis and Minshall 2008; Tunis and Minshall 2010) compared self-monitoring 1, 2 or 3 times per day to no self-monitoring but not as incremental comparisons against the marginal value of each extra test.

All the CUAs included or modelled people with existing type 2 diabetes. Most of the CUAs considered patients new to self-monitoring; only 1 CUA (Tunis and Minshall 2010) considered patients who had previously used self-monitoring.

Cohorts of people with type 2 diabetes covered a variety of generic diabetes treatment regimens. Three CUAs (Cameron et al. 2010; Farmer et al. 2009; Simon et al. 2008) modelled patients treated with diet and oral antidiabetic drugs together, 4 CUAs (Pollock et al. 2010; Tunis et al. 2010; Tunis and Minshall 2008; Tunis and Minshall 2010) modelled only patients treated with oral antidiabetic drugs and 1 CUA (Palmer et al. 2006) presented analyses separately for patients treated with diet, oral antidiabetic drugs and insulin. In their sensitivity analyses, 1 CUA (Cameron et al. 2010) also presented results separately for patients treated with diet, oral antidiabetic drugs and insulin.

The level of HbA1c change used within the health economic modelling ranged from a 1.5 mmol/mol (0.14%) reduction (Farmer et al. 2009; Simon et al. 2008) to a 11 mmol/mol (1.02%) reduction (Pollock et al. 2010; Tunis et al. 2010). Only 3 CUAs (Cameron et al. 2010; Farmer et al. 2009; Simon et al. 2008) sourced their HbA1c change from RCT or systematic reviews; 4 CUAs (Pollock et al. 2010; Tunis et al. 2010; Tunis and Minshall 2008; Tunis and Minshall 2010) sourced their HbA1c change from an American observational study

(Karter et al. 2006) and 1 CUA (Palmer et al. 2006) assumed their HbA1c change. One CUA (Cameron et al. 2010) employed a level of change (3 mmol/mol [0.25%] reduction) that was closest to that found in the clinical evidence review. Five CUAs (Palmer et al. 2006; Pollock et al. 2010; Tunis et al. 2010; Tunis and Minshall 2008; Tunis and Minshall 2010) modelled an increase in testing frequency linked with assumed (but not evidence based) greater HbA1c reductions.

The included CUAs differed in their assumptions of how long their change in HbA1c levels because of self-monitoring would be maintained. The 2 CUAs based on the DiGEM RCT (Farmer et al. 2009; Simon et al. 2008), the Canadian HTA (Cameron et al. 2010) and the Swiss-based CUA (Pollock et al. 2010) assumed the change in HbA1c resulting from self-monitoring would last for 1 year. The other 4 CUAs (Palmer et al. 2006; Tunis et al. 2010; Tunis and Minshall 2008; Tunis and Minshall 2010) assumed the change in HbA1c resulting from self-monitoring would last for a patient lifetime.

The 2 CUAs based on the DiGEM RCT (Farmer et al. 2009; Simon et al. 2008) were most applicable and had the fewest limitations. The Canadian HTA (Cameron et al. 2010) had few limitations but was not directly applicable as it used non-UK costs; 1 CUA (Palmer et al. 2006) was directly applicable but was limited by assuming levels of HbA1c change and lacking adequate details of costs and utilities used (as noted in previous NICE guidance CG66). Four CUAs (Pollock et al. 2010; Tunis et al. 2010; Tunis and Minshall 2008b; Tunis and Minshall 2010) that were not based in the UK and used an HbA1c change from American observational data were only partially applicable and had serious limitations.

The included CUAs gave heterogeneous cost-effectiveness results. The most applicable CUAs with fewest limitations (Farmer et al. 2009; Simon et al. 2008) found self-monitoring to be not cost effective (dominated) compared with no self-monitoring. The Canadian HTA (Cameron et al. 2010) found self-monitoring not to be cost effective compared with no self-monitoring using Canadian costs and thresholds (ICER $114,000 per QALY); 1 UK-based CUA (Palmer et al. 2006) found self-monitoring to be cost effective compared with no self-monitoring (ICERs ranged from £4600 per QALY for people on oral antidiabetic drugs or insulin to £15,per QALY 600 for people on diet alone). Using a variety of thresholds, 4 partially applicable CUAs with serious limitations (Pollock et al. 2010 (ICERs CHF9200 per QALY for 1 test per day, CHF13,000 per QALY for 2 tests per day and CHF17,300 per QALY or for 3 tests per day); Tunis et al. 2010 (ICERs between €1600 per QALY and €15,400 per QALY depending on country and testing frequency); Tunis and Minshall 2008 (ICERs $7900 per QALY for 1 test per day and $6600 per QALY for 3 tests per day); Tunis and Minshall 2010 (ICERs $26,200 per QALY for 1 test per day, $18,600 per QALY for 2 tests per day and £25,400 per QALY for 3 tests per day) found self-monitoring to be cost effective compared with no self-monitoring . No CUAs found self-monitoring to be cost saving compared with no self-monitoring, meaning that the trade-offs between cost and benefits and the opportunity costs of self-monitoring to the rest of the NHS had to be considered.

An association between modelled HbA1c change and incremental net monetary benefit (at £20,000/QALY threshold) seemed apparent in the included CUAs (see figure 1). Greater HbA1c reductions assumed to be achievable by self-monitoring of blood glucose led to higher HbA1c gains.

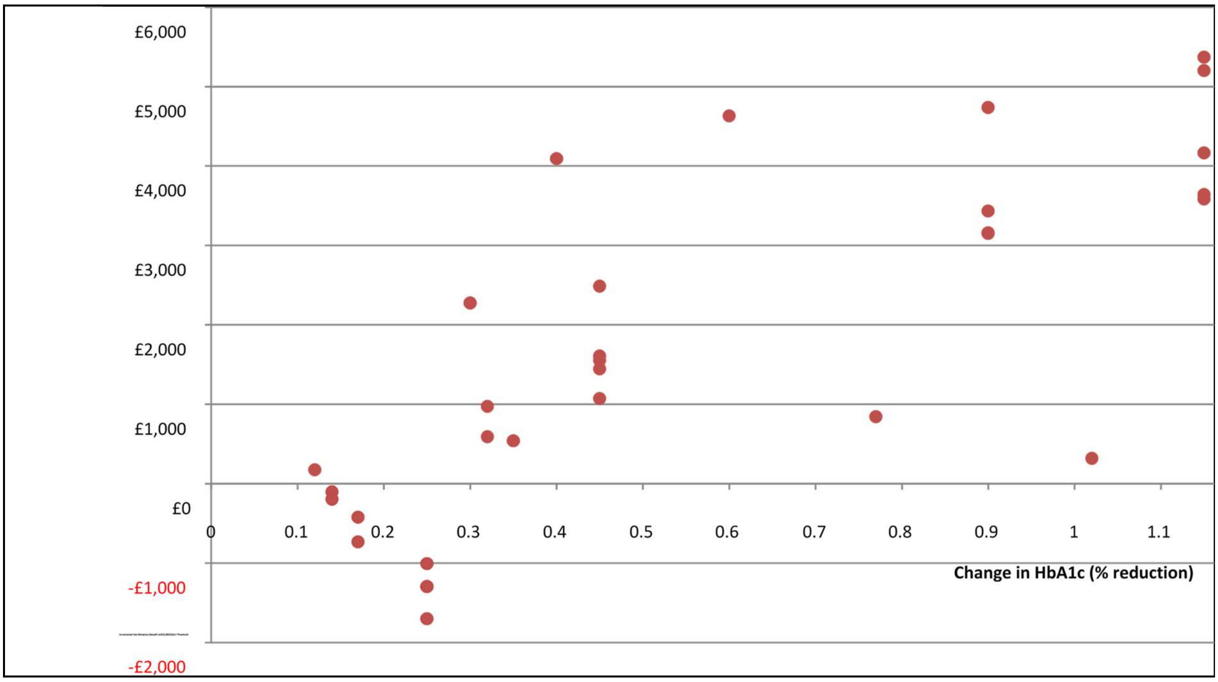


Figure 1: Self-monitoring of blood gluose - HbA1c reduction used in included CUAs

The CUAs displayed high levels of uncertainty in their cost effectiveness results. The 2 CUAs that found self-monitoring to be not cost effective compared with no self-monitoring found the reverse would be true in fewer than 40% of PSA iterations (Cameron et al. 2010; Farmer et al. 2009). Three of the 5 CUAs (Palmer et al. 2006; Tunis et al. 2010; Tunis and Minshall 2008) that found self-monitoring to be cost effective compared with no self-monitoring showed this to be the case in fewer than 60% of replications; 1 of the 5 CUAs (Tunis and Minshall 2010) did not report uncertainty and the least applicable study (Pollock et al. 2010) reported self-monitoring to be cost effective compared to no self-monitoring in fewer than 72% of replications.

The 2 CUAs based on the DiGEM RCT (Farmer et al. 2009; Simon et al. 2008) included a disutility associated with performing self-monitoring. Two other CUAs (Cameron et al. 2010; Palmer et al. 2006) included such a disutility in their sensitivity analyses and found doing so decreased the cost effectiveness of self-monitoring compared with no self-monitoring (increased the incremental cost effectiveness ratios).

Table 40: Economic evidence table for self monitoring of blood glucose

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Costs	Effects	ICER		
Cameron et al. (2010) People with existing type 2 diabetes treated with diet and exercise or OADs SMBG v none Canada **Partly applicable**[a,b,c,e] **Minor limitations**[a]	Effects: systematic review Costs: Canadian standard sources ($Can, 2008) Utilities: US confounder-controlled EQ-5D catalogue. No disutility from SMBG	UKPDS model with lifetime horizon (40 years) 1.3 strips/day (9/week) HbA1c baseline: 8.4% HbA1c effect: -0.25%, lasts for 1 year Discounted at 5% Assumed no pre-existing complications	$2711	0.024 QALYs	$114,000/ QALY	SMBG not cost effective compared to no SMBG at $100,000/ QALY threshold Clinical benefits of SMBG and associated savings do not offset the cost of the strips Monitoring once or twice per week could be cost effective	ICERs sensitive to treatment: diet $292,000/ QALY; OADs: $92,000/ QALY; insulin: $92,000/ QALY ICERs sensitive to strip cost and testing frequency. 50% reduction in either makes SMBG cost effective ICERs sensitive to HbA1c change. If HbA1c reduction is doubled, ICER is around $50,000/QALY ICERs sensitive to disutility from SMBG – if applied, ICER is around $180,000/QALY In PSA, SMBG is cost effective in <10% of replications at $CAN50,000/QALY and 40% of replications at $CAN100,000/QALY
Farmer et al. (2009) People with existing type 2 diabetes on diet and exercise or OADs More or less intense SMBG v usual care England **Directly applicable**[c] **Minor limitations**[f,n]	Effects: DiGEM RCT Costs: UKPDS model (£UK, 2005) Utilities: EQ-5D from UKPDS. Includes disutility from SMBG	UKPDS model with lifetime horizon. Lifetime model of Simon et al. (2008) 0.9 strips/day (6/week) HbA1c baseline: 7.5% HbA1c effect: no impact post RCT period Control: usual care "Less" intensive: SMBG with no intervention "More" intensive: SMBG with intervention and education	Less £59 More £56	Less -0.004 QALYs More -0.020 QALYs	Less Dominated More Dominated	SMBG dominated by no SMBG. Lifetime QALY gains are outweighed by initial negative impacts of SMBG; lifetime savings did not offset SMBG costs	Lifetime cost effectiveness results provide no convincing evidence for routine SMBG in people with type 2 diabetes not treated with insulin In PSA SMBG is cost effective at £20,000/QALY threshold in less than 40% of replication for the less intense arm and less than 15% for the more intense arm

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental Costs	Incremental Effects	Incremental ICER	Conclusions	Uncertainty
Palmer et al. (2006) People with existing type 2 diabetes, by treatment type SMBG v no SMBG England **Directly applicable** **Some limitations**[g,i,j]	Effects: HbA1c assumed Costs: SMBG published acquisition costs, diabetic specific complication costs (£UK, 2004) Utilities: sources not given. No disutility from SMBG	CDM model with lifetime horizon (length not stated) Test frequency: Diet and exercise 1/day, OADs 2/day Insulin 3/day HbA1c baseline: Diet and exercise 7.9% OADs 8.6% Insulin 8.5% HbA1c change: 1 test/day -0.3% 2 tests/day -0.4% 3 tests/day -0.6% Effect lasts for lifetime	Diet £2564 OADs £1013 Insulin £1171	Diet 0.165 QALYs OADs 0.225 QALYs Insulin 0.255 QALYs	Diet £15,515/ QALY OADs £4508/ QALY Insulin £4593/ QALY	ICERs for SMBG v no SMBG all fell well below the accepted threshold. However, uncertainty is large	ICERs sensitive to time horizon. (only insulin cost effective at 10 years), length of effect (diet and exercise not cost effective if only 5 years) and applying SMBG disutility (diet and exercise not CE). In PSA, SMBG cost effective at £30,000 in the following %s: Diet and exercise 51% OADs 51% Insulin 55%
Pollock et al. (2010) People with existing type 2 diabetes treated with OADs SMBG 1, 2 or 3 times/day v none Switzerland **Partly applicable**[a,b,d,e] **Some limitations**[h,k]	Effects: HbA1c observational study Costs: Swiss unit costs used where available. No other details given (CHF, 2006) Utilities: UKPDS and other literature. No disutility from SMBG	CDM with lifetime horizon (30 years) HbA1c baseline: 8.6% HbA1c change: 1 test/day -0.32% 2 tests/day -0.77% 3 tests/day -1.02% Lasts for 1 year Discounted at 3% Analysis not incremental, all compared to 0/day	1/day 528 2/day 1650 3/day 2899 (all CHF)	1/day 0.058 .QALYs 2/day 0.128 QALYs 3/day 0.167 QALYs	1/day CHF9177/ QALY 2/day CHF12,928 / QALY 3/day CHF17,342 / QALY	SMBG is cost effective compared to no SMBG, as ICERs are below accepted Swiss thresholds	ICERs sensitive to HbA1c effect (cost effective as long as hbA1c effect of 0.08% or more), time horizon (not cost effective at 5 years) and using Swiss cohort baseline data In PSA, SMBG cost effective at CHF thresholds in following %s: CHF30,000 CHF80,000 1/day 60% 67% 2/day 68% 81% 3/day 72% 84%

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental Costs	Incremental Effects	Incremental ICER	Conclusions	Uncertainty
Simon et al. (2008) People with existing type 2 diabetes treated with diet exercise or OADs SMBG v none England **Directly applicable**[c] **Minor limitations**[n,o]	Effects: DiGEM RCT Costs: person level data from DiGEM RCT and standard UK unit costs (£UK, 2005) Utilities: EQ-5D from DiGEM RCT; UK tariff. No disutility from SMBG	RCT – 1 year time horizon 0.9 strips/day (6/week) HbA1c baseline: 7.5% HbA1c effect for 1 year: Less -0.14% More -0.17% Control: standardised usual care "Less" intensive: SMBG with no intervention "More" intensive: SMBG with intervention and education	Less £92 More £84	Less -0.008 QALYs More -0.036 QALYs	Less Dominated More Dominated	SMBG is dominated by SMBG. SMBG significantly more expensive than no SMBG and negative impact on QoL	Missing data techniques analysed, results do not change
Tunis and Minshall (2008) People with existing type 2 diabetes treated with OADs SMBG v none USA **Partly applicable**[a,b,d,e] **Some limitations**[h,k,l]	Effects: HbA1c observational study Costs: relevant literature ($US, 2006) Utilities: UKPDS and other literature. No disutility from SMBG	CDM with lifetime horizon HbA1c baseline: 8.6% HbA1c change 0 tests/day 0.13% 1 test/day -0.32% 3 tests/day -1.02% Lasts for lifetime Discounted at 3% New SMBG users only Analysis not incremental Funded by industry	1/day $808 3/day $2161	1/day 0.103 QALYs 3/day 0.327 QALYs	1/day $7856/ QALY 3/day $6601/ QALY	SMBG appears cost effective compared to no SMBG at accepted US thresholds but uncertainty is large. Some costs are offset by reduced complications and small QALY increases	ICERs sensitive to time horizon 1/day 3/day 5 years $23,380 $29,137 10 years $9346 $518 Lifetime $7856 $6601 ICERs sensitive to compliance (assessed via strip cost): 100% $6601 66% $10362 33% $28676 In PSA, SMBG cost effective at US thresholds in the following % $20k $50k 1/day 51.6% 52.6% 3/day 56.7% 60.7%

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental Costs	Incremental Effects	Incremental ICER	Conclusions	Uncertainty
Tunis et al. (2010) People with existing type 2 diabetes treated with OADs SMBG 1, 2 or 3 times/day v none France, Germany, Italy, Spain **Partly applicable**[a,b,d,e] **Some limitations**[h,l,m]	Effects: HbA1c observational study. Country specific for other therapies, treatment programmes, ESRD and mortality Costs: Country specific SMBG costs and complication costs (€2007, country specific discounting) Utilities: UKPDS and other literature. No disutility from SMBG	CDM with lifetime horizon (40 years) HbA1c baseline: 8.6% HbA1c change: 0 tests /day +0.13% 1 test/day -0.32% 2 tests /day -0.77% 3 tests /day -1.02% Lasts for lifetime Discounted at country specific rates Analysis not incremental, all compared to 0/day Funded by industry	France 1/day €959 2/day €1296 3/day €2101 Ger 1/day €213 2/day €493 3/day €1561 Italy 1/day €1386 2/day €2766 3/day €4660 Spain 1/day €325 2/day €532 3/day €1237	France 1/day 0.079 2/day 0.206 3/day 0.264 Ger 1/day 0.130 2/day 0.250 3/day 0.309 Italy 1/day 0.109 2/day 0.232 3/day 0.303 Spain 1/day 0.089 2/day 0.172 3/day 0.215	France 1/day €12,114 2/day €6282 3/day €7958 Germany 1/day €1633 2/day €1974 3/day €5045 Italy 1/day €12,694 2/day €11,934 3/day €15,368 Spain 1/day €3661 2/day €3101 3/day €5751	SMBG at any frequency up to 3/day appears cost effective in all countries, compared to no SMBG (at accepted thresholds). However uncertainty is large Cost differences driven by different SMBG acquisition costs	ICERs sensitive to time horizon – not cost effective at 5 years for any countries or tests/day ICERs not sensitive to SMBG disutility (-0.036 in year 1 only). ICERs modestly increased, but remained within thresholds. In PSA, SMBG cost effective at €30,000/QALY threshold (€10,000 and €50,000 also given, similar %s) % Fr Ger It Sp 1/day 53 55 53 54 2/day 56 58 54 58 3/day 58 59 55 59 Different ICERs by country highlight the need for country specific analyses

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental Costs	Incremental Effects	Incremental ICER	Conclusions	Uncertainty
Tunis and Minshall (2010) People with existing type 2 diabetes treated with OADs SMBG 1, 2 or 3 times/day v none USA **Partly applicable**[a,b,d,e] **Some limitations**[h,k,l]	Effects: HbA1c observational study Costs: relevant literature ($US, 2006) Utilities: UKPDS and other literature. No disutility from SMBG	CORE model with lifetime horizon (40 years) HbA1c baseline: 7.6% HbA1c change: 0 tests/day -0.02% 1 test/day -0.14% 2 tests/day -0.34% 3 tests/day -0.37% Lasts for lifetime (assumed) Previous SMBG users Analysis not incremental, Funded by industry	1/day $1225 2/day $2147 3/day $3349	1/day 0.047 QALYs 2/day 0.116 QALYs 3/day 0.132 QALYs	1/day $26,208/ QALY 2/day $18,572/ QALY 3/day $25,436/ QALY	SMBG appears cost effective compared to no SMBG at US thresholds. However, uncertainty is large. Some costs are offset by reduced complications and small QALY increases	ICERs sensitive to time horizons. No option cost effective at 5 years, only 2/day cost effective at 10 years. ICERs are worse than for new users (Tunis and Minshall, 2008) because of smaller treatment gain and lower baseline HbA1c In PSA, percentages not presented as assume would not be favourable for SMBG

a Not UK based analysis
b Not UK baseline characteristics or treatment values
c Only includes patients on diet and exercise and OADs
d Only includes patients on OADs
e Not UK discount rates
f Limited details reported on modelling of future HbA1c trajectories
g Baseline characteristics from observational study, rather than meta-analysis or RCT
h Treatment effect from observational study, rather than meta-analysis or RCT
i Treatment effect not source sourced systematically
j Utility sources not specified
k Limited cost details reported
l Potential conflict of interest
m PSA not well reported
n Standard care arm may be better quality than real life
o Limited time horizon

Study, Population, Comparators, Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Costs	Effects	ICER		
CHF: Swiss francs CDM: Centre for Outcomes Research Diabetes Model DiGEM: diabetes glycaemic education and monitoring trial EQ-5D: EuroQoL five dimension health-related quality of life questionnaire Fr: France Ger: Germany HbA1c: glycosylated haemoglobin ICER: incremental cost effectiveness ratio It: Italy OADs: oral antidiabetic drugs PSA: probabilistic sensitivity analysis QALY: quality-adjusted life year QoL: quality of life RCT: randomised controlled trial SMBG: self-monitoring of blood glucose Sp: Spain UKPDS: United Kingdom Prospective Diabetes Study UK: United Kingdom US: United States of America							

8.3.2.4 Evidence statements

8.3.2.4.1 This section was updated in 2015Clinical evidence

None of the studies reported evidence on diabetes-related complications.

SMBG versus no SMBG

Evidence from a meta-analysis of 17 trials showed a small, clinically unimportant reduction in HbA1c levels with SMBG compared to no SMBG at up to 1 year. None of the subgroup analyses based on existing treatment (that is diet alone or combined with oral antidiabetic and/or insulin medicines), type of SMBG (standard or enhanced) or overall prescribed frequency of SMBG testing (that is less than once a day, 1 to 2 times a day or more than twice a day) showed a clinically important reduction in HbA1c levels. The quality of the evidence was low.

Evidence from a meta-analysis of the 6 trials reporting data on fasting blood glucose showed no significant changes in the 5 trials that included people who were treated with diet and/or oral antidiabetic medicines up to 1 year, but a significant reduction at 6 months in a trial of older adults who were on insulin therapy and undertaking SMBG (standard or enhanced) compared to no SMBG. Subgroup analyses based on overall prescribed frequency of SMBG testing showed no significant differences in fasting blood glucose in people undertaking SMBG compared to no SMBG. The quality of the evidence was low.

The low-quality trial including older adults on insulin therapy also reported data on postprandial blood glucose levels and found a significant reduction in those undertaking SMBG (standard or enhanced) compared to no SMBG at 6 months.

A meta-analysis of 6 trials that reported any hypoglycaemic event showed a significantly increased risk in those undertaking SMBG compared to no SMBG for people on diet and/or oral antidiabetic medicines (4 studies), but no difference in risk for people on diet alone (1 low-quality study) or on diet, oral antidiabetic and/or insulin medicines (1 low-quality study) up to 1 year. Subgroup analyses based on overall prescribed frequency of SMBG testing only showed a significantly increased risk in those undertaking SMBG less than once a day compared to no SMBG (2 studies). Overall, the quality of the evidence was low. A meta-analysis of the 3 trials that reported severe hypoglycaemic events showed low event rates and no significant difference in risk in those undertaking SMBG compared to no SMBG. One moderate-quality trial showed no significant difference in risk in adverse events in people undertaking SMBG compared to no SMBG. The quality of the evidence was low.

Different forms of SMBG

SMBG plus education versus conventional SMBG

Overall, 2 meta-analyses were conducted on HbA1c levels and any hypoglycaemic events for 3 studies that examined SMBG plus education compared to standard SMBG on people treated with diet and/or oral antidiabetic and/or insulin medicines up to 1 year. Overall, no significant differences in HbA1c levels and hypoglycaemic events were observed in people undertaking SMBG plus education compared to SMBG alone. However, 1 very-low-quality trial showed a significant clinically relevant reduction in HbA1c levels at 3 months in people on oral antidiabetic and/or insulin medicines who were undertaking SMBG plus education compared to SMBG alone. Overall, the quality of the evidence was low.

SMBG plus telecare versus conventional SMBG

A meta-analysis of 5 trials showed a non-significant reduction in HbA1c levels up to 44 weeks in people on diet, oral antidiabetic and/or insulin undertaking SMBG plus telecare compared to SMBG only (3 studies), but a significant and clinically important reduction in HbA1c levels was observed in favour of SMBG plus telecare compared to SMBG alone in 2 trials that did not specify the diabetes treatment that people were receiving. Overall, the quality of the evidence was low. Two low-quality trials also reported data on fasting blood glucose up to 44 weeks which showed no significant differences in people on diet, oral antidiabetic medicines and/or insulin undertaking SMBG plus telecare compared to SMBG. One low-quality trial additionally reported data on postprandial blood glucose levels and any hypoglycaemic events, and showed no significant differences at 26 weeks between people on diet, oral antidiabetic and/or insulin undertaking SMBG plus telecare compared to SMBG alone in either of these outcomes.

Automated mobile telephone glucometer versus standard glucometer

One small, low-quality trial showed no significant differences in blood glucose measures (HbA1c, fasting and postprandial blood glucose) at 3 months in SMBG using an automated glucometer compared to a standard glucometer in people with unspecified current diabetes treatments.

SMBG plus continuous glucose monitoring (CGM) versus conventional SMBG

Overall, a meta-analysis of 2 trials showed a significant and clinically important reduction in HbA1c levels in people on insulin undertaking SMBG plus CGM compared to those on SMBG alone up to 12 months. The quality of the evidence was very low. One low-quality trial reported no significant differences in fasting and postprandial blood glucose at 3 months in people on insulin undertaking SMBG plus CGM compared to those on SMBG alone.

Frequency and location of SMBG testing

Two moderate-to-low-quality trials showed no clinically important differences in HbA1c levels in people treated with oral antidiabetic medicines undertaking monthly versus fortnightly self-monitoring or 4 times weekly versus once weekly monitoring. There was an increased risk of any hypoglycaemic event with increased monitoring.

High-to-moderate-quality evidence from 1 trial in people with type 2 diabetes treated with insulin showed that there were no clinically important differences in HbA1c levels or hypoglycaemia associated with forearm versus fingertip testing.

8.3.2.4.2 Health economic evidence

Two directly applicable CUAs with minor limitations found that, for people with type 2 diabetes treated with diet or oral antidiabetic drugs, SMBG was more costly and produced less QALYs than no SMBG.

Four partly applicable CUAs with potentially serious limitations that based their treatment effect on the same US observational study found SMBG to be cost effective, though there was substantial uncertainty in their results.

8.3.3 Evidence to recommendations

Table 41: Linking evidence to recommendations

Relative value of different outcomes	The GDG agreed that impact on blood glucose levels, hypoglycaemia and diabetes-related complications were critical to decision making. The GDG noted that while self-monitoring of blood glucose (SMBG) provides the potential for tight glycaemic control and therefore reduced risk of diabetes-related complications, the possible impact of such control on hypoglycaemic events is important in determining the safety and acceptability to patients. The GDG agreed that all outcomes were weighted equally, and noted their importance in decision-making with respect to treatment choices and associated patient compliance, safety and costs. However, specific to blood glucose measures, the GDG agreed that HbA1c was more important than fasting and postprandial blood glucose.
Trade-off between benefits and harms	The GDG discussed the evidence presented for SMBG compared with no SMBG and agreed that overall, while a statistically significant difference was observed in HbA1c levels in favour of SMBG, the small reduction at less than 5 mmol/mol (0.5%; the threshold for minimal important difference) was not clinically meaningful. In addition, the GDG noted that no specific subgroup in terms of current diabetes treatment, type or frequency of SMBG was shown to have a clinically meaningful reduction in HbA1c levels. The GDG discussed the higher incidence of any hypoglycaemia observed in the SMBG group compared with no SMBG, and agreed that most of the reported events in the studies were minor or asymptomatic. The GDG considered it likely that the greater occurrence of hypoglycaemic events in the SMBG group was related to increased detection, rather than an increased risk of events associated with self-monitoring. The GDG noted that asymptomatic hypoglycaemia also occurs in people who do not have diabetes, and discussed the relative importance of these events compared with symptomatic hypoglycaemia. The GDG noted the low numbers of severe hypoglycaemic events that were reported in the studies in both SMBG and no SMBG groups. The GDG discussed the role of baseline HbA1c level and its possible association with hypoglycaemic events, and noted that hypoglycaemia can occur for various reasons at different baseline HbA1c levels. The GDG discussed the evidence presented for the different forms of SMBG, and noted that generally there was no difference in HbA1c levels and hypoglycaemic events between enhanced SMBG (education, telecare, automated glucometer) and conventional SMBG. The GDG noted that there was little evidence on frequency and location of SMBG testing, but findings from the 3 included studies also showed no difference in HbA1c levels and hypoglycaemic events between the groups comparing more frequent (every 2 weeks or 4 times a week) and

	less frequent (monthly or once a week) SMBG and different sites of testing (forearm or fingertip). The GDG discussed the conflicting evidence presented for continuous glucose monitoring compared with standard SMBG from 2 small, low-quality trials in people on insulin, where 1 trial showed no difference in HbA1c levels at 3 months while the second trial showed a clinically important reduction in HbA1c levels at 12 months. The GDG agreed that there was still uncertainty regarding the effectiveness of continuous glucose monitoring. The GDG noted the overall lack of evidence on diabetes-related complications.
Consideration of health benefits and resource use	All of the modelled cost–utility analyses (CUAs) were based on existing economic models, meaning that many of the underlying assumptions, probabilities and utilities in the CUAs were the same. Given this, the GDG agreed that key factors in assessing the quality of the evidence were the country costs used and the source of the HbA1c change estimates. The GDG considered the CUAs based on UK evidence that took their HbA1c change level from RCTs were the most applicable evidence with fewest limitations. These studies found self-monitoring to be not cost effective compared with no self-monitoring. CUAs based on observational evidence from the USA used a higher level of HbA1c change, but the GDG considered that the potential role of confounders in the observational evidence rendered that evidence too unreliable to be used in CUAs. Evidence was presented that showed a roughly linear increase in net monetary benefit with increasing HbA1c change modelled. The GDG did not consider that the larger HbA1c changes modelled in some CUAs were likely to be achievable. The GDG noted the clinical evidence review found a 2 mmol/mol (0.22%) decrease in HbA1c associated with self-monitoring and this was unlikely to be cost effective compared with modelled changes in HbA1c. Also, the GDG considered that the CUAs that assumed the HbA1c impact of self-monitoring would last for a patient lifetime were unrealistic. The GDG considered that the high degree of uncertainty displayed by CUAs that found self-monitoring to be cost effective compared with no self-monitoring meant that it could not conclude such studies gave convincing evidence of cost effectiveness of the intervention. Also, the GDG noted the correlation between industry funding and positive cost-effectiveness conclusions compared with the negative cost-effectiveness conclusions of non-industry-funded studies. The GDG highlighted a number of gaps in the economic evidence. Few CUAs reported results for people with type 2 diabetes using insulin and no CUAs reported results for newly diagnosed patients. No health economic evidence of a quality level high enough to be included was found to assess the marginal benefits of increasing the frequency of self-monitoring.

	Overall, the GDG considered the economic evidence did not make it possible to state conclusively that self-monitoring is or is not likely to be cost effective compared with no self-monitoring, but the most applicable evidence with least limitations suggested that self-monitoring is not likely to be cost effective compared with no self-monitoring.
Quality of evidence	The GDG noted that the quality of the evidence varied from high to very low, but agreed overall that the quality was low. Specific to the comparison of SMBG and no SMBG, the GDG noted that although most of the trials were based in western countries, only 1 study was conducted in the UK and that most participants were on diet and/or oral antidiabetic medicines, rather than diet alone or insulin. The GDG noted that while people on insulin therapy are able to titrate their dose based on what they eat, this is not normally the case for people who are controlled by oral blood glucose lowering therapies, and this may have an impact on their compliance with the use of self-monitoring. For the comparisons on different forms of SMBG, 4 of the 14 trials were conducted in Korea, where people with type 2 diabetes are generally slimmer and may have different diet and lifestyles compared with people living in the UK. In addition, some trials reported mean HbA1c levels at baseline close to 53 to 58 mmol/mol (7 to 7.5%) showing good blood glucose control, which the GDG agreed may not be representative of people with type 2 diabetes in the UK. The GDG also noted that 1 of these trials restricted inclusion to people aged 60 years and over, and agreed that older adults tend to have more comorbidities and therefore drug therapy selection may vary. The GDG noted that people who are recruited into trials may be more likely to be motivated to carry out self-monitoring. In addition, the group agreed that the differing quality of information across the trials may have influenced the results. The GDG agreed that it would be difficult to draw conclusions based on current treatments and intensity of treatment regimens, because the evidence base largely covered mixed populations of people on several different blood glucose lowering therapies without any subgroup analyses.
Other considerations	The GDG discussed the recommendations from the Driver and Vehicle Licensing Agency (DVLA), and noted that accidents involving driving were not an outcome for this review question. The GDG noted that the DVLA recommends that people driving cars and motorcycles need to inform the DVLA if they start insulin therapy. More recent guidance is available for people driving buses and lorries, which states that drivers on insulin or oral blood glucose medicines (including sulfonylureas and meglitinides) need to show adequate control by regular self-monitoring. The GDG discussed people treated with sulfonylureas in particular, and noted the increased risk of hypoglycaemia, similar to insulin therapy. Because of the different pharmacodynamics of these drug classes, it was

suggested that hypoglycaemic events experienced with sulfonylureas may be slower to occur, and come on so gradually that people are less aware of them, and in addition they may last for longer compared with insulin-induced events. The GDG discussed the negative impact this would have on people, for example, falls, and also other implications, in terms of medication selection and target-setting for HbA1c levels.

The GDG discussed the effects of corticosteroids, including increased insulin resistance, which may lead to higher plasma glucose levels. The GDG discussed the greater risks of hyperglycaemia for people with type 2 diabetes who start on corticosteroid therapy and agreed that these people would benefit from short-term self-monitoring.

The GDG discussed other clinical scenarios that may benefit from short-term SMBG such as acute illnesses or infections. The GDG discussed the potential benefits such as prevention of hospital admissions but also the additional costs associated with people in care homes who are unable to self-monitor. The GDG also discussed the implication of what constitutes intercurrent illnesses because this may include a range of conditions from an upper respiratory viral infection or urinary tract infection to more severe infections. This would mean that everyone with type 2 diabetes and acute intercurrent illnesses may require self-monitoring but the GDG agreed that no evidence had been identified to indicate that short-term SMBG would be beneficial in this clinical situation. Therefore, the GDG agreed that it would be useful to make clinicians aware of the potential risk of worsening hyperglycaemia during acute intercurrent illnesses in people with type 2 diabetes and to draft a research recommendation on this issue. The GDG agreed that treatment should be reviewed and that individuals should be reminded about what action to take when they are unwell. The GDG noted that community pharmacists are well placed to support and advise individuals in these situations and to provide routine advice at the point of supplying new diabetic medicines.

The GDG noted the limited evidence related to people on insulin, and agreed that it may not be appropriate to extrapolate the evidence base from people with type 1 diabetes because of differences in the characteristics of this group (for example people with type 1 diabetes will have been testing blood glucose levels for several years, as the age of onset is much younger, and they may also be more familiar with the effect of dietary intake on blood glucose levels, that is, glycaemic index and carbohydrate counting).

The GDG noted that self-monitoring of urine glucose (SMUG) is not used in clinical practice. In particular, it was noted that for people treated with newer SGLT-2 inhibitors such as dapagliflozin, sugars are excreted through the urine and so testing urine glucose levels would not be appropriate. In addition, it was noted that continuous glucose monitoring is not routinely used for people with type 2 diabetes.

	The GDG discussed the importance of individual preferences for SMBG because while some people may find it useful, others may find it has a negative impact on quality of life. The GDG also noted the lack of evidence concerning the frequency of SMBG and specific target values when SMBG is used. The GDG was unable to make any recommendations on these issues and chose instead to draft 2 research recommendations. When making recommendations for the use of self-monitoring, the GDG considered the following points: • Overall, the evidence showed a small reduction in HbA1c levels that was not clinically important. • There was uncertainty around whether self-monitoring was cost effective, but the GDG considered that it was unlikely to be at the magnitude of HbA1c changes reported. • Some medications have been shown to increase the risk of hypoglycaemia. Overall, a strong 'do not do' recommendation was made for the majority of people with type 2 diabetes, because the GDG agreed that self-monitoring would not be of sufficient benefit for most people. However, exception groups were added to this recommendation, because the GDG agreed it was important to offer targeted self-monitoring to people at higher risk of experiencing hypoglycaemic events. This included people who are taking insulin therapy, oral antidiabetic medicines that increase the risk of hypoglycaemia, or if there was evidence of hypoglycaemic episodes. The GDG also added a further recommendation for healthcare professionals to refer to the DVLA to ensure that targeted self-monitoring was carried out in accordance with legislative guidance.

8.3.4 Recommendations and research recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng28

Research recommendations

3. **What is the effectiveness of short-term self-monitoring of blood glucose during acute intercurrent illnesses in adults with type 2 diabetes?**

   Why this is important

   There is an increased risk of hyperglycaemia during acute intercurrent illnesses in adults with type 2 diabetes. However, there is little evidence on the clinical and cost effectiveness of short-term self-monitoring of blood glucose levels during acute illnesses. Robust evidence from randomised controlled trials is needed to determine the comparative effectiveness of self-monitoring with no self-monitoring during episodes of acute illnesses. Outcomes should include change in treatment and prevention of hospital admissions.

4. **What is the optimal frequency for self-monitoring of blood glucose in adults with type 2 diabetes?**

5. **What are the optimal blood glucose targets for self-monitoring in adults with type 2 diabetes?**

Why this is important

It is widely recognised that self-monitoring of blood glucose is a multicomponent intervention. As well as being educated about how to use a self-monitoring device to assess blood glucose levels, adults with type 2 diabetes need to be able to understand their results and act on the observed readings. In adults for whom self-monitoring is appropriate, there is limited evidence to guide clinical practice in prescribing self-monitoring regimens, in terms of frequency of testing and optimal blood glucose targets. Given the inconvenience and expense of self-monitoring, robust evidence from randomised controlled trials is needed to guide the optimal use of this intervention.

8.4 Drug treatment to control blood glucose

This section was updated in 2015 and used as part of the evidence base for the 2022 update. See www.nice.org.uk/guidance/ng28/evidence for the 2022 evidence review.

Lifestyle interventions such as diet and physical activity are commonly used to initially manage type 2 diabetes. However, it is uncommon for people to maintain glycaemic control to target levels for extended periods of time using only these interventions. Because type 2 diabetes is a progressive condition, with secretion of insulin decreasing over time, blood glucose lowering medicines are often indicated. The choice, order and combination in which these treatments are used will reflect consideration of the following:

- prevention of microvascular and arterial damage
- glycaemic control
- assessment of the inconvenience
- risks of side effects.

The benefits, side effects and relative cost-effectiveness differ among pharmacological classes, and to a lesser extent between individual drugs within the same class. The clinical questions covered in this section are concerned with the selection of optimal drug treatment strategies for people with type 2 diabetes, taking into consideration individual characteristics such as occupation and body mass index.

8.4.1 Clinical introduction

8.4.1.1 Approach to drug treatment

The approach to drug treatment to control blood glucose levels in people with type 2 diabetes was discussed in detail with the GDG. Because of the progressive nature of the condition, the main assumption underpinning the analysis for this review question, is that augmenting existing drug treatments with additional medicines will provide better glycaemic control (see Figure 2). The rationale for this is that the added medicines will have a different mode of action that is complementary to the existing drug treatment.

For the 2022 update the treatment pathway was divided into initial treatment and treatment options if further interventions are needed. This latter category covers the first intenstification of treatment, second intensification of treatment and third intenstification of treatment as outlined in Figure 2 below.

The 2022 evidence review can be found at www.nice.org.uk/guidance/ng28/evidence

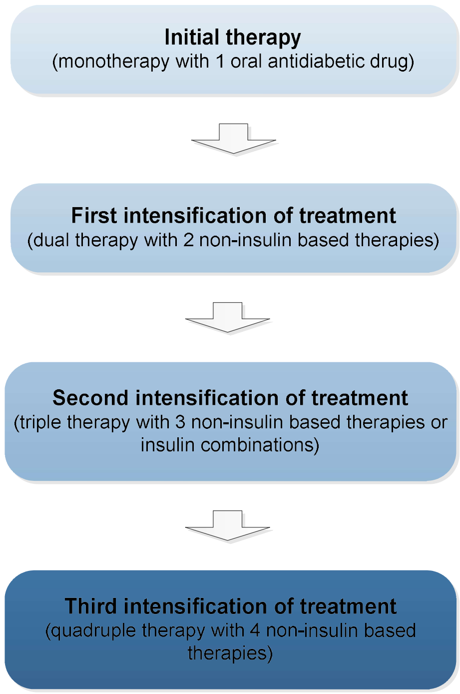


Figure 2: Overview of intensification of drug treatment as blood glucose control declines

8.4.1.2 Drug treatment to control blood glucose in Clinical Guidelines 66 and 87

Pharmacological management of blood glucose levels was originally covered as part of CG66 and CG87. The searches in CG66 were conducted from 2001 to 2007 (see Appendix G for search strategies from CG66) and searches in CG87 were conducted from 1990 to 2008 (see Appendix I for search strategies from CG87).

In previous versions of this guideline, the GDG also prioritised a series of pairwise comparisons that were of particular clinical interest and where possible, meta-analyses were conducted to combine the results of studies for different outcomes.

8.4.1.3 Drug treatment to control blood glucose in the update (2015)

For the current update, further searches have been carried out for drug treatments previously reviewed in CG66 (metformin, sulfonylureas, acarbose and insulin) with a date restriction of 2007 to June 2014; for drugs covered in CG87 (DPP-4 inhibitors that is saxagliptin, sitagliptin and vildagliptin; GLP-1 mimetics that is exenatide and liraglutide; insulin that is glargine and detemir; thiazolidinediones that is pioglitazone) with a date restriction of 2008 to June 2014; and for interventions not previously covered (DPP-4 inhibitors that is linagliptin; GLP-1 mimetics that is lixisenatide) with no date restrictions (see Appendix C for update search strategies).

The evidence that was originally included in CG66 and CG87 was re-reviewed as part of the update. For this update, a series of 4 network meta-analyses (NMAs) were proposed rather than a series of pairwise comparisons. Details of the definitions and included drug comparisons for each phase of treatment are set out in Table 43. Overall, the following phases of clinical treatment were agreed and formed the area of 4 sub-review questions:

- initial therapy (monotherapy)
- first intensification (dual therapy)

- second intensification (triple therapy and treatment combinations containing insulin)
- third intensification (quadruple therapy)

The aim of these sub-review questions was to identify which medicines were most effective in each phase, once treatment initiation or intensification was considered to be clinically indicated. Importantly, this meant that drug comparisons across the phases of treatment (for example, initial therapy with metformin compared to first intensification with metformin plus sulfonylurea) were not included in this review question. Table 42 provides information on the different drug treatments that were considered for this review question. For each treatment phase, the review also focused on the specific drug comparisons listed in Table 43 that the GDG prioritised as clinically important.

The evidence for each treatment phase (that is initial therapy, followed by first, second and third intensification) is reviewed and analysed separately, although the results from each sub-review question will be used to inform a single treatment algorithm for people with type 2 diabetes (see section 1.4).

8.4.1.4 Assumptions underpinning analytical approach

With regard to both the decision problems adopted and the evidence considered relevant to those problems, the approach adopted by the GDG had important assumptions and implications that should be made explicit.

The GDG advised that differences in previous treatment history in cohorts recruited to randomised controlled trials (RCTs) are likely to reflect prescriber preferences, rather than fundamental clinical differences. Therefore, it was assumed that the treatment effects observed in trials solely reflect the regimens to which people had been randomised in each study, and not the treatments they had previously received. This assumption was especially relevant for first intensification and second intensification. The assumption implies that, as long as trials met the eligibility criteria for the relevant decision problem, the identity of the treatments that had failed to control participants' HbA1c prior to recruitment should not be considered a material determinant of treatment effect. By this logic, the GDG was content to assume that, for example, it was valid to pool trials in which metformin+sulfonylurea were given to people for whom metformin monotherapy had proved inadequate in controlling HbA1c with trials in which metformin+sulfonylurea were given to people for whom sulfonylurea monotherapy had proved inadequate.

The GDG recognised that the prevailing approach to pharmacotherapy in type 2 diabetes contrasts with that adopted in other clinical areas, where people for whom 1 treatment proves inadequate would commonly discontinue that treatment and switch to another, with the result that people may be on different monotherapies or combinations at different phases of the treatment pathway. In those contexts, treatment history may become a critical component of potentially important clinical heterogeneity. In contrast, the common clinical pathways in type 2 diabetes are well established, and this is reflected in many of the RCTs providing evidence for this review. In particular:

- Most people meeting the GDG's definition of first intensification of pharmacotherapy have poorly controlled HbA1c despite prior treatment with an appropriate dose of metformin monotherapy;
- Many participants in second intensification trials have, prior to recruitment, experienced suboptimal blood glucose control on combination treatment with metformin-sulfonylurea.

The fair degree of homogeneity apparent in this evidence has advantages and disadvantages, from the perspective of evidence synthesis. It is positive because it reinforces the appropriateness of pooling the data (the so-called ‘consistency’ of treatment effects). On the other hand, it is unhelpful that any inferences drawn beyond the common pathway invariably rely on a degree of extrapolation. For example, the GDG considered it would be helpful to make recommendations for people for whom metformin is contraindicated, but no

RCTs were identified of treatments in this population. Therefore, the GDG had little option but to assume that the best options for those who cannot take metformin are the non-metformin options that provide greatest effects in trials in the broader population (even though that population predominantly comprises metformin-tolerant people).

One important implication of this approach was that the GDG believed it was appropriate to exclude RCTs from 2 categories:

- *a* versus *a+b* (commonly *a+placebo* versus *a+b*). These trials were not considered relevant because, from the perspective of the specified decision problems, they conflate different phases of treatment (that is, people who require 1 treatment and those who need 2). The GDG believed it was reasonable to take it as given that intensification of therapy has effects, and the question of the appropriate point in the treatment pathway at which to intensify treatment should be examined separately (see sections 8.1 and 8.2).
- *a*+(*c*, *d* or *e*) versus *b*+(*c*, *d* or *e*). Because the GDG's interest was in the particular combination of medicines that may be given, experimental designs in which a single agent was added to a heterogeneous collection of 'background' therapies were not considered informative, unless they contained enough detail to isolate the effect of particular combinations (in this example, a trial would only be considered to provide relevant evidence if it reported subgroup results for *a+c* versus *b+c*, *a+d* versus *b+d* and *a+e* versus *b+e*; such comparisons would be entered into synthesis as independent observations. In practice, no such trials were identified).

8.4.2 Review question

The overarching review question for this section is “Which pharmacological blood glucose lowering therapies should be used to control blood glucose levels in people with type 2 diabetes?”

The overall review question was broken down into 4 further sub-questions:

- Which pharmacological blood glucose lowering therapies should be used initially to control blood glucose levels in people with type 2 diabetes?
- When first intensification of treatment is indicated, which blood glucose lowering therapies should be used to control blood glucose levels?
- When second intensification of treatment is indicated, which blood glucose lowering therapies should be used to control blood glucose levels?
- When third intensification of treatment is indicated, which blood glucose lowering therapies should be used to control blood glucose levels?

Table 42: Blood glucose lowering drug treatments included in the review

Drug class	Drug	Route of administration	Recommended daily doses
Alpha-glucosidase inhibitors	Acarbose	Oral	50 to 600 mg
Biguanides	Metformin Metformin modified-release	Oral	500 to 3000 mg 500 to 2000 mg
Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)	Linagliptin Saxagliptin Sitagliptin Vildagliptin	Oral	5 mg 5 mg 100 mg 100 mg
Meglitinides	Nateglinide* Repaglinide	Oral	180 to 540 mg 0.5 to 16 mg
Sulfonylureas	Glibenclamide/ Glyburide Gliclazide	Oral	2.5 to 15 mg

Drug class	Drug	Route of administration	Recommended daily doses
	Gliclazide modified release Glimepiride Glipizide Tolbutamide		40 to 320 mg 30 to 120 mg 1 to 6 mg 2.5 to 20 mg 500 to 2000 mg
Thiazolidinediones	Pioglitazone	Oral	15 to 45 mg
Glucagon-like peptide-1 mimetics (GLP-1 mimetics)	Exenatide* Exenatide modified-release* Liraglutide* Lixisenatide*	Subcutaneous	10 to 20 mcg 2 mg 0.6 to 1.8 mg 10 to 20 mcg
Insulin	Biphasic insulin aspart Insulin aspart Insulin degludec Insulin detemir Insulin glargine Insulin lispro Neutral protamine Hagedorn insulin (NPH insulin)	Subcutaneous	variable

*Information taken from the British National Formulary and summary of product characteristics; * not licensed for monotherapy*

Table 43: Definitions of treatment phases and included drug comparisons to control blood glucose

Phase of clinical treatment	Definition	Included drug comparisons
Initial therapy (monotherapy)	This phase refers to treatment with a single non-insulin based blood glucose lowering therapy. This is generally appropriate for people who are newly diagnosed with type 2 diabetes or who are at an early stage and have previously been treated on diet and exercise alone	The following drug comparisons were included for initial therapy: • 1 oral antidiabetic versus 1 oral antidiabetic • 1 oral antidiabetic versus placebo
First intensification (dual therapy)	This phase refers to treatment with 2 non-insulin based blood glucose lowering therapies in combination. This is generally appropriate for people with type 2 diabetes who are not achieving adequate glycaemic control with a single non-insulin based oral therapy	The following drug comparisons were included for first intensification: • 2 non-insulin therapies versus 2 non-insulin therapies
Second intensification (triple therapy)	This phase refers to treatment with either 3 non-insulin based blood glucose lowering therapies (triple therapy) or any treatment combination containing insulin. This is generally appropriate for people with type 2 diabetes who are not achieving adequate glycaemic control with 2 non-insulin based therapies	The following drug comparisons were included for second intensification: • 3 non-insulin therapies versus 3 non-insulin therapies • Insulin versus 3 non-insulin therapies • Insulin + 1 non-insulin therapy versus 3 non-insulin therapies • Insulin + 2 non-insulin therapies versus 3 non-insulin therapies • Insulin versus insulin + 1 non-insulin therapy • Insulin versus insulin + 2 non-insulin therapies • Insulin + 1 non-insulin therapy versus insulin + 1 non-insulin therapy • Insulin + 2 non-insulin therapies versus insulin + 2 non-insulin therapies • Insulin + 1 non-insulin therapy versus insulin + 2 non-insulin therapies
Third intensification (quadruple therapy)	This phase refers to possible treatment with 4 non-insulin based blood glucose lowering therapies in combination. This is generally appropriate for people with type 2 diabetes who are not achieving adequate glycaemic control with therapies considered at second intensification	The following drug comparisons were included for third intensification: • 4 non-insulin therapies versus 3 non-insulin therapies

Non-insulin therapy includes both oral and injectable non-insulin agents; all included drug comparisons followed current summary of product characteristics (SPC) and licensed indications

RCTs with a minimum of 12 weeks of treatment and follow-up in people with type 2 diabetes were included for this review question. Several main exclusion criteria were used across all sub-review questions and these are outlined below:

- Non-randomised evidence (including observational, cohort, case–control and case series studies, uncontrolled or single arm trials), narrative reviews, conference abstracts, letters, editorials and trial protocols.
- Studies including a mixed population of people with type 1 and 2 diabetes, unless subgroup analyses were reported or 85% or more of the study population have type 2 diabetes.
- Comparisons with unlicensed indications (for example, GLP-1 mimetics for use in initial therapy), unlicensed modes of delivery (for example, inhaled insulin), drugs not included in the scope and drug comparisons not of interest (for example, comparisons across treatment phases).
- Studies focusing on markers of cardiovascular disease or other diabetic complications without any blood glucose measures (HbA1c).
- Unclear washout of existing drug treatments, where a proportion or all participants continued previous medicines that will likely confound study results (papers were excluded unless this represented a small proportion of patients that is less than 5%).
- Unclear if analyses were adjusted in trials where rescue medication was given.

Further specific criteria are reported in the evidence review for each sub-question. For the full excluded list, see Appendix L.

The outcomes that were selected by the GDG as critical and important to decision making for the clinical evidence review are listed below.

Table 44: Critical and important outcomes

Critical outcomes	Important outcomes
• Change in blood glucose levels (HbA1c)*	• Change in body weight*
• Hypoglycaemia*	
• Adverse events (total dropouts, dropouts due to adverse events*, nausea)	
**Treatment options reporting all of these 4 outcomes were included in health economic model*	

The detailed protocol is available in Appendix C.

Sensitivity analyses to determine whether participants' previous exposure to blood glucose lowering therapies affected the network meta-analyses results, for change in HbA1c at 12 months and hypoglycaemia at study end point were undertaken for each treatment phase. These critical outcomes were selected as they represented the more important outcomes and provided evidence for benefits and harms. One-year follow-up was prioritised for HbA1c as this was used in the health economic model. Table 43 describes the typical population characteristics for each treatment phase, which were used to inform the sensitivity analyses.

- For initial therapy, people are usually drug naïve and are managed using dietary changes only, with no previous experience of taking blood glucose lowering pharmacological treatments. Some of the included studies for initial therapy had participants who were previously on drug treatments. Therefore, sensitivity analyses on people who were completely drug naïve were undertaken. The sensitivity analyses showed that, overall, there was little difference in the direction of effect for changes in HbA1c and hypoglycaemia, between drug-naïve people and the full population which included people who were previously exposed and "washed-off" of prior anti-hyperglycaemic medications (see Table 45 and Appendix J). Therefore, the full analyses were used and reported in section 8.4.4.2.

- For first intensification of treatment, sensitivity analyses were undertaken on the typical population for this phase of treatment, that is, people who were previously on 1 oral antidiabetic medicine, including those whose medication had failed to adequately control blood glucose levels. No major differences were observed in the direction of effect for changes in HbA1c and hypoglycaemia, between people on 1 oral antidiabetic medicine and the full population which included studies of mixed populations of people who were drug naïve, or on 1 or more oral antidiabetic medicines at screening (see Table 45 and Appendix J). Therefore, the full analyses were used and reported in section 8.4.8.2.
- For second intensification of treatment, sensitivity analyses were undertaken on the typical population for this phase of treatment, that is, people who were previously on 2 non-insulin based therapies, including those whose medication had failed to adequately control blood glucose levels. No major differences in the direction of effect for changes in HbA1c and hypoglycaemia, between people on 2 antidiabetic medicines and the full population which included studies of mixed populations of people who did not necessarily fail on/or were previously exposed to 2 drugs, or studies of people who failed on 1 oral antidiabetic drug were observed (see Table 45 and Appendix J). Therefore, the full analyses were used and reported in section 8.4.12.2.

Table 45: Direction and magnitude of effect for full dataset and sensitivity analysis for change in HbA1c at 12 months and hypoglycaemia at study endpoint

	HbA1c at 12 months [mean change (95% CrI)]		Hypoglycaemia at study endpoint [HR (95% CrI)]	
Options	**Full dataset**	**Sensitivity analysis**	**Full dataset**	**Sensitivity analysis**
Initial therapy (relative effectiveness compared to placebo)				
Acarbose	-0.42 (-0.73, -0.14)	-0.28 (-0.83, 0.10)	1.91 (0.63, 5.18)	0.71 (0.06, 4.76)
Metformin	-0.83 (-1.33, -0.36)	-1.07 (-2.02, -0.12)	1.50 (0.95, 2.33)	1.30 (0.61, 2.94)
Pioglitazone	-0.79 (-1.33, -0.31)	-1.08 (-2.06, -0.13)	1.54 (0.92, 2.79)	1.40 (0.64, 3.20)
Repaglinide	-0.79 (-1.33, -0.31)	-1.24 (-2.29, -0.19)	5.16 (2.62, 11.36)	5.11 (2.57, 12.34)
Sulfonylurea	-0.68 (-1.17, -0.23)	-0.97 (-1.87, -0.09)	6.13 (3.99, 9.55)	5.14 (2.36, 12.59)
Sulfonylurea (modified-release)	-0.75 (-1.80, 0.27)	-1.01 (-2.37, 0.33)	3.19 (0.94, 10.35)	not available
First intensification (relative effectiveness compared to metformin-sulfonylurea)				
Metformin-exenatide	0.20 (-0.49, 0.88)	0.20 (-0.45, 0.84)	0.29 (0.07, 1.22)	0.18 (0.03, 1.22)
Metformin-nateglinide	-0.24 (-0.63, 0.17)	0.08 (-0.56, 0.76)	0.49 (0.17, 1.45)	0.55 (0.05, 6.68)
Metformin-pioglitazone	-0.04 (-0.47, 0.36)	0.05 (-0.46, 0.54)	0.06 (0.02, 0.17)	0.08 (0.02, 0.32)
Metformin-saxagliptin	0.06 (-0.59, 0.71)	0.06 (-0.54, 0.70)	0.03 (0.01, 0.11)	0.03 (0.00, 0.33)
Metformin-vildagliptin	0.03 (-0.38, 0.43)	0.08 (-0.33, 0.47)	0.33 (0.09, 1.16)	0.73 (0.08, 8.69)
Pioglitazone-sulfonylurea	0.16 (-0.50, 0.82)	0.16 (-0.47, 0.77)	0.70 (0.15, 3.14)	0.70 (0.06, 8.64)
Second intensification (relative effectiveness compared to metformin-NPH insulin)				

Options	HbA1c at 12 months [mean change (95% CrI)]		Hypoglycaemia at study endpoint [HR (95% CrI)]	
	Full dataset	Sensitivity analysis	Full dataset	Sensitivity analysis
Insulin glargine-metformin-sulfonylurea	0.05 (-0.27, 0.36)	-1.05 (-4.69, 2.71)	0.05 (-0.27, 0.36)	1.61 (0.06, 49.19)
Insulin lispro mix 50 and mix 25	0.08 (-0.63, 0.80)	-0.90 (-5.38, 3.65)	5.41 (2.07, 14.65)	5.88 (0.09, 355.00)
Metformin-NPH insulin-repaglinide	-1.28 (-2.12, -0.45)	-1.71 (-4.35, 0.97)	1.69 (0.49, 6.23)	1.71 (0.14, 20.65)
NPH insulin	0.39 (0.09, 0.71)	-0.70 (-3.35, 1.99)	1.62 (0.98, 2.66)	1.92 (0.17, 22.48)
NPH insulin-sulfonylurea	0.88 (0.51, 1.25)	-0.11 (-3.77, 3.61)	1.31 (0.79, 2.22)	1.42 (0.05, 40.10)

8.4.3 Health economic methods

8.4.3.1 Health economic evidence – search methodology

Previous guidelines (CG66 and CG87) have conducted health economic literature searches focused on specific drug comparisons that did not included initial therapy comparisons. For the current guideline, 1 systematic literature review with no date restrictions was undertaken to identify all existing cost–utility analyses (CUAs) addressing all 3 review sub–questions and yielded 3963 citations (see Appendix C for the search strategy).

In total 81 CUAs of pharmacological management of type 2 diabetes were found. Of these 81 CUAs, 79 were funded by a pharmaceutical manufacturer and found the sponsor's drug to be cost effective (see appendix F for a full list of the 81 CUAs). Two HTA-type studies found that the older, less expensive drugs provided better value for money than newer drugs.

For this guideline, in addition to meeting the NICE reference case (National Institute for Health and Care Excellence 2012) and covering included drug comparisons, 2 additional exclusion criteria were agreed by the GDG:

- Trial-based evaluations (that is, not extrapolated to lifetime outcomes) were excluded
- Non UK based CUAs were excluded.

As no directly applicable studies with only minor limitations were found that covered all the comparators under consideration for each sub-question for this guideline, an original economic analysis was undertaken.

8.4.3.2 Original health economic modelling – methods

A full description of the health economic model can be found in in Appendix F; a summary is presented here. The model was developed in line with the NICE reference case (National Institute for Health and Care Excellence 2012). A single health economic model structure was developed to address all 3 sub-questions for review question 1.

Along with the option of building a completely new model, a number of health economic diabetes models already exist (Mount Hood 4 Modeling Group 2007, Yi et al, 2010). The GDG selected the UKPDS Outcomes Model version 1 (UKPDS OM1, Clarke et al. 2004) as it matched the NICE reference case (National Institute for Health and Care Excellence 2012), was internally and externally validated and allowed greatest flexibility for modelling of additional short term outcomes.

The UKPDS OM1 does not directly allow the modelling of outcomes that the GDG considered important (weight changes, hypoglycaemia and treatment dropouts because of intolerance).Therefore, original functionality was added to the UKPDS OM1 HbA1c profiling (see figure 3). The UKPDS OM1 has annual model cycles; therefore, for HbA1c and weight, only treatment effect data at 12 months were used. Only treatments for which data on all 4 outcomes at the given time-points were available could be included in the health economic model. The model was built in Microsoft Excel 2010 (32 bit). Base-case models were run separately for each review sub-question and used 50,000 generated people run through 1000 loops of the UKPDS OM1.

Following the initial, 1-year treatment effect, HbA1c was modelled to follow the UKPDS risk equations (Clarke et al. 2004). For initial therapy and first intensification, people intensified treatment to pre-specified higher therapy levels when their HbA1c rose above 58 mmol/mol (7.5%).

Treatment dropouts because of intolerance led to pre-specified treatment switches that were limited to 2 further treatments within the same level of therapy. The model retained no memory of a person's intolerances between therapy levels. When a person was modelled to switch treatments, the HbA1c treatment effect for the new treatment was not applied, but the treatment effects for weight, hypoglycaemia and dropouts because of intolerance were modelled.

Body weight was assumed to increase at a rate of 0.1kg per year for all people. In line with the available clinical evidence, treatment-related weight losses were modelled to only last 1 year, after which the weight loss was regained. However, the GDG advised that treatment-related weight gains would remain indefinitely.

Rates of all hypoglycaemic episodes were modelled, of which the same proportion (2%, Donnelly et al. 2005) were assumed to be severe events. For each therapy level, relative treatment effects were taken from the clinical NMA and applied to baseline rates for given treatments from epidemiological studies.

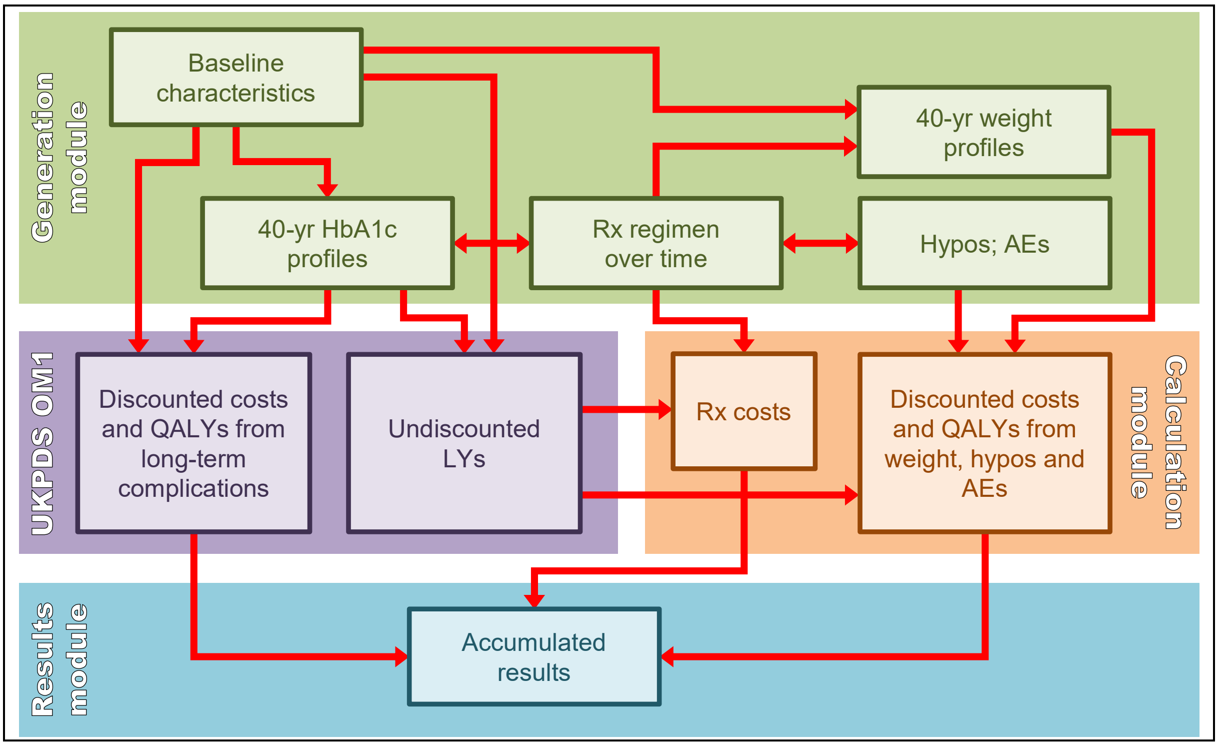


Figure 3: Schematic representation of original health economic model

8.4.3.3 Baseline data

Baseline population characteristics were different for each therapy level (see table 46) and were largely taken from a large UK database of people registered with GPs (The Health Improvement Network (THIN) 2014). For the initial therapy analysis, characteristics were taken from when people were prescribed their first non-insulin anti-diabetes agent (British National Formulary section 6.1.2, Joint Formulary Committee 2014). Based on an analysis of diabetes duration in included RCTs, first intensification characteristics were taken from the THIN database when people had a diabetes duration of 4.5 years and second intensification characteristics were takenf rom the THIN database when duration was 8.5 years.

To allow baseline population heterogeneity to be accurately modelled through the UKPDS OM1, individual person data were randomly sampled from a multivariate distribution taking account of the correlations between variables.

Ethnicity is not well recorded at an individual level in the THIN dataset, so this characteristic was taken from type 2 diabetes respondents in the Health Survey for England (Health and Social Care Information Centre [HSCIC] 2012). Ethnicity correlation data were taken from the same data set for the variables that were available. It was not possible to source ethnicity data specific to each therapy level.

In addition to baseline population characteristics, HbA1c profiles were generated for each person. A minimum value of 6.0% was applied to sampling distribution for the generation of baseline HbA1c.

Table 46: Baseline characteristics used to populate UKPDS OM1

Category	Characteristic	Initial Therapy	First Intensification	Second Intensification
Demographics	Number of people	90,219	74,144	43,075
	Ethnicity – white	94.6%	94.6%	94.6%
	Ethnicity – African-Caribbean	2.7%	2.7%	2.7%
	Ethnicity – Asian Indian	2.7%	2.7%	2.7%
	Gender (% male)	57.1%	55.9%	55.8%
	Age (years)	59.8	62.7	65.4
	Duration of diabetes (years)	2.0	4.5	8.5
	Weight (kg)	89.9	87.7	86.7
	Height (cm)	168	168	168
Risk Factors at Diagnosis	Atrial fibrillation	0.81%	0.78%	0.63%
	Peripheral vascular disease	0.51%	0.53%	0.47%
	Smoking – current smoker	19.1%	18.0%	19.0%
	Smoking – past smoker	33.2%	33.6%	30.7%
	Total cholesterol (mmol/l)	5.3	5.3	5.5
	HDL (mmol/l)	1.17	1.21	1.21
	Systolic blood pressure (mmHg)	139.6	141.3	143.2
	HbA1c	8.2%	7.8%	7.9%
Current Risk Factors	Smoking – current smoker	18.1%	15.1%	13.4%
	Smoking – past smoker	34.0%	35.8%	36.4%
	Total cholesterol (mmol/l)	5.0	4.5	4.4
	HDL (mmol/l)	1.18	1.23	1.23
	Systolic blood pressure (mmHg)	137.5	136.3	136.2

Category	Characteristic	Initial Therapy	First Intensification	Second Intensification
	HbA1c	8.4%	7.3%	7.6%
Years since pre-existing complications (% of people)	IHD	3.2 (2.7%)	2.8 (5.2%)	5.3 (9.7%)
	CHF	2.5 (0.5%)	2.4 (1.2%)	3.9 (2.3%)
	Amputation	2.0 (0.1%)	2.4 (0.2%)	3.8 (0.4%)
	Blindness	2.3 (0.4%)	2.5 (1.4%)	4.8 (2.2%)
	Renal	3 (0.2%)	2.3 (0.5%)	3.8 (1.0%)
	Stroke	2.7 (0.5%)	2.5 (0.9%)	4.2 (1.8%)
	MI	2.9 (0.8%)	2.6 (1.4%)	4.6 (2.5%)

(a) Not all variables are recorded for all people. Therefore, whilst the total number of people in the dataset is shown, each variable may have a different denominator
(b) Ethnicity data source: Health Survey for England 2009-2011
(c) THIN data as at 31 August 2013
(d) For definitions of variables, see appendix F

8.4.3.4 Resource use and costs

NHS inpatient and primary care consultation resource use associated with long-term complications were modelled by the UKPDS OM1 and costed using the UKPDS costs (Clarke et al. 2003). Treatment switches because of intolerance were assumed to incur the cost of 1 GP appointment. Severe hypoglycaemic episodes were costed at £380 per episode (ref Hammer et al. 2009). Weight change incurred no cost.

Weighted average doses of the drugs used in the included RCTs were used to calculate the drug resource use for each arm. Drug unit costs were based on published prices (NHS Drug Tariff 2014). Consumables and staff time resource used were agreed by the GDG; unit costs were based on current average usage (Health and Social Care Information Centre 2014) and published prices (Curtis 2013).

All resource use and costs were measured from an NHS and PSS perspective (National Institute for Health and Care Excellence 2014) and inflated to 2012–13 prices (Curtis 2013).

8.4.3.5 Utilities

Baseline utility (0.785) and utility decrements associated with modelled long-term complications were taken from the UKPDS RCT (Clarke et al. 2002). Treatment switches because of intolerance assumed an annual utility decrement equivalent to 6 weeks of nausea (-0.005, Matza et al. 2007). Symptomatic hypoglycaemic episode utility decrements (-0.014) were modelled on a natural logarithmic scale; severe hypoglycaemic episodes utility decrements (-0.047) were modelled on a binomial scale. Both were taken from Currie et al. (2006). Utility decrements associated with weight change (-0.0061 per kg) are applied for BMIs above 27.7 kg/m^2 (Bagust and Beale 2005).

8.4.3.6 Results and sensitivity analyses

Results reported were the means of the probabilistic sensitivity analyses. Probabilistic sensitivity analyses were run for each sub review question, using 1000 iterations of 50,000 people run through 100 UKPDS OM1 loops. One-way sensitivity analyses were run for key variables and results were based on 50,000 people run through 1000 UKPDS OM1 loops.

8.4.3.7 Model limitations

The health economic modelling has addressed a number of limitations of previous analyses, including the use of detailed, appropriate baseline population data, the use of 12-month treatment-effect data, fully incremental analyses of relevant options and the presentation of a thoroughgoing, valid PSA. However, a number of limitations remain. All type 2 diabetes health economic models rely on extrapolating short-term biological markers to predict long-term outcomes. Treatment-related weight change and hypoglycaemia effects were key model drivers that are based on extrapolations of short-term trial-based data; moreover, these effects are assumed to have quality-of-life impacts that are informed by a small, methodologically limited evidence-base. In these respects, the analysis presented here is no more susceptible to bias than any other health economic analysis of its type; however, it is acknowledged that, if these shortcomings were addressed, this and other analyses might reach different conclusions.

8.4.4 Clinical evidence review for initial therapy

In total 17,037 references were found for the main review question and 122 papers were included for initial therapy which relate to 114 trials.

This sub-review question addressed which initial non-insulin based oral treatment option is most effective when people with type 2 diabetes have inadequate blood glucose control. Most people are at an early stage in diabetes and are generally drug naïve, having been treated with dietary changes alone.

RCTs of at least 12 week treatment duration examining either any oral antidiabetic drug compared to each other or any oral antidiabetic drug compared to placebo were included (see section 8.4.2 for main exclusion criteria). As people are more likely to be drug naïve when they start initial therapy, it was important to ensure included trials used current licensed doses. Therefore, the following additional exclusion criteria were applied:

- Trials of monotherapy using only doses of blood glucose lowering therapies above the recommended daily dose.
- Trials reporting no information relating to doses.
- Trials termed monotherapy with people who were not drug naïve or had washout periods of less than 4 weeks.

8.4.4.1 Description of included studies for initial therapy

A total of 36,938 participants from 114 RCTs were included. The majority of studies were carried out in multiple centres across different countries. The mean age ranged from 45.6 to 74.4 years, with 6 studies not reporting this information. Mean HbA1c levels at baseline ranged from 42 to 107 mmol/mol (6.0% to 11.9%), with 5 studies not reporting this information. The mean BMI ranged from 23.2 to 39.8 kg/m^2, with 8 studies not reporting this information. Mean duration of diabetes ranged from 10.4 weeks to 17.3 years, with 51 studies not reporting this information. Follow-up periods ranged from 12 to 260 weeks. For full details of the included studies, see Appendix E.

8.4.4.2 Network meta-analyses for initial therapy

To facilitate comparison across all available treatment options, 10 network meta-analyses were performed for all 3 critical and 1 important outcomes – change in HbA1c at 3, 6, 12 and 24 months, hypoglycaemia at study end point, adverse events (that is, dropouts due to adverse events, total dropouts and nausea) at study end point and change in body weight at 12 and 24 months. Placebo was selected as the reference treatment as it was the most common comparator. Full details of methods and additional NMA outputs are provided in Appendix J.

Generally, well-connected networks were produced for shorter follow-up times although these tended to be sparser and contained fewer treatment options at 12 and 24 months. Pairwise comparisons that did not form part of the main network were not presented as they would not add to the GDG decision making.

On the whole, the quality of the evidence was moderate to low as networks were generally well connected. However, some included trials were not double-blind and did not report adequate details of randomisation and allocation concealment methods. It was noted that random-effects models tended to estimate a fairly large inter-study heterogeneity term, which will reduce the precision of effect estimates.

Table 47: GRADE profile for network meta-analyses for initial therapy

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in blood glucose (HbA1c)						
3 months	68	serious[1]	not serious[2]	not serious[3]	not serious	Moderate
6 months	62	serious[1]	not serious[2]	not serious[3]	not serious	Moderate
12 months	21	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
24 months	6	serious[1]	not serious[2]	not serious[3]	not serious	Moderate
Hypoglycaemia at study end point						
Study end point	44	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Adverse events at study end point						
Dropouts due to adverse events	73	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Total dropouts	73	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Nausea	29	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Change in body weight						
12 months	12	serious[1]	serious[5]	not serious[3]	serious[4]	Low[6]
24 months	6	serious[1]	serious[5]	not serious[3]	serious[4]	Low[6]

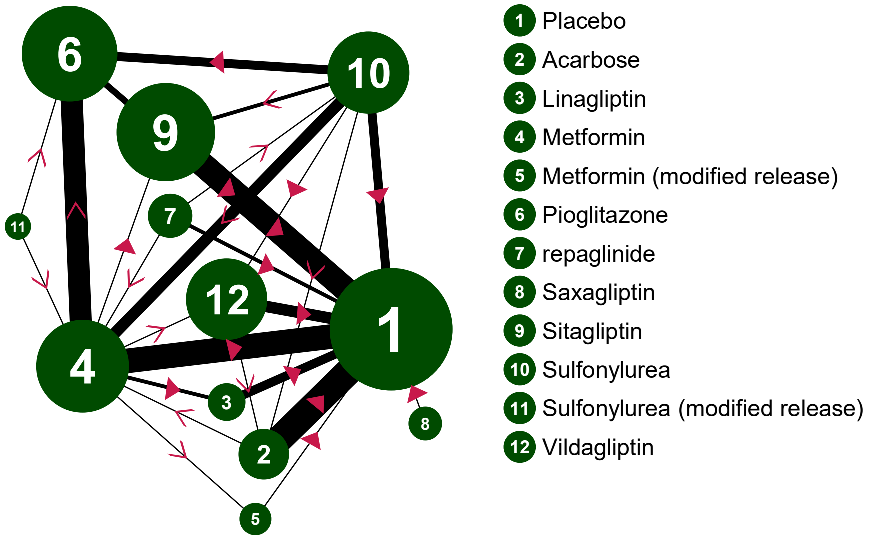
[1]Downgrade 1 level: baseline HbA1c ranged from 5.3 to 12.7%
[2]Assessed based on residual deviance, deviance information criterion and tau^2 (tau^2<0.5)
[3]Considered not serious as population, interventions, comparator and outcomes are as defined in protocol
[4]Downgrade 1 level: no interventions had probability of being best and worse ≥0.5
[5]Downgrade 1 level: tau^2≥0.5
[6]Maximum downgrade by 2 levels

8.4.4.3 Change in blood glucose (HbA1c) at 3, 6, 12 and 24 months

Results of the NMAs are summarised below for the 11 treatment options that were compared with placebo at 3 and 6 months and the 8 and 6 treatment options assessed at 12 and 24 months respectively.

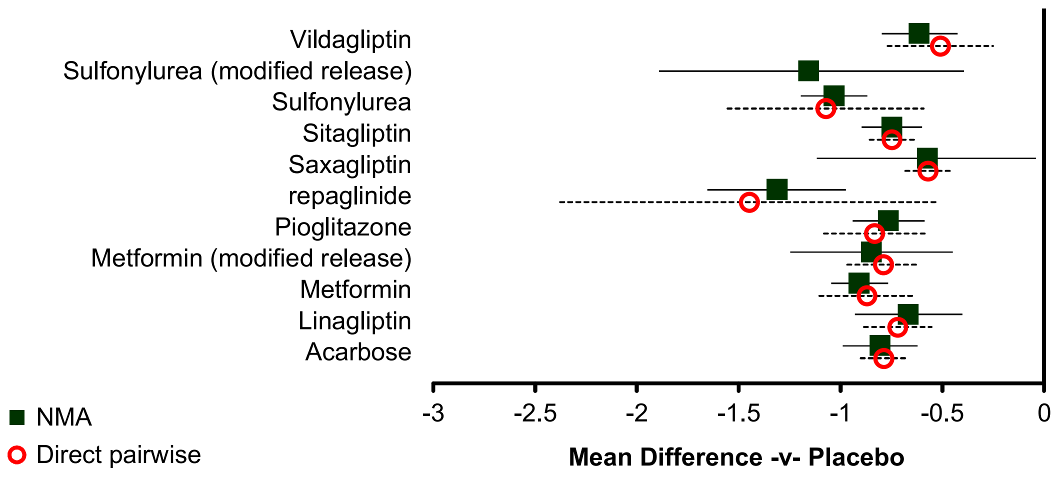
At the 4 follow-up time points, all treatments are shown to be consistently more effective than placebo, though with varying levels of precision. At longer follow-up periods, the 95% credible intervals are generally wider, and at 12 months in particular, they tend to overlap making it difficult to distinguish between the various treatments. Where available, there is reasonable agreement between the NMA evidence and direct pairwise treatment effect estimates which compared different options with placebo in the underlying evidence. The inclusion of indirect evidence alongside direct evidence slightly reduces uncertainty, and also results in some small changes in effect estimates. However, there is substantial overlap between the 95% credible/confidence intervals, suggesting reasonable consistency between direct and indirect evidence.

The rankings of each treatment option, summarised in the tables similarly support the conclusion that the option that is least likely to be effective is placebo. At 3 and 6 months, repaglinide and sulfonylurea demonstrated consistently high rankings with narrow credible intervals. Repaglinide also had the highest ranking at 12 months, though with a lower probability and wider credible intervals. The option with the highest individual probability of maximum effectiveness is pioglitazone at 24 months.



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 4: Network meta-analysis of change in HbA1c (3 months) – evidence network

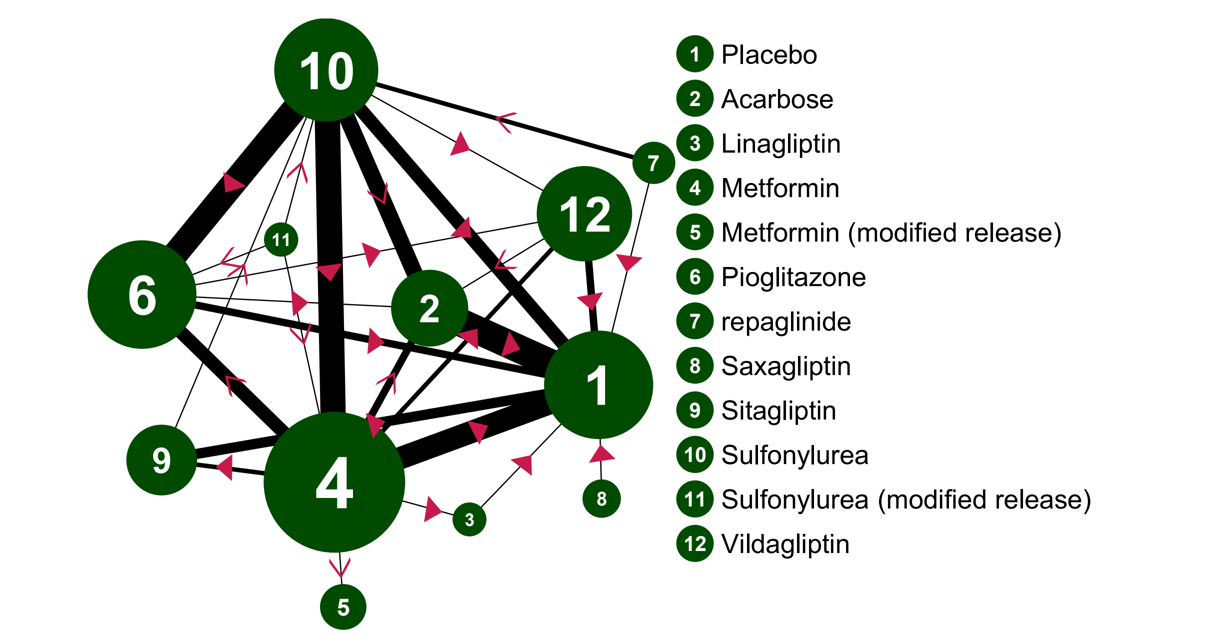


Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 5: Network meta-analysis of change in HbA1c (3 months) – relative effect of all options compared with common comparator (placebo)

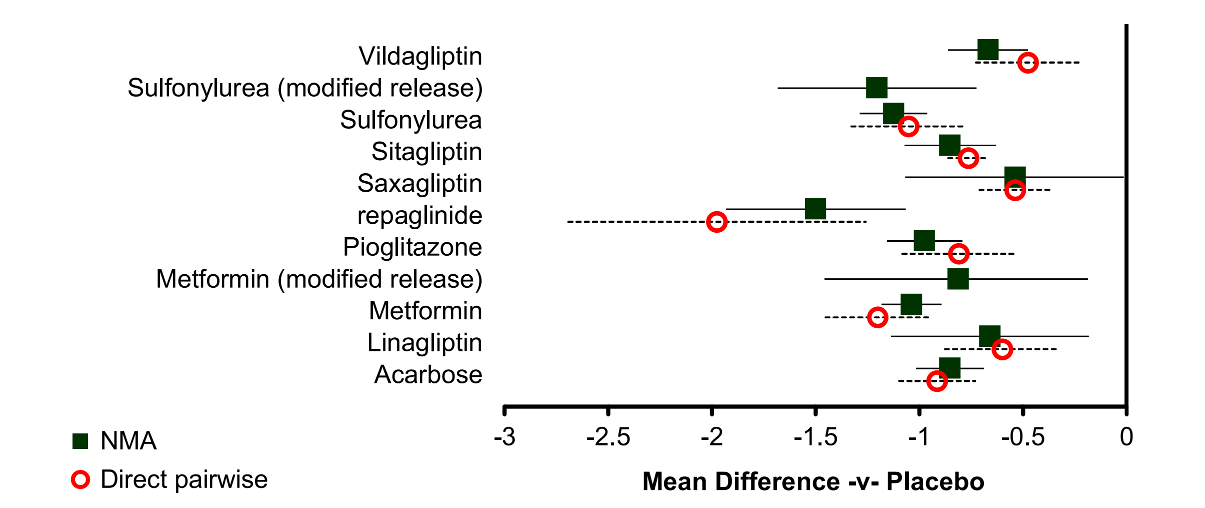
Table 48: Network meta-analysis of change in HbA1c (3 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	12 (12, 12)
Acarbose	0.000	6 (3, 10)
Linagliptin	0.000	9 (4, 11)
Metformin	0.000	4 (3, 7)
Metformin (modified release)	0.020	5 (2, 11)
Pioglitazone	0.000	7 (4, 10)
repaglinide	0.611	1 (1, 3)
Saxagliptin	0.005	10 (2, 11)
Sitagliptin	0.000	7 (4, 10)
Sulfonylurea	0.020	3 (2, 5)
Sulfonylurea (modified release)	0.344	2 (1, 11)
Vildagliptin	0.000	10 (6, 11)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 6: Network meta-analysis of change in HbA1c (6 months) – evidence network

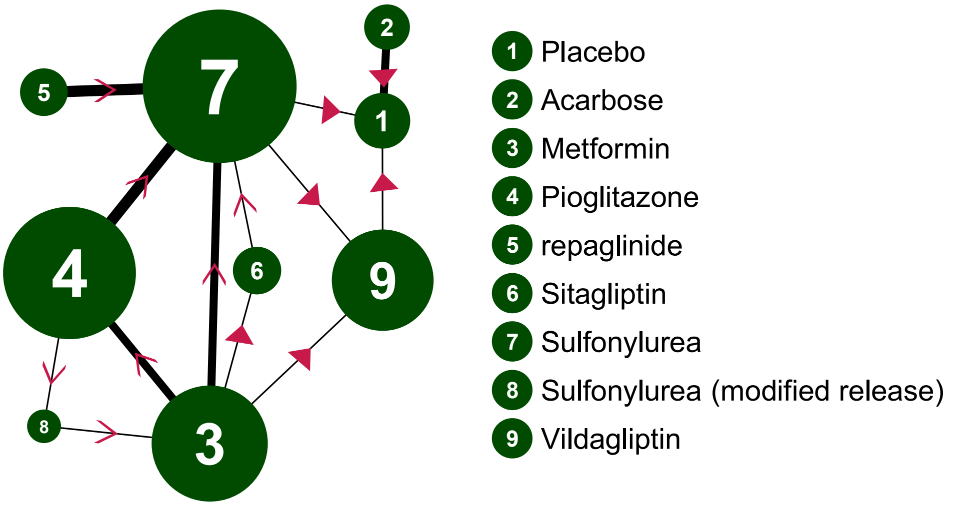


Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 7: Network meta-analysis of change in HbA1c (6 months) – relative effect of all options compared with common comparator (placebo)

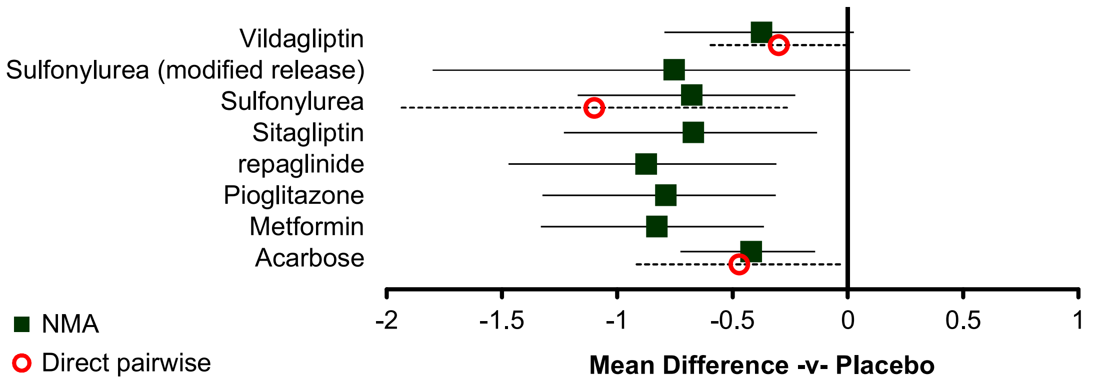
Table 49: Network meta-analysis of change in HbA1c (6 months) – rankings for each comparator

	Probability best	Median rank (95%Crl)
Placebo	0.000	12 (11, 12)
Acarbose	0.000	7 (5, 9)
Linagliptin	0.002	9 (3, 11)
Metformin	0.002	4 (2, 6)
Metformin (modified release)	0.027	8 (1, 11)
Pioglitazone	0.000	5 (3, 8)
repaglinide	0.797	1 (1, 3)
Saxagliptin	0.002	10 (4, 11)
Sitagliptin	0.000	7 (4, 10)
Sulfonylurea	0.010	3 (2, 5)
Sulfonylurea (modified release)	0.160	2 (1, 8)
Vildagliptin	0.000	9 (7, 11)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 8: Network meta-analysis of change in HbA1c (12 months) – evidence network

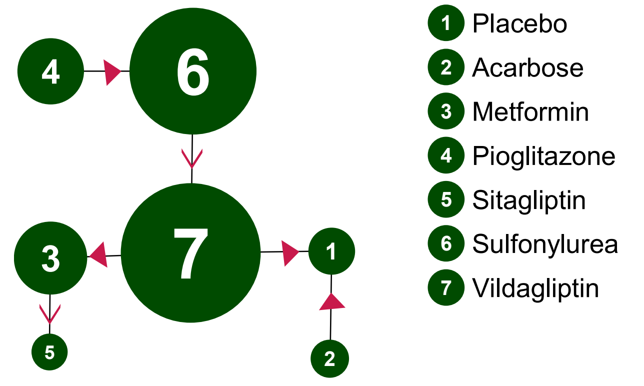


Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 9: Network meta-analysis of change in HbA1c (12 months) – relative effect of all options compared with common comparator (placebo)

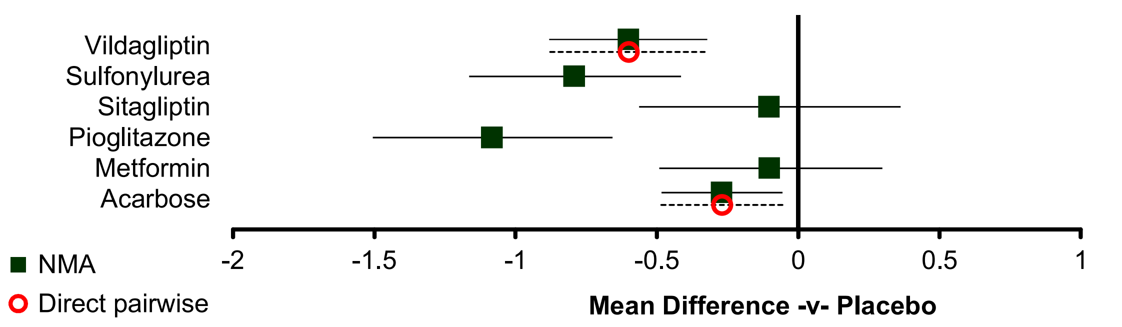
Table 50: Network meta-analysis of change in HbA1c (12 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	9 (8, 9)
Acarbose	0.023	7 (2, 8)
Metformin	0.159	3 (1, 5)
Pioglitazone	0.086	3 (1, 6)
repaglinide	0.364	2 (1, 6)
Sitagliptin	0.030	5 (1, 8)
Sulfonylurea	0.002	5 (3, 7)
Sulfonylurea (modified release)	0.335	4 (1, 9)
Vildagliptin	0.001	7 (5, 8)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 10: Network meta-analysis of change in HbA1c (24 months) – evidence network



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

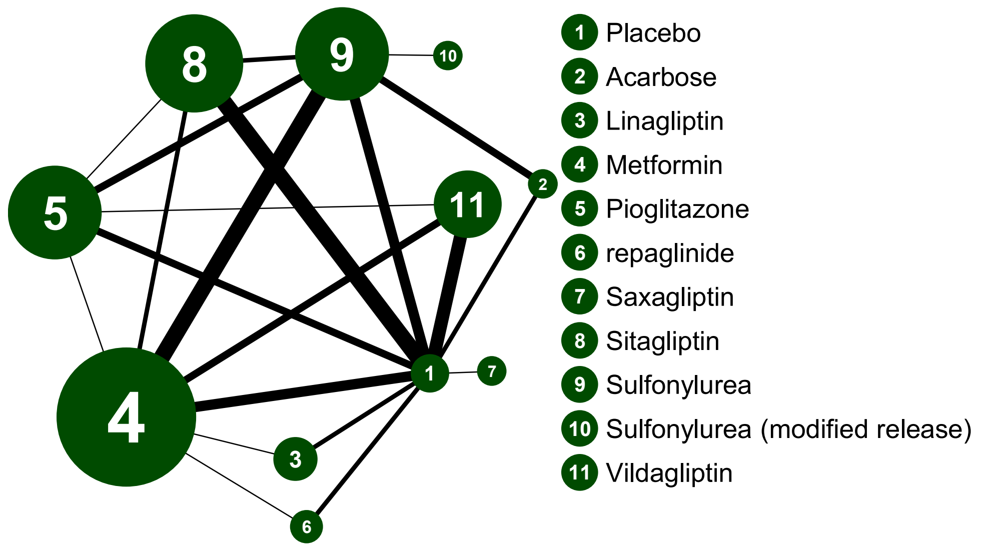
Figure 11: Network meta-analysis of change in HbA1c (24 months) – relative effect of all options compared with common comparator (placebo)

Table 51: Network meta-analysis of change in HbA1c (24 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	7 (5, 7)
Acarbose	0.000	4 (3, 6)
Metformin	0.000	6 (4, 7)
Pioglitazone	0.996	1 (1, 1)
Sitagliptin	0.000	6 (4, 7)
Sulfonylurea	0.002	2 (2, 3)
Vildagliptin	0.001	3 (2, 4)

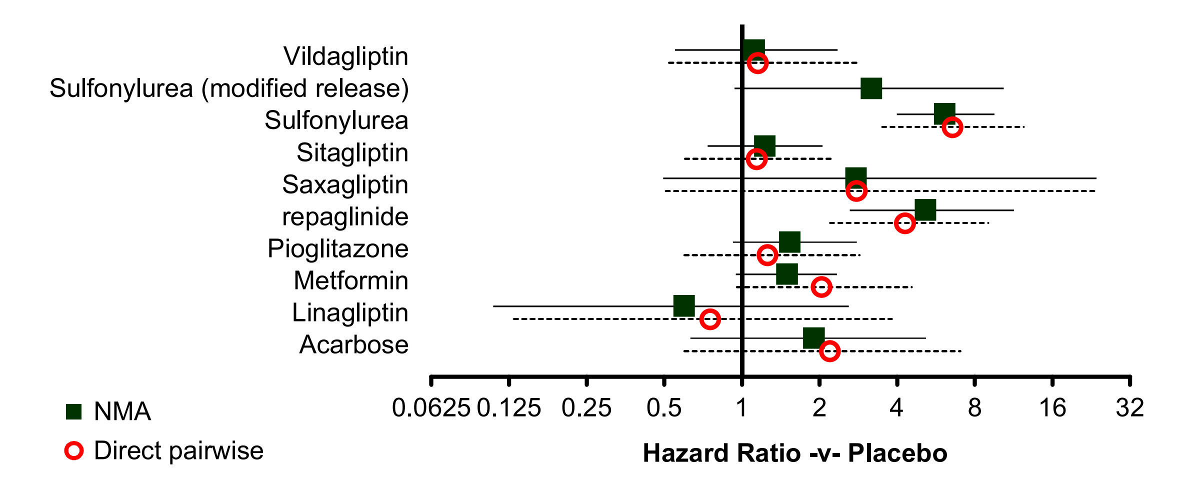
8.4.4.4 Hypoglycaemia at study end point

Results of the NMA are summarised below for the 10 treatment options that were compared with placebo. There is reasonable agreement between the NMA evidence and direct pairwise treatment effect estimates as demonstrated by the substantial overlap between the credible/confidence intervals. In general, there was lower incidence of hypoglycaemic events in the placebo group compared to the active interventions. While linagliptin had the highest individual probability of maximum effectiveness, it was associated with wide credible intervals (ranging from 1 to 8), indicating that this treatment option could credibly be ranked as low as 8^{th}.



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 12: Network meta-analysis of hypoglycaemic events (study end point) – evidence network



Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 13: Network meta-analysis of hypoglycaemic events (study end point) – relative effect of all options compared with common comparator (placebo)

Table 52: Network meta-analysis of hypoglycaemic events (study end point) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.100	3 (1, 5)
Acarbose	0.032	7 (1, 10)
Linagliptin	0.663	1 (1, 8)
Metformin	0.002	6 (3, 8)
Pioglitazone	0.005	6 (2, 8)
repaglinide	0.000	10 (8, 11)
Saxagliptin	0.052	8 (1, 11)
Sitagliptin	0.033	4 (1, 7)
Sulfonylurea	0.000	10 (9, 11)
Sulfonylurea (modified release)	0.008	8 (3, 11)
Vildagliptin	0.106	3 (1, 8)

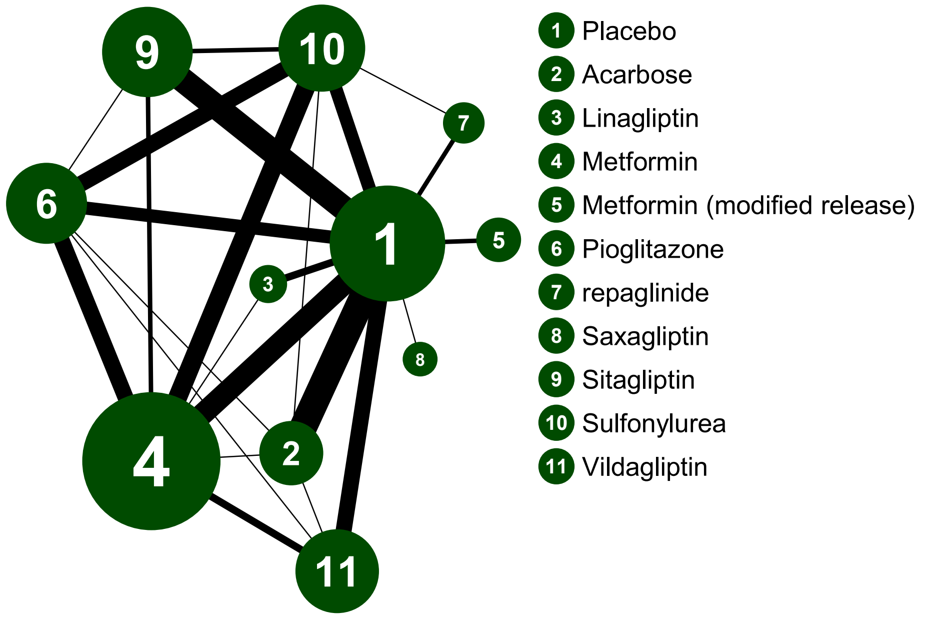
8.4.4.5 Adverse events at study end point

Results of the 3 NMAs are summarised below. For dropouts due to adverse events and total dropouts, 10 treatment options were compared with placebo, while 8 treatment options were compared with placebo for nausea.

There is moderate agreement between the NMA evidence and direct pairwise treatment effect estimates. There is substantial overlap between the credible/confidence intervals suggesting reasonable consistency between the direct and NMA evidence.

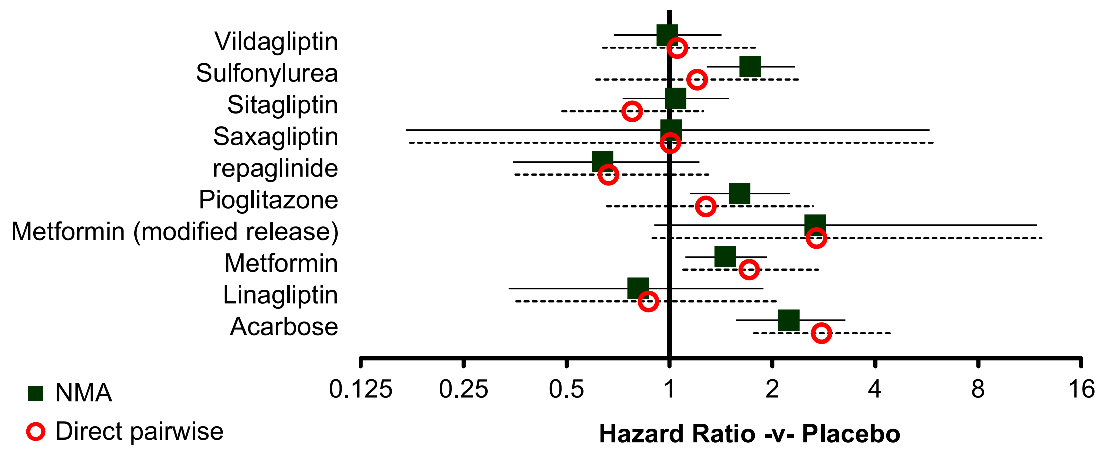
In general, active treatment options were effective at preventing total dropouts. However, active treatment options in the main were associated with higher dropouts due to adverse events and nausea when compared to placebo. Repaglinide and sulfonylurea (modified release) were associated with the highest probability of maximum effectiveness and highest median ranks for dropouts due to adverse events and total dropouts respectively, but these rankings were associated with wide credible intervals (1 to 6 and 1 to 11 respectively).

Similarly, placebo was associated with lower incidence of nausea when compared to active treatment options.



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 14: Network meta-analysis of dropouts due to adverse events (study end point) – evidence network

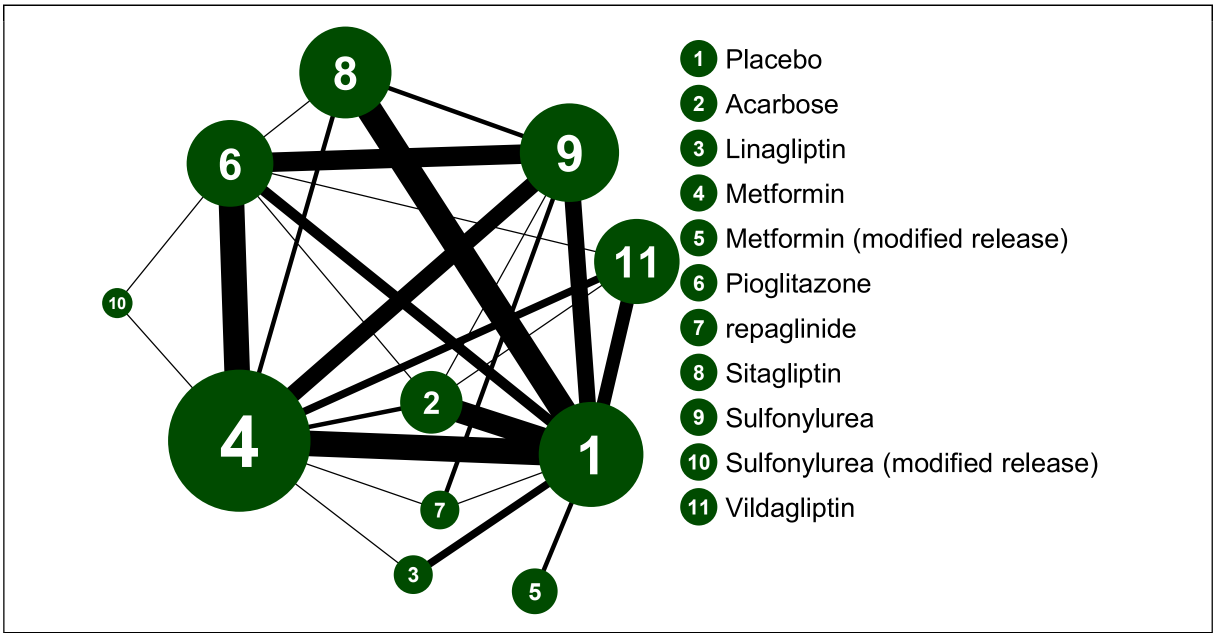


Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 15: Network meta-analysis of dropouts due to adverse events (study end point) – relative effect of all options compared with common comparator (placebo)

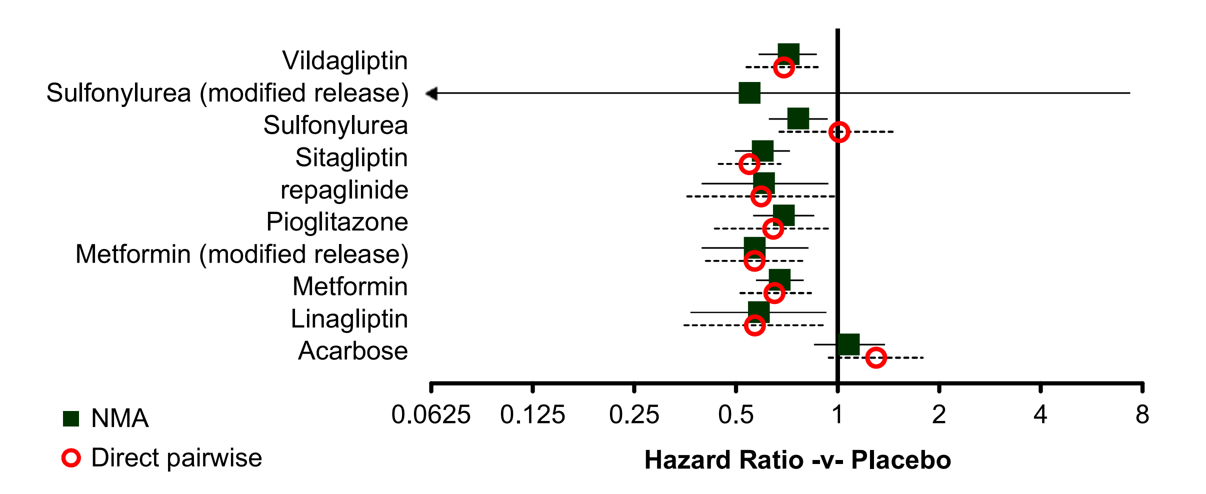
Table 53: Network meta-analysis of dropouts due to adverse events (study end point) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.004	4 (2, 6)
Acarbose	0.000	10 (8, 11)
Linagliptin	0.231	3 (1, 9)
Metformin	0.000	7 (5, 9)
Metformin (modified release)	0.003	11 (3, 11)
Pioglitazone	0.000	8 (6, 10)
repaglinide	0.462	2 (1, 6)
Saxagliptin	0.261	4 (1, 11)
Sitagliptin	0.013	5 (2, 7)
Sulfonylurea	0.000	9 (7, 10)
Vildagliptin	0.026	4 (1, 7)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 16: Network meta-analysis of total dropouts (study end point) – evidence network

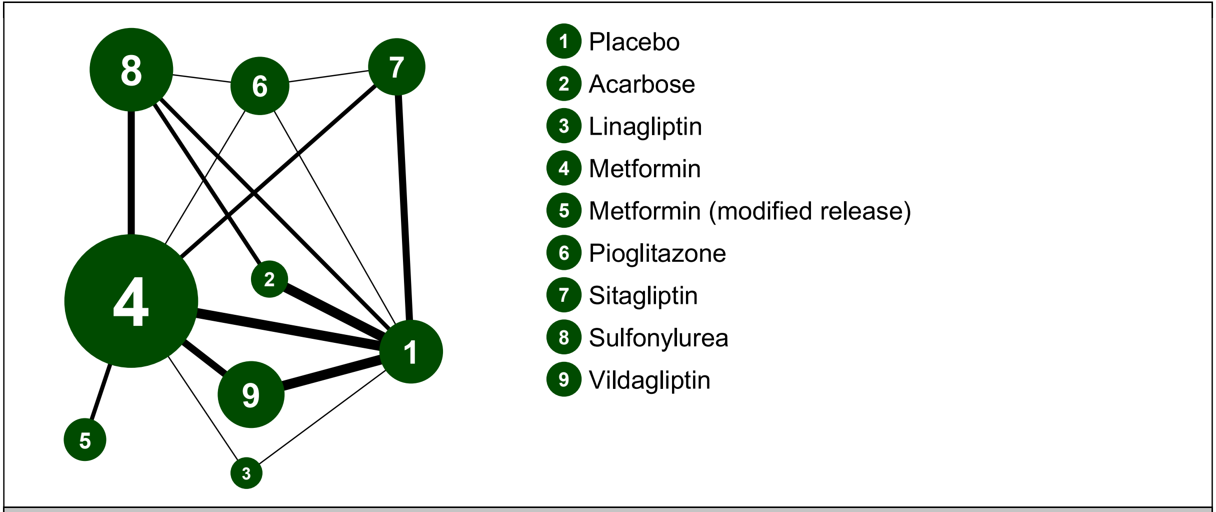


Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 17: Network meta-analysis of total dropouts (study end point) – relative effect of all options compared with common comparator (placebo)

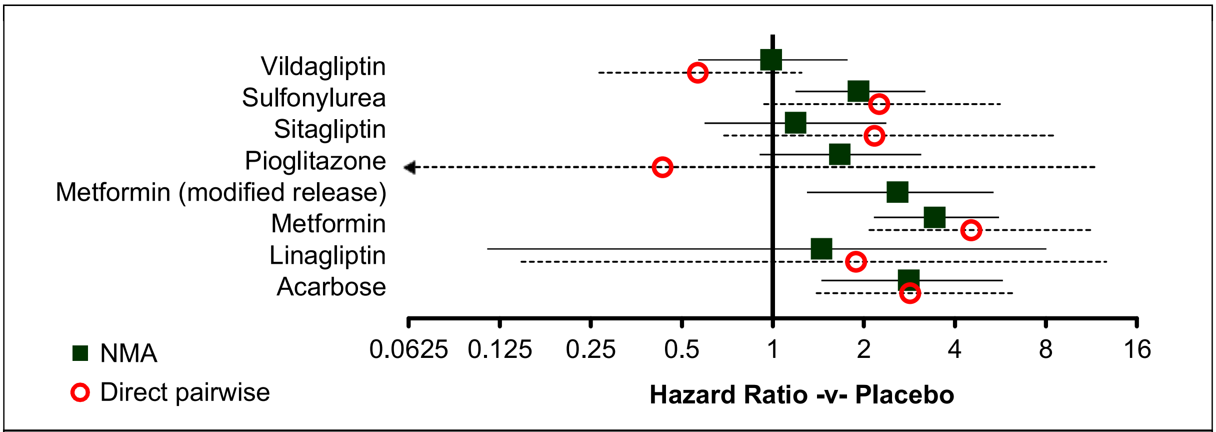
Table 54: Network meta-analysis of total dropouts (study end point) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	10 (9, 11)
Acarbose	0.000	11 (9, 11)
Linagliptin	0.167	3 (1, 9)
Metformin	0.003	5 (3, 8)
Metformin (modified release)	0.173	3 (1, 9)
Pioglitazone	0.004	6 (2, 9)
repaglinide	0.125	4 (1, 9)
Sitagliptin	0.061	3 (1, 7)
Sulfonylurea	0.000	8 (5, 9)
Sulfonylurea (modified release)	0.465	2 (1, 11)
Vildagliptin	0.003	7 (3, 9)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 18: Network meta-analysis of nausea (study end point) – evidence network



Values greater than 1 favour placebo; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

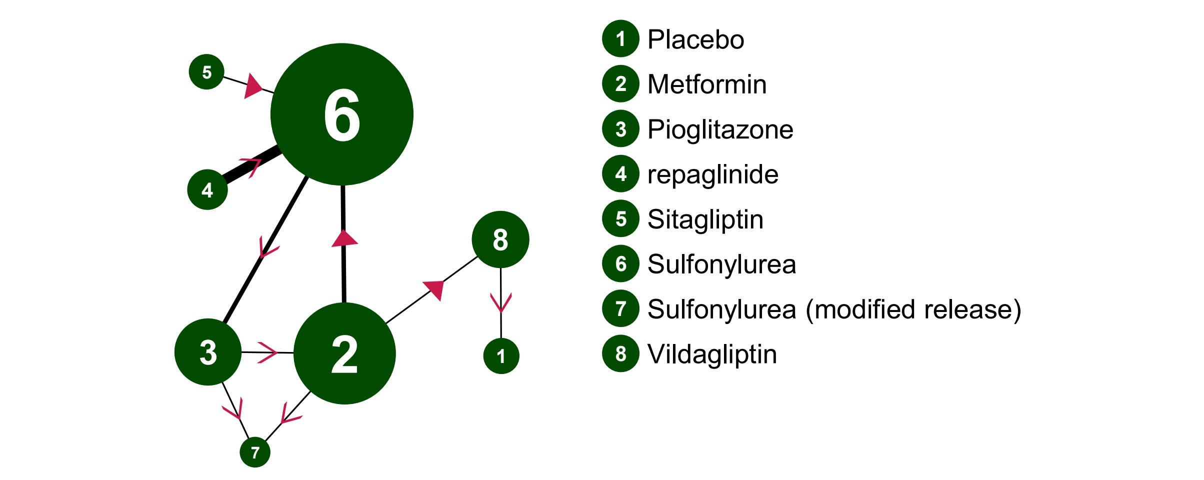
Figure 19: Network meta-analysis of nausea (study end point) – relative effect of all options compared with common comparator (placebo)

Table 55: Network meta-analysis of nausea (study end point) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.256	2 (1, 4)
Acarbose	0.000	8 (4, 9)
Linagliptin	0.306	4 (1, 9)
Metformin	0.000	8 (7, 9)
Metformin (modified release)	0.000	7 (4, 9)
Pioglitazone	0.006	5 (2, 7)
Sitagliptin	0.139	3 (1, 6)
Sulfonylurea	0.000	6 (4, 7)
Vildagliptin	0.292	2 (1, 4)

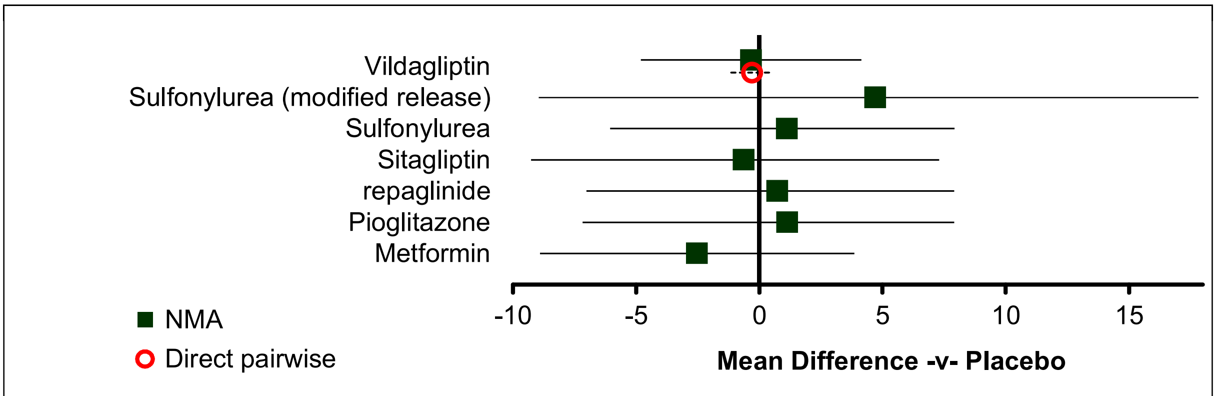
8.4.4.6 Change in body weight at 12 and 24 months

Results of the 2 NMAs are summarised below for the 7 and 5 treatment options that were compared with placebo at 12 and 24 months respectively. Where available, there was reasonable agreement in the NMA evidence and direct pairwise treatment effect estimates, with substantial overlap between the credible/confidence intervals. In general, metformin and sitagliptin (at 24 months only) were shown to be most effective at weight loss compared to placebo. However, the credible intervals associated with these relative effects were considerably wide. Metformin had the highest individual probability of maximum effectiveness and highest ranking at 12 and 24 months, with consistently narrow credible intervals surrounding the rankings (1 to 3 and 1 to 2 respectively).



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 20: Network meta-analysis of change in body weight (12 months) – evidence network

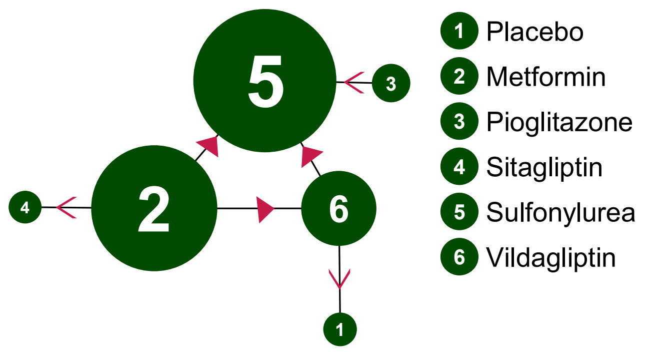


Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 21: Network meta-analysis of change in body weight (12 months) – relative effect of all options compared with common comparator (placebo)

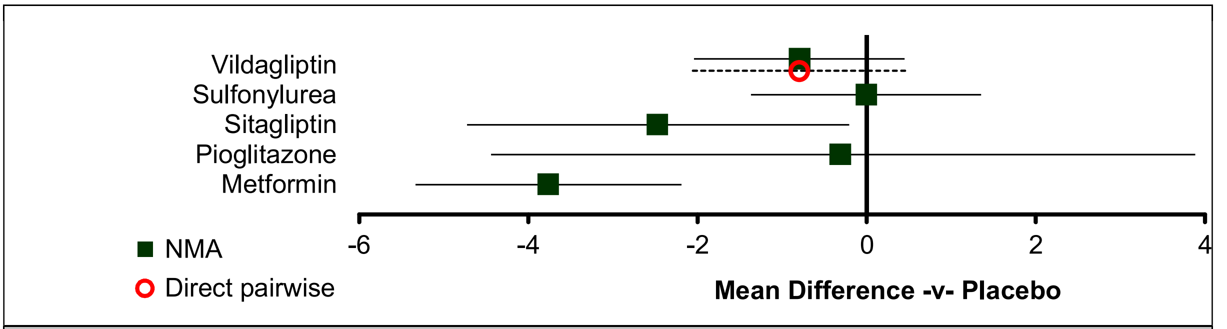
Table 56: Network meta-analysis of change in body weight (12 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.103	4 (1, 8)
Metformin	0.576	1 (1, 4)
Pioglitazone	0.018	6 (2, 8)
repaglinide	0.018	5 (2, 8)
Sitagliptin	0.141	3 (1, 8)
Sulfonylurea	0.001	6 (3, 8)
Sulfonylurea (modified release)	0.101	8 (1, 8)
Vildagliptin	0.043	4 (1, 8)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 22: Network meta-analysis of change in body weight (24 months) – evidence network



Values greater than 0 favour placebo; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 23: Network meta-analysis of change in body weight (24 months) – relative effect of all options compared with common comparator (placebo)

Table 57: Network meta-analysis of change in body weight (24 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Placebo	0.000	5 (3, 6)
Metformin	0.893	1 (1, 2)
Pioglitazone	0.047	4 (1, 6)
Sitagliptin	0.060	2 (1, 4)
Sulfonylurea	0.000	5 (4, 6)
Vildagliptin	0.000	3 (3, 5)

8.4.5 Health economic evidence for initial therapy

For initial therapy, no CUAs met the UK inclusion criteria and only 2 studies were found worldwide. Therefore, an original economic analysis was undertaken.

For initial therapy, 7 treatments could be modelled. People accrued an average of 18.3 undiscounted life years, of which 3.4 years were spent on initial therapy and 3.1 were spent on first intensification therapy. There was little difference in lifetime complication rates, because of small differences in HbA1c treatment effects and the normalising effects of treatment intensification.

People accumulated an average of 9.0 lifetime discounted QALYs, with most loss coming from weight profiles and differences driven by weight treatment effects. Treatment-related costs accounted for most variation in lifetime discounted costs.

Initial therapy with metformin incurred the lowest lifetime discounted costs and gained most lifetime discounted QALYs and therefore metformin dominated all other treatment options (see table 58).

Table 58: Mean lifetime incremental cost–utility results for initial therapy

	Lifetime discounted		Incremental		
Therapy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Metformin -> Met-SU -> Met-I(NPH)	£19,250	9.033			
Repaglinide -> Met-SU -> Met-I(NPH)	£19,298	8.974	£48	-0.059	Dominated
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,412	8.973	£163	-0.060	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,580	8.950	£330	-0.082	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,043	8.912	£794	-0.121	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,457	8.990	£1207	-0.043	Dominated
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,627	8.954	£1377	-0.078	Dominated

(a) Met-SU = Metformin-Sulfonylurea
(b) Met-I(NPH) = Metformin-NPH insulin

For people who could not tolerate metformin, repaglinide was the most cost-effective treatment option (see table 59). If people were unwilling to take repaglinide at initial therapy (as it would require switching to 2 different drugs at first intensification), pioglitazone was the treatment option with the lowest lifetime discounted costs; sitagliptin had an ICER of £62,500 per QALY compared with pioglitazone (see table 60).

If people could not tolerate metformin, could not tolerate or did not wish to take repaglinide and were contraindicated for pioglitazone, sulfonylurea was the treatment option with the lowest lifetime discounted costs and sitagliptin had an ICER of £22,300 per QALY (see Table 61).

Table 59: Mean lifetime incremental cost–utility results for initial therapy when metformin is not a treatment option

	Lifetime discounted		Incremental		
Therapy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Repaglinide -> Met-SU -> Met-I(NPH)	£19,298	8.974			
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,412	8.973	£115	-0.001	Dominated
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,580	8.950	£282	-0.024	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,043	8.912	£746	-0.062	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,457	8.990	£1159	0.016	£73,287
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,627	8.954	£170	-0.035	Dominated

(a) Met-SU = Metformin-Sulfonylurea
(b) Met-I(NPH) = Metformin-NPH insulin

Table 60: Mean lifetime incremental cost–utility results for initial therapy when metformin and repaglinide are not treatment options

	Lifetime discounted		Incremental		
Therapy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
Pioglitazone -> Met-SU -> Met-I(NPH)	£19,412	8.973			
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,580	8.950	£167	-0.023	Dominated
Placebo -> Met-SU -> Met-I(NPH)	£20,043	8.912	£631	-0.061	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,457	8.990	£1044	0.017	£62,473
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,627	8.954	£170	-0.035	Dominated

(a) Met-SU = Metformin-Sulfonylurea
(b) Met-I(NPH) = Metformin-NPH insulin

Table 61: Mean lifetime incremental cost–utility results for initial therapy when neither metformin, repaglinide nor pioglitazone are treatment options

Therapy	Lifetime discounted		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Sulfonylurea -> Met-SU -> Met-I(NPH)	£19,580	8.950			
Placebo -> Met-SU -> Met-I(NPH)	£20,043	8.912	£464	-0.039	Dominated
Sitagliptin -> Met-SU -> Met-I(NPH)	£20,457	8.990	£877	0.039	£22,256
Vildagliptin -> Met-SU -> Met-I(NPH)	£20,627	8.954	£170	-0.035	Dominated

(a) Met-SU = Metformin-Sulfonylurea
(b) Met-I(NPH) = Metformin-NPH insulin

Over 1000 PSA iterations, metformin was the most cost effective of the initial therapy treatments in 88% of iterations at a maximum acceptable ICER of £20,000 per QALY (see figure 24).

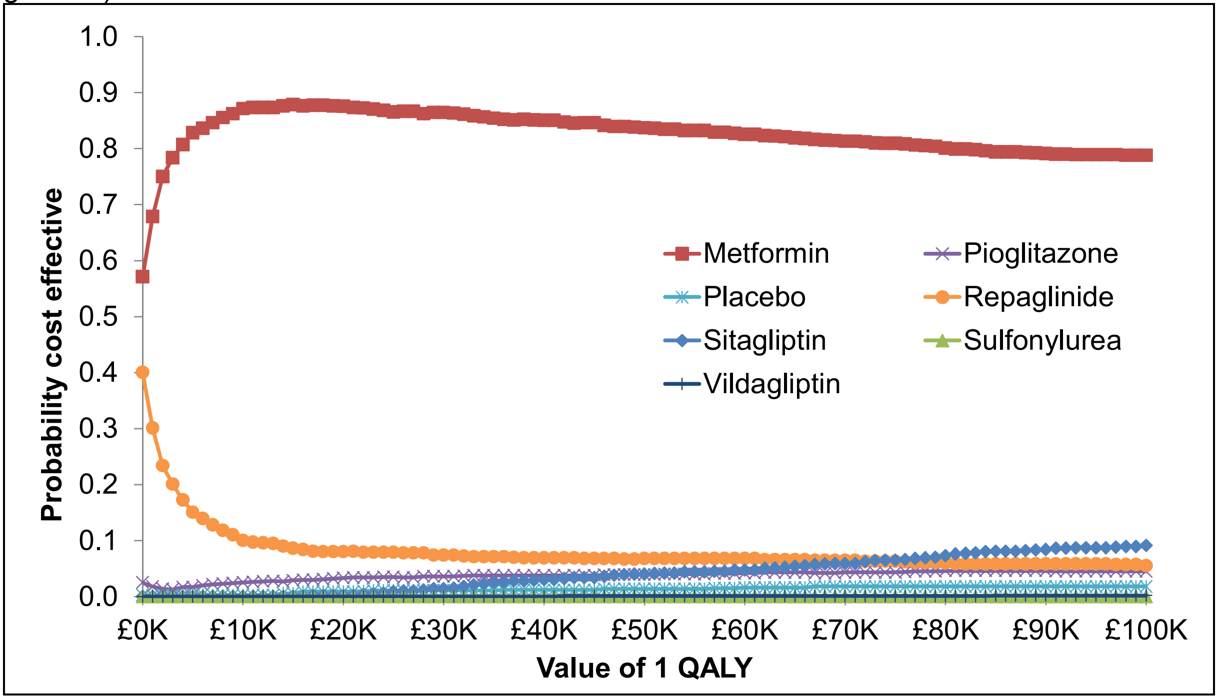


Figure 24: Cost-effectiveness acceptability curve for initial therapy

For people who could not tolerate metformin, repaglinide was the most cost-effective initial therapy at a maximum acceptable ICER of £20,000 per QALY in 45% of iterations, with pioglitazone the most cost-effective initial therapy in 35% of iterations (see figure 25).

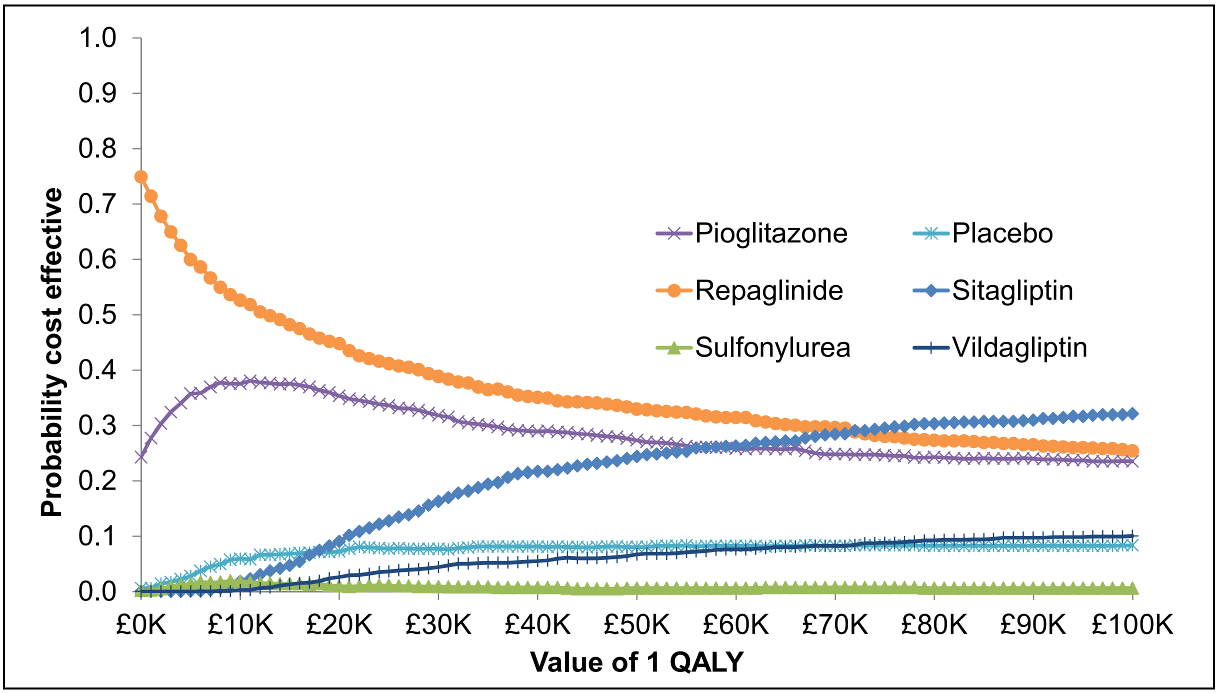


Figure 25: Cost-effectiveness acceptability curve for initial therapy when metformin is not a treatment option

For people who could not tolerate metformin, could not tolerate or choose not to initiate therapy with repaglinide and were contraindicated for pioglitazone, sitagliptin (most cost-effective in 38% of iterations) and sulfonylurea (most cost-effective in 37% of iterations) were the most cost-effective initial therapy treatment options at a maximum acceptable ICER of £20,000/QALY (see figure 26).

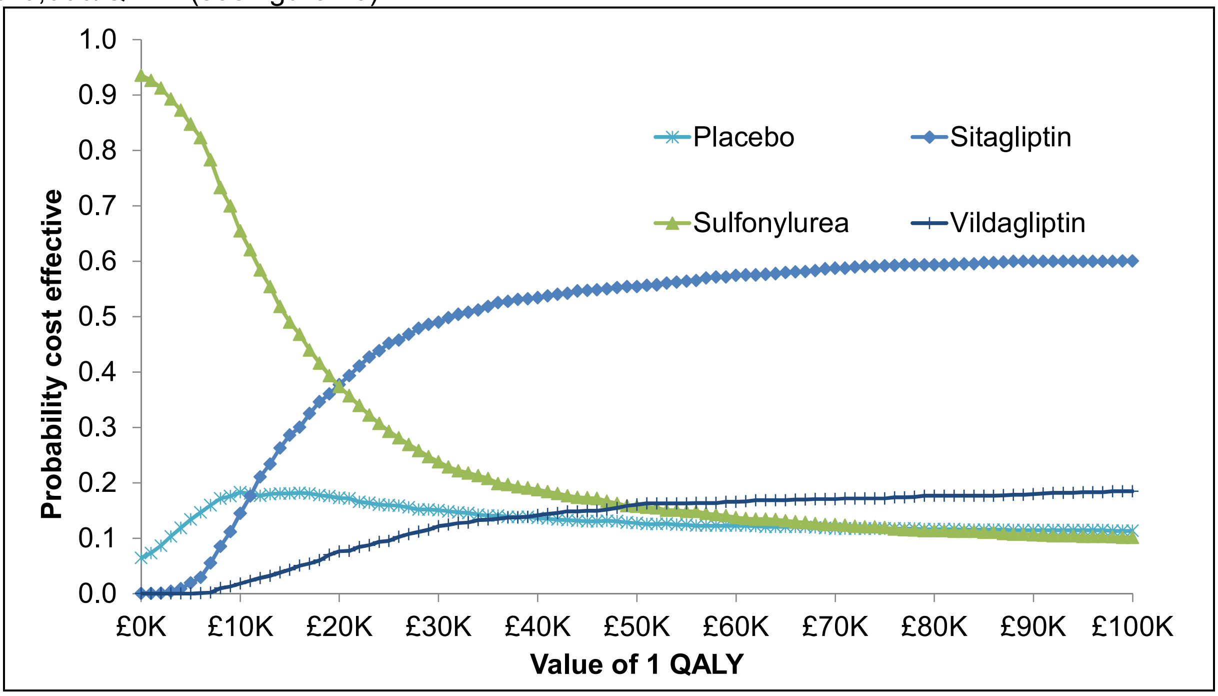


Figure 26: Cost-effectiveness acceptability curve for initial therapy when neither metformin, repaglinide nor pioglitazone are treatment options

8.4.6 Evidence statements for initial therapy

8.4.6.1 Clinical evidence

8.4.6.1.1 Change in blood glucose

Evidence from 4 network meta-analyses including data from 68, 62, 21 and 6 RCTs at 3, 6, 12 and 24 months respectively for HbA1c levels showed that repaglinide was consistently associated with higher rankings at 3 (median rank 1 [95% credible interval 1 to 3]), 6 (median rank 1 [1 to 3]) and 12 months of follow-up (median rank 2 [1 to 6]). Sulfonylurea demonstrated high rankings at 3 (median rank 3 [2 to 5]), 6 (median rank 3 [2 to 5]) and 24 months (median rank 2 [2 to 3]). Pioglitazone had the highest ranking at 24 months (median rank 1 [1, 1]). The quality of the evidence was moderate to low.

8.4.6.1.2 Hypoglycaemia at study end point

Evidence from a single network meta-analysis of 44 RCTs showed that repaglinide (median rank 10 [8 to 11]) and sulfonylurea (median rank 10 [9 to 11]) were associated with low rankings which may suggest higher rates of hypoglycaemia. In contrast, linagliptin (median rank 1 [1 to 8]) had the highest ranking but was associated with wide credible intervals. The quality of the evidence was low.

8.4.6.1.3 Adverse events at study end point

Evidence from 3 network meta-analyses incorporating data from 73, 73 and 29 RCTs for adverse events, total dropouts and nausea respectively showed that repaglinide, sulfonylurea (modified release) and vildagliptin were associated with the highest rankings for dropouts due to adverse events, total dropouts and nausea respectively. However, these rankings were associated with wide credible intervals. The quality of the evidence was low.

8.4.6.1.4 Change in body weight

Evidence from 2 network meta-analyses incorporating 12 and 6 RCTs at 12 and 24 months respectively showed that metformin was associated with the highest ranking at 12 (median rank 1 [1 to 3]) and 24 (median rank 1 [1 to 2]) months, suggesting that it is effective in weight loss. Sulfonylurea (standard and modified release) and pioglitazone were associated with lower rankings which may suggest worse weight related outcomes. The quality of the evidence was low.

8.4.6.2 Health economic evidence

A directly applicable health economic model with potentially serious limitations found metformin was less costly and more effective than all other modelled options for initial therapy. For people who could not take metformin, repaglinide was the most cost-effective option. If people were unwilling to take repaglinide, pioglitazone was the most cost-effective option; for people who could not take metformin, repaglinide or pioglitazone, sulfonylurea or sitagliptin were cost-effective modelled options.

8.4.7 Evidence to recommendations for initial therapy

Table 62: Linking evidence to recommendations

Relative value of different outcomes	The GDG agreed that the critical outcomes to consider were glycaemic control (change in HbA1c), hypoglycaemia and adverse events. The GDG agreed that an important outcome to consider was change in body weight.

	Oral anti-diabetic medicines are only used when diet and lifestyle have not demonstrated an optimal benefit, in terms of lowering or maintaining HbA1c levels. These interventions are important because type 2 diabetes is a progressive condition and review in previous chapters has shown the increased risk of complications and mortality associated with higher levels of HbA1c. While the GDG noted that glycaemic control was important in mitigating the increased risk of microvascular and macrovascular complications associated with hyperglycaemia, they also acknowledged that tight glycaemic control may be associated with increased risk of hypoglycaemia. Increased rates of hypoglycaemia can lead to non-compliance with therapy and the person experiencing increased stress and anxiety associated with a detrimental effect on quality of life. It may also increase the risk of hypoglycaemia unawareness leading to more severe hypoglycaemia. Drug intolerability (because of adverse effects) and change in body weight have a negative impact on overall diabetes management and on the person's quality of life. Type 2 diabetes is associated with clinical obesity and medication that results in weight gain will likely further impact on the person's self-esteem and negatively affect quality of life. The relative importance of each outcome is further dependent on several factors: • Short-term (3 and 6 months) versus long-term (12 and 24 months) evaluation. For example, glucose levels are important at 3 and 6 months, but at 12 and 24 months both glucose levels and adverse events are important. Adverse events and change in body weight are also likely to be reflected at longer time points. • Severity of hyperglycaemia. • Individual circumstances, such as comorbidities. As medicine reviews for new treatments are usually at 3 and 6 months and maintenance reviews are held annually, these are important time points to note initially the presence of adverse effects and the effect of the medicine on glycaemic control.
Trade-off between benefits and harms	The GDG discussed the results of the network meta-analyses (NMAs) and noted that there were more data available at 3, 6 and 12 months, whereas at 24 months there was less evidence resulting in sparser networks and a limited number of interventions. Overall, the networks included 12 comparators including placebo. Of these 12 comparators, 7 included data for all required outcomes in the health economic model. The 5 interventions that were not included in the health economic model were acarbose, metformin (modified release), sulfonylurea (modified release), linagliptin and saxagliptin. Of these, the GDG referred to their experience that linagliptin and saxagliptin would be expected to perform well if data were available for inclusion in these analyses. The GDG agreed that, while standard-release metformin was not associated with the greatest reduction in HbA1c in the reviewed evidence, the additional cardiovascular benefits associated with metformin use are very important in the overall long-term management of type 2 diabetes. Moreover, metformin was

	associated with fewer hypoglycaemic events, and weight loss at 12 and 24 months, which are considered important for people's quality of life. The GDG also discussed the use of gradual dosing and titration of metformin which may help to reduce gastrointestinal adverse events. The GDG noted that there was limited evidence on alternative forms of metformin for people who cannot tolerate standard-release metformin. The GDG agreed that based on clinical experience, a trial of modified-release metformin should be considered as an alternative for people who are unable to tolerate standard-release metformin because of gastrointestinal side effects. The GDG agreed that the additional cardiovascular benefits associated with metformin use warranted a trial of modified-release metformin. The GDG also noted that this routinely occurs in standard practice. The GDG noted that no studies were identified that investigated the effects of different drug treatments in people intolerant of metformin therapy or for whom it was contraindicated. The GDG discussed the evidence surrounding the remaining drug interventions within the NMAs and agreed that in the absence of specific data on people who could not tolerate metformin or for whom it was contraindicated, the effectiveness of alternative treatments in the analyses should be extrapolated to inform equal treatment options for this small group of people that could be switched depending on tolerability. The GDG noted that although sulfonylureas were associated with clinically important reductions in HbA1c in the short term at 3 and 6 months, they were consistently associated with greater hypoglycaemic events and weight gain at 12 and 24 months. The GDG noted that the occurrence of hypoglycaemic events was consistent with their experiences in clinical practice. The GDG discussed the value of using sulfonylureas to achieve rapid blood glucose control (rescue therapy) in clinical practice, but considered that the use of sulfonylureas as an immediate second option if metformin is contraindicated or not tolerated was not supported by the evidence base, because of the short-term efficacy in change in HbA1c and associated increased risks of adverse events including hypoglycaemia. The GDG agreed that use of sulfonylurea as rescue therapy should consider the balance of good glycaemic control and the risk of poor weight outcomes and hypoglycaemia in discussion with patients and therefore treatment should be reviewed once agreed targets have been met. The GDG noted the limited evidence (2 trials) available for modified-release sulfonylurea which did not show it to be better than alternative options. The GDG noted that the main advantage of modified-release sulfonylurea was the need to take fewer tables but agreed that there were alternative drugs within the sulfonylurea class that could be administered once a day. The GDG agreed that given the greater cost associated with modified-release sulfonylurea and lack of evidence, this option could not be recommended. The GDG then considered repaglinide, which was shown to be consistently associated with the largest reduction in HbA1c at 3, 6 and 12 months, but also with a greater number of hypoglycaemic events. The GDG also noted that the occurrence of hypoglycaemic events was consistent with their experience in clinical practice. The GDG considered the change in body weight associated with

	repaglinide, and agreed that while it was associated with weight gain it fared better than sulfonylureas for this outcome. The GDG recognised that repaglinide is a secretagogue not widely used in current UK clinical practice and that a recommendation to offer repaglinide as an alternative initial therapy when metformin is contraindicated or not tolerated would lead to a large change in practice but considered that given the consistent findings of significantly large clinically important reductions in HbA1c up to 1 year shown in the evidence, healthcare professionals should be made aware of the available clinical and cost-effectiveness evidence supporting the use of this drug. Moreover, the high likelihood that treatment intensification would become necessary meant that the potential role of repaglinide as an initial therapy option is constrained by the fact that it is presently only licensed in combination with metformin. This means that if repaglinide does not lead to optimal results as initial therapy, then there are no licensed options to intensify with another antihyperglycaemic medicine. The GDG considered that people should be made aware of this constraint before starting drug treatment. The GDG discussed the impact that these constraints may have on implementation and clinical practice. The GDG discussed the evidence on the use of pioglitazone and sitagliptin, which showed similar profiles in terms of change in HbA1c and adverse events. While pioglitazone was associated with the greater reduction in HbA1c at 24 months, sitagliptin was associated with less hypoglycaemia and weight loss at 12 and 24 months. The GDG discussed the long-term safety concerns associated with the use of pioglitazone and DPP-4 inhibitors, and agreed that Medicines and Healthcare products Regulatory Agency (MHRA) guidance and patient suitability should be considered. For example, pioglitazone is not recommended for people with active bladder cancer, a history of bladder cancer or uninvestigated haematuria, or for people with heart failure or a risk of osteoporosis. The GDG noted that there was limited information on the long-term safety of DPP-4 inhibitors but considered the evidence was strong enough to recommend these as treatment options if both metformin and repaglinide were contraindicated, not tolerated or not preferred. While vildagliptin generally showed less reduction for change in HbA1c at 3, 6 and 12 months, a relatively greater reduction was observed at 24 months. High to middle rankings were observed for hypoglycaemia, dropouts due to adverse events, nausea and changes in body weight at 12 and 24 months. However, overall, many point estimates were associated with large credible intervals indicating uncertainty around the data.
Consideration of health benefits and resource use	The GDG were happy to recommend metformin as initial therapy for people with type 2 diabetes, because it clearly dominated the other treatments that could be modelled. The GDG noted that, if metformin is associated with longer term cardiovascular benefits over and above those associated with reduction of HbA1c, these would not be reflected in the economic model. While such future outcomes would be discounted, the GDG noted their inclusion may further improve the cost effectiveness of metformin. Equally, the model did not reflect potential long-term safety concerns of pioglitazone, DPP-4 inhibitors and sulfonylureas that could decrease their cost effectiveness.

	Because of a lack of included evidence, it was not possible to include modified-release metformin within the health economic modelling. On the basis of their clinical experience, the GDG considered that modified-release metformin would be likely to have similar HbA1c, hypoglycaemia and weight treatment effects to standard-release metformin. A perceived reduction in gastrointestinal adverse events may give modified-release metformin a lower dropout rate because of adverse events than standard-release metformin. On balance, the GDG was happy to recommend modified-release metformin as an alternative to standard-release metformin because it was likely to be similarly cost-effective (or at least more cost-effective than non-metformin alternatives). For people not able to take metformin, either because it is contraindicated or not tolerated, repaglinide was the most cost-effective option. However, the GDG noted that repaglinide is not licensed for combination use with any drug other than metformin. This means that future intensifications of treatment – that is, when HbA1c is no longer controlled by initial drug treatment alone – would not be straightforward for people taking repaglinide and could incur further costs related to extra healthcare professional appointments. Thus, the GDG discussed what the most cost-effective initial therapy was for people who could not take metformin and did not wish to take repaglinide. Of the remaining drugs modelled, pioglitazone had the lowest lifetime discounted costs. The GDG discussed the known contraindications for pioglitazone and that the vast majority of people would be taking metformin. The GDG agreed that repaglinide, sulfonylurea or sitagliptin were alternative options for initial therapy. Cost and quality-adjusted life year (QALY) differences between treatment options at initial therapy were small because of the normalising effect of future intensifications in the economic model – simulated people were only on their initial therapies for an average of 3.4 years. QALY differences were driven by differences in weight gained, both from initial therapy itself and differences in time until intensification. Cost differences were largely because of the costs of the drugs themselves. The economic model used a 1-year cycle and the GDG noted that this may not fully reflect the clinical utility of treatments such as sulfonylurea and repaglinide that may achieve shorter term HbA1c benefits that may not be sustained at 1 year. In contrast, the economic model did reflect the low rankings at 1 year for hypoglycaemia and body weight for these treatments. The GDG appreciated the ability of the model to combine all modelled outcomes. The GDG queried whether dosing differences may have driven different uptake patterns, because sulfonylureas are generally taken once daily whereas repaglinide is taken multiple times daily. However, it was noted that metformin is also taken multiple times daily so the GDG considered it was unlikely that any disutility or increased dropout rate would be associated with repaglinide because of multiple daily tablets. It was noted by the GDG that, unlike the health economic evidence, the clinical evidence did not provide support for a strict hierarchy of non-metformin treatment options. Also, the clinical evidence for non-metformin treatment options was not directly relevant to the

	population in question, because it covered populations taking non-metformin treatment options as alternative treatment options rather than because of intolerances to or contraindications for metformin therapy. Given this lack of direct evidence, the likely small proportion of the type 2 diabetes population who would be taking non-metformin treatment options and that all the non-metformin treatment options are associated with safety concerns, intensification issues and/or weight gain, the GDG agreed it was appropriate to recommend that people with type 2 diabetes could be considered for any of the alternative treatment options as part of their individiualised care.
Quality of the evidence	The GDG agreed that the overall quality of the evidence for initial therapy was generally moderate.
Other considerations	When defining the decision problem for this question, the GDG preferred not to make an *a priori* assumption of class effect across DPP-4 inhibitors. Therefore, each individual option for which evidence was available was analysed separately. Having reviewed the assembled evidence for each phase of treatment, the GDG noted that it was difficult to judge whether the different DPP-4 inhibitors could, in fact, be considered interchangeable: • In a few areas, a case could be made for the superiority of 1 option over another (for example, at initial therapy, sitagliptin seemed to have somewhat superior benefits to vildagliptin at similar net costs). • In other areas, all the DPP-4 inhibitors for which evidence was available appeared to have very similar benefits, harms and costs (for example, in combination with metformin at first intensification). • Elsewhere in the treatment pathway, evidence was extremely limited (for example, sitagliptin–metformin–sulfonylurea was the only treatment combination for which evidence was available at second intensification) or absent (for example, at first intensification, there was no evidence that could be used to assess the relative clinical effectiveness and cost effectiveness of DPP-4 inhibitors in combination with pioglitazone or sulfonylureas). Having considered these different situations, the GDG concluded that the most helpful recommendations would be ones that treated DPP-4 inhibitors as a class. Had it been presented with evidence that suggested that 1 or more of the options was superior to others across all phases of treatment, the GDG would clearly have been inclined to favour such option(s) in its recommendations. However, the picture that had emerged was much more sporadic, and the GDG was not confident that any apparent dissimilarities between options represented real differences that would be expected in clinical practice. Moreover, the GDG was mindful that a series of recommendations that alternated between treating DPP-4 inhibitors as a class, in some parts of the treatment pathway, and focusing on individual options in others would be confusing to readers of the guideline, even if those recommendations could be directly allied with the available evidence. For all of these reasons, the GDG took the view that recommendations should consistently refer to DPP-4 inhibitors as a class. It was a natural extension of this principle that prescribers should be encouraged to select the individual DPP-4 inhibitor with the lowest acquisition cost available to them, where all other factors are equal for example, licensed indications/combinations.

	The GDG discussed the multiple factors that should be considered when selecting drug treatments. The GDG agreed that the benefits and risks should be discussed with the person and selecting specific drugs should involve an assessment of the effectiveness of the medicine(s) (in terms of metabolic response), safety (MHRA guidance) and tolerability of the medicine(s), person's clinical circumstances (for example, comorbidities, polypharmacy), person's preferences and needs, licensed indications or combinations and costs (where 2 medicines in the same class are appropriate, the option with the lowest acquisition cost should be selected).

8.4.8 Clinical evidence review for first intensification

In total 17,037 references were found for the main review question and 47 papers were included for first intensification which relate to 34 trials.

This sub-review question addressed which treatment combination of 2 non-insulin based options is most effective when people with type 2 diabetes have inadequate blood glucose control, typically following management with diet and a single oral antidiabetic medicine.

RCTs of at least 12 week treatment duration comparing dual therapies of 2 non-insulin based treatments were included. In contrast to initial therapy, it was assumed that most patients would be titrated to the maximal tolerated doses of previous oral therapy before starting a trial. Therefore, trials that did not report specific doses of continued previous therapy were still included (see section 8.4.2 for the main exclusion criteria).

8.4.8.1 Description of included studies for first intensification

A total of 17,835 participants in 34 RCTs were included. The majority of studies were carried out in multiple centres across different countries. The mean age ranged from 50.8 to 63.2 years, with 3 studies not reporting this information. Mean HbA1c levels at baseline ranged from 54 to 77 mmol/mol (7.1% to 9.2 %), with 1 study not reporting this information. The mean BMI ranged from 22.9 to 51.5 kg/m^2, with 1 study not reporting this information. Mean duration of diabetes ranged from 1.9 to 8.6 years, with 8 studies not reporting this information. Follow-up periods ranged from 12 to 156 weeks. For full details of the included studies see Appendix E.

8.4.8.2 Network meta-analyses for first intensification

To facilitate comparison across all available treatment options, 10 network meta-analyses were performed for all 3 critical and 1 important outcomes – change in HbA1c at 3, 6, 12 and 24 months, hypoglycaemia at study end point, adverse events (that is, dropouts due to adverse events, total dropouts and nausea) at study end point and change in body weight at 12 and 24 months. Metformin-sulfonylurea was selected as the reference treatment option as this combination was considered to reflect current standard clinical practice. Full details of methods and additional NMA outputs are provided in Appendix J.

Generally, well-connected networks were produced for shorter follow-up times although these tended to be sparser and contained fewer treatment options at 12 and 24 months. Pairwise comparisons that did not form part of the main network were not presented as they would not add to the GDG decision making.

On the whole, the quality of the evidence was moderate to low as networks were relatively well-connected by a star shaped network with metformin-sulfonylurea treatment in the middle. However some included trials were not double-blind and did not report adequate details of randomisation and allocation concealment methods. It was noted that random-effects models tended to estimate a fairly large inter-study heterogeneity term, which will reduce the precision of effect estimates.

Table 63: GRADE profile for network meta-analyses for first intensification

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in blood glucose (HbA1c)						
3 months	20	not serious[1]	not serious[2]	not serious[3]	serious[4]	Moderate
6 months	22	not serious[1]	not serious[2]	not serious[3]	serious[4]	Moderate
12 months	16	not serious[1]	not serious[2]	not serious[3]	serious[4]	Moderate
24 months	6	not serious[1]	not serious[2]	not serious[3]	serious[4]	Moderate
Hypoglycaemia at study end point						
Study end point	21	not serious[1]	serious[5]	not serious[3]	serious[4]	Low
Adverse events at study end point						
Dropouts due to adverse events	27	not serious[1]	serious[5]	not serious[3]	serious[4]	Low
Total dropouts	29	not serious[1]	not serious[2]	not serious[3]	serious[4]	Moderate
Nausea	11	not serious[1]	serious[5]	not serious[3]	serious[4]	Low
Change in body weight						
12 months	8	not serious[1]	serious[5]	not serious[3]	serious[4]	Low
24 months	8	not serious[1]	serious[5]	not serious[3]	serious[4]	Low

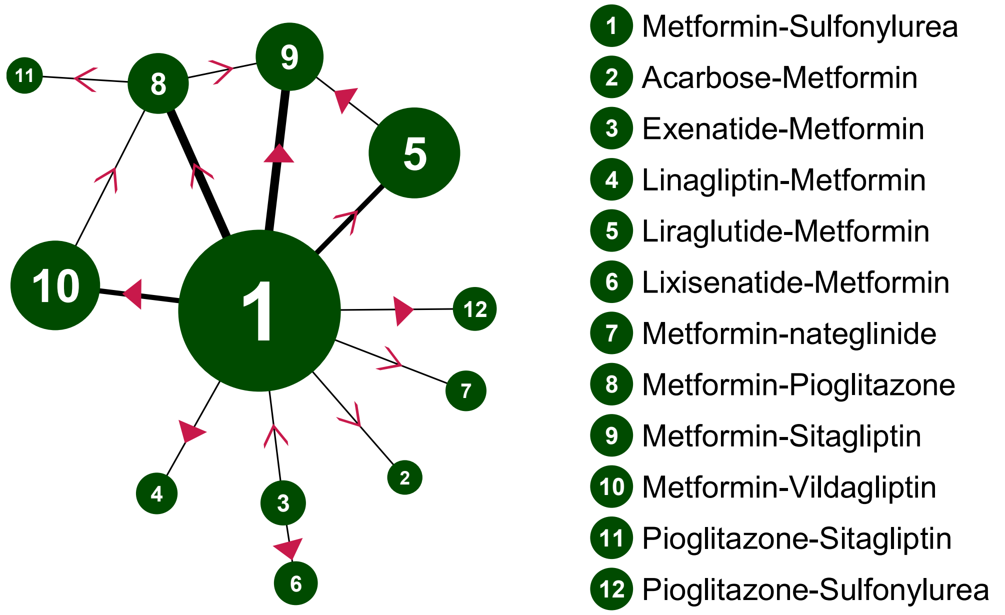
[1]Baseline HbA1c ranged from 7.1 to 9.9%
[2]Assessed based on residual deviance, deviance information criterion and tau^2 (tau^2<0.5)
[3]Considered not serious as population, interventions, comparator and outcomes are as defined in protocol
[4]Downgrade 1 level: no interventions had probability of being best and worse ≥0.5
[5]Downgrade 1 level: tau^2≥0.5

8.4.8.3 Change in blood glucose (HbA1c) at 3, 6, 12 and 24 months

Results of the NMAs are summarised below for the 11 treatment options that were compared with metformin-sulfonylurea at 3 and 6 months, and the 10 and 6 treatment options assessed at 12 and 24 months respectively.

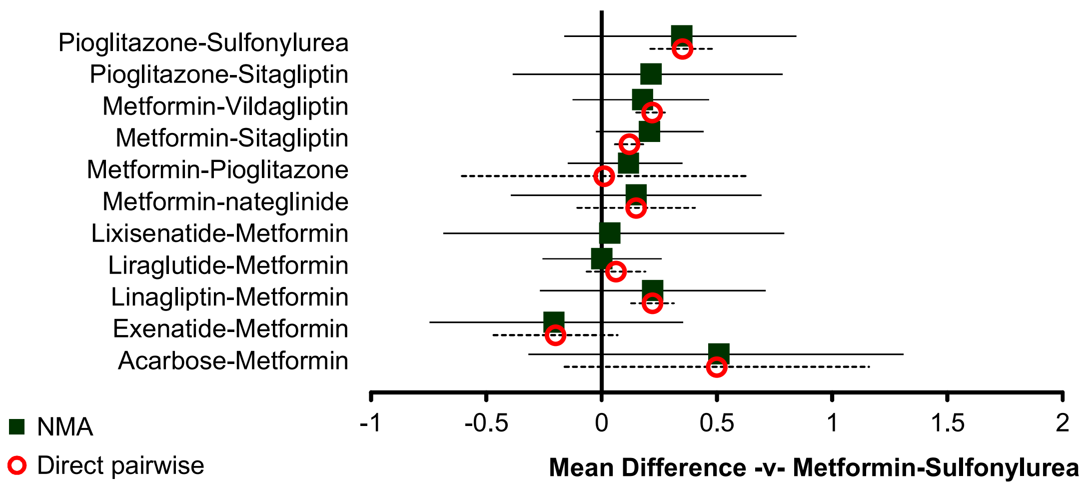
Across all 4 follow-up time points, metformin-based combinations were shown to be the most effective in reducing HbA1c levels when compared to metformin-sulfonylurea. However, these relative effects were generally associated with wide credible intervals, which except for 2 treatment combinations at 6 months, crossed the line of no effect. At 3 months, metformin-exenatide had the highest ranking (median rank 1 [95% credible interval 1 to 9]), while metformin-liraglutide (median rank 1 [1 to 2]), metformin-nateglinide (median rank 2 [1 to 8]) and metformin-pioglitazone (median rank 2 [1 to 7]) had the highest ranking at 6, 12 and 24 months respectively. The only non-metformin based combination that was more effective than metformin-sulfonylurea was sitagliptin-sulfonylurea (median rank 2 [1 to 4]) at 6 months.

Where available, there is reasonable agreement between the NMA evidence and direct pairwise treatment effect estimates which compared different options with metformin-sulfonylurea in the underlying evidence, as demonstrated by the substantial overlap between the credible/confidence intervals.



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 27: Network meta-analysis of change in HbA1c (3 months) – evidence network

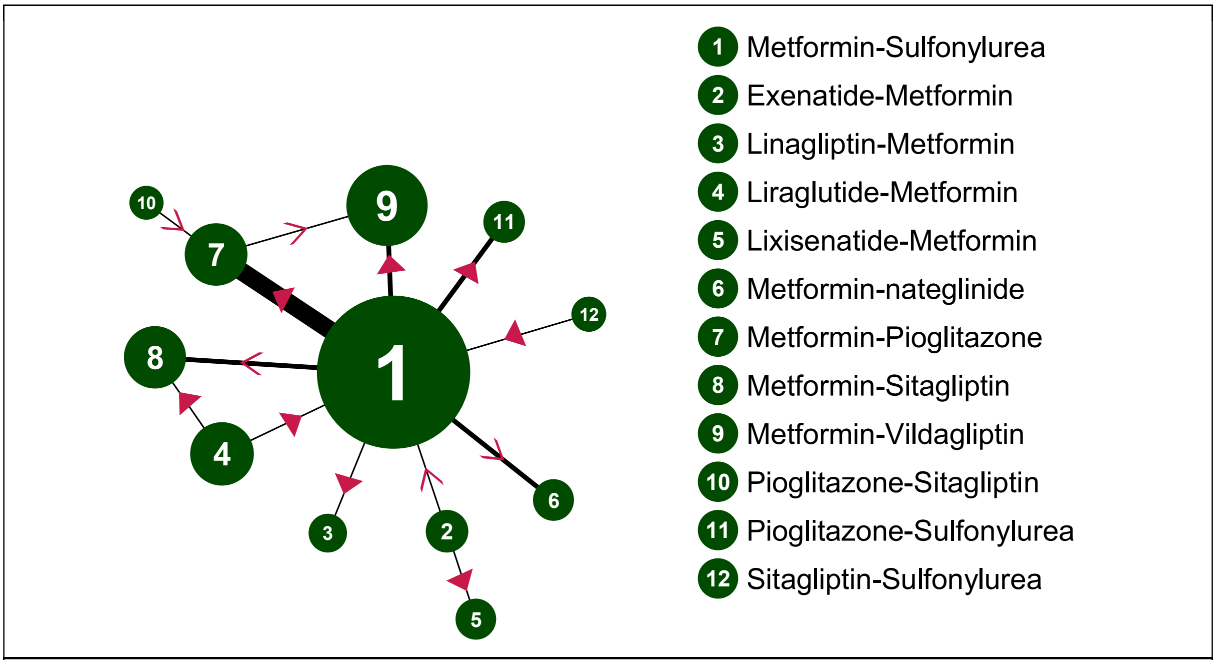


Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 28: Network meta-analysis of change in HbA1c (3 months) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

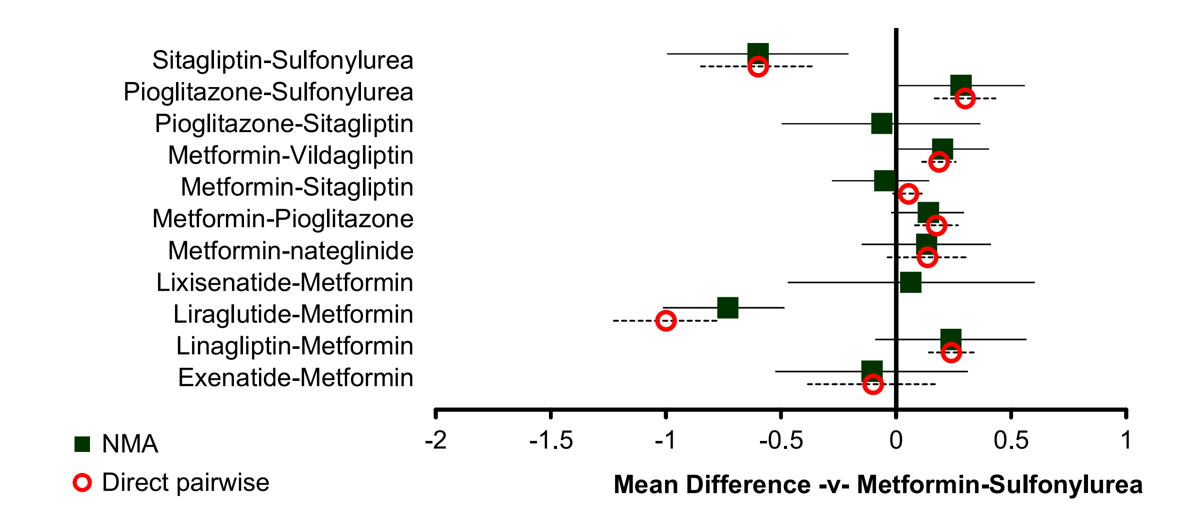
Table 64: Network meta-analysis of change in HbA1c (3 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-Sulfonylurea	0.030	4 (1, 7)
Acarbose-Metformin	0.036	11 (1, 12)
Exenatide-Metformin	0.512	1 (1, 9)
Linagliptin-Metformin	0.038	8 (1, 12)
Liraglutide-Metformin	0.094	4 (1, 9)
Lixisenatide-Metformin	0.103	5 (1, 12)
Metformin-nateglinide	0.082	7 (1, 12)
Metformin-Pioglitazone	0.014	6 (2, 10)
Metformin-Sitagliptin	0.001	8 (4, 11)
Metformin-Vildagliptin	0.012	7 (2, 11)
Pioglitazone-Sitagliptin	0.064	8 (1, 12)
Pioglitazone-Sulfonylurea	0.014	10 (2, 12)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 29: Network meta-analysis of change in HbA1c (6 months) – evidence network

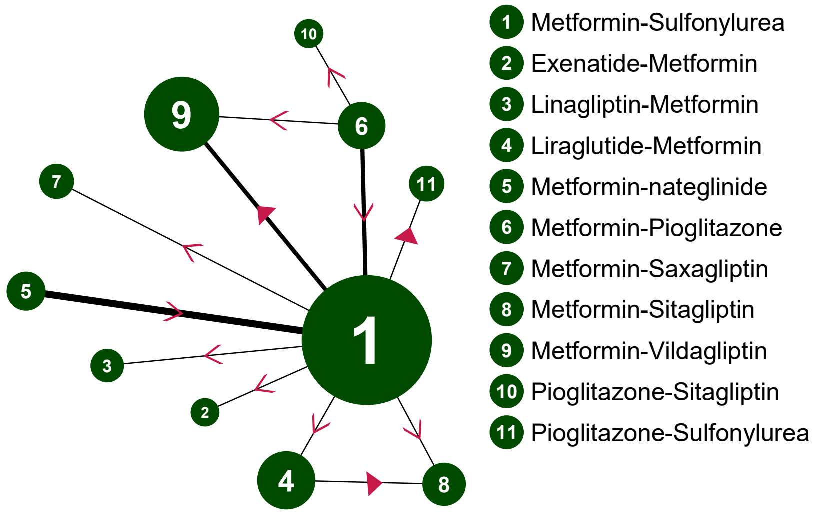


Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 30: Network meta-analysis of change in HbA1c (6 months) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

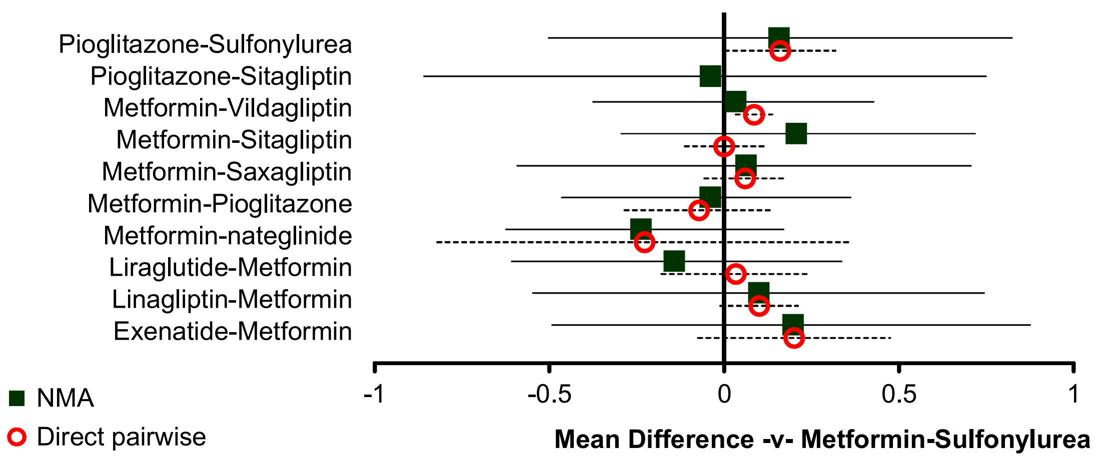
Table 65: Network meta-analysis of change in HbA1c (6 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-Sulfonylurea	0.000	6 (4, 8)
Exenatide-Metformin	0.003	4 (2, 10)
Linagliptin-Metformin	0.000	10 (4, 12)
Liraglutide-Metformin	0.712	1 (1, 2)
Lixisenatide-Metformin	0.003	7 (3, 12)
Metformin-nateglinide	0.000	8 (3, 12)
Metformin-Pioglitazone	0.000	9 (5, 11)
Metformin-Sitagliptin	0.000	5 (3, 9)
Metformin-Vildagliptin	0.000	10 (6, 12)
Pioglitazone-Sitagliptin	0.003	5 (2, 12)
Pioglitazone-Sulfonylurea	0.000	11 (6, 12)
Sitagliptin-Sulfonylurea	0.278	2 (1, 4)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 31: Network meta-analysis of change in HbA1c (12 months) – evidence network

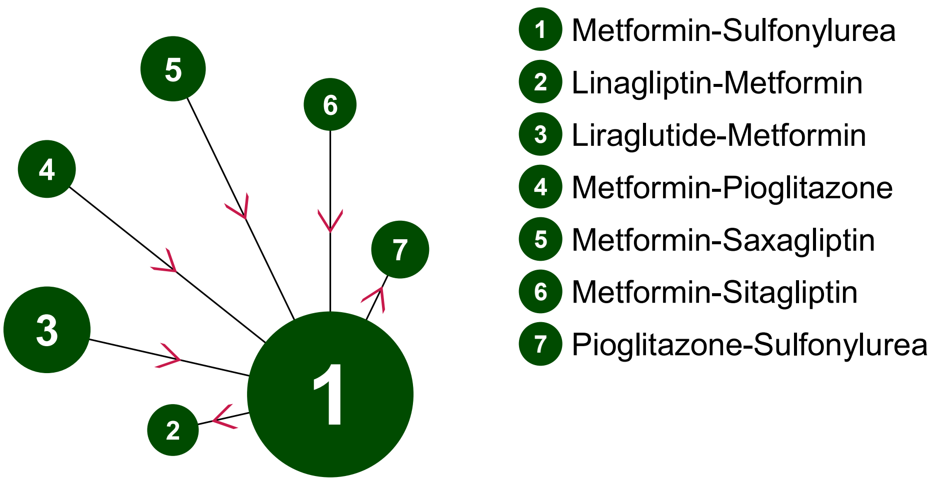


Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 32: Network meta-analysis of change in HbA1c (12 months) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

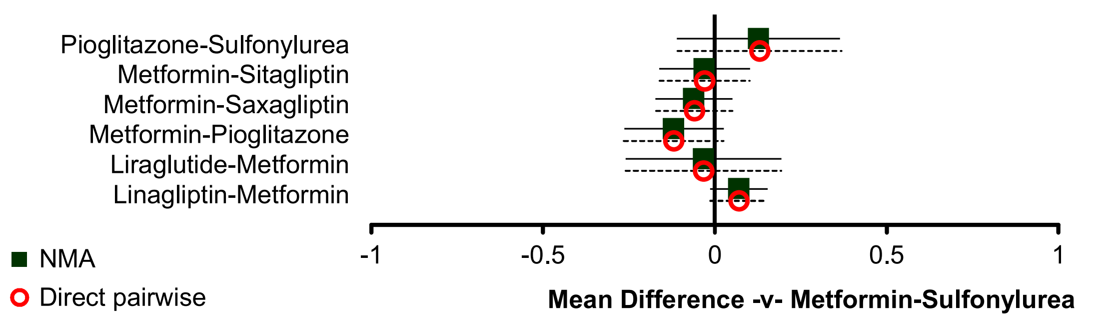
Table 66: Network meta-analysis of change in HbA1c (12 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-Sulfonylurea	0.001	6 (3, 9)
Exenatide-Metformin	0.044	9 (1, 11)
Linagliptin-Metformin	0.061	7 (1, 11)
Liraglutide-Metformin	0.179	3 (1, 9)
Metformin-nateglinide	0.327	2 (1, 8)
Metformin-Pioglitazone	0.039	5 (1, 10)
Metformin-Saxagliptin	0.081	7 (1, 11)
Metformin-Sitagliptin	0.007	9 (2, 11)
Metformin-Vildagliptin	0.025	6 (2, 11)
Pioglitazone-Sitagliptin	0.191	5 (1, 11)
Pioglitazone-Sulfonylurea	0.047	8 (1, 11)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 33: Network meta-analysis of change in HbA1c (24 months) – evidence network



Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

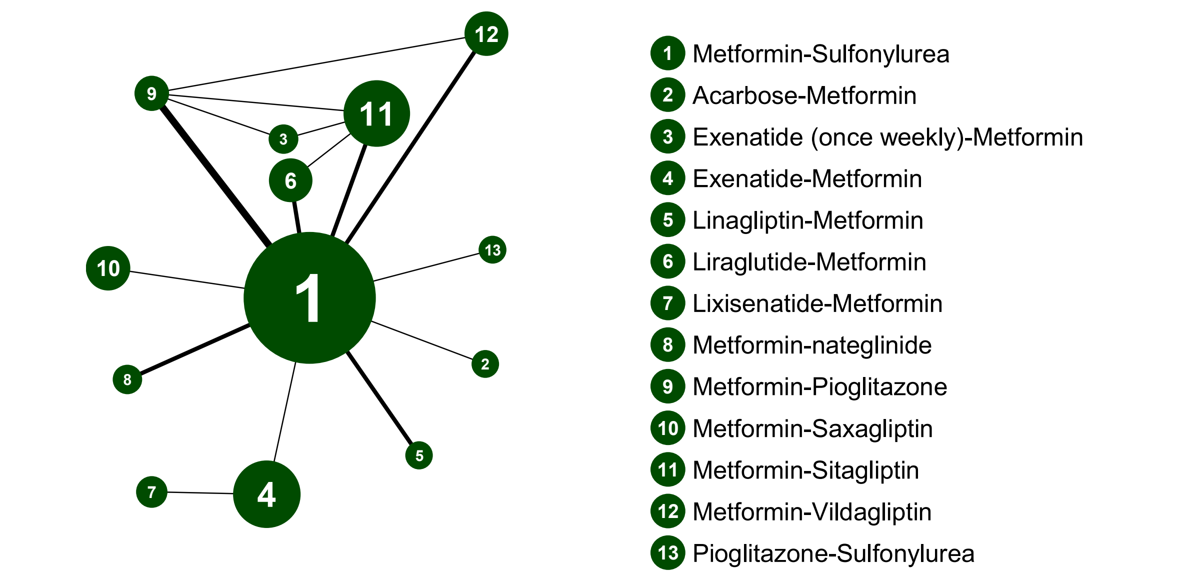
Figure 34: Network meta-analysis of change in HbA1c (24 months) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

Table 67: Network meta-analysis of change in HbA1c (24 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-Sulfonylurea	0.001	4 (3, 6)
Linagliptin-Metformin	0.000	6 (4, 7)
Liraglutide-Metformin	0.201	3 (1, 7)
Metformin-Pioglitazone	0.538	1 (1, 5)
Metformin-Saxagliptin	0.155	3 (1, 6)
Metformin-Sitagliptin	0.088	3 (1, 7)
Pioglitazone-Sulfonylurea	0.018	7 (2, 7)

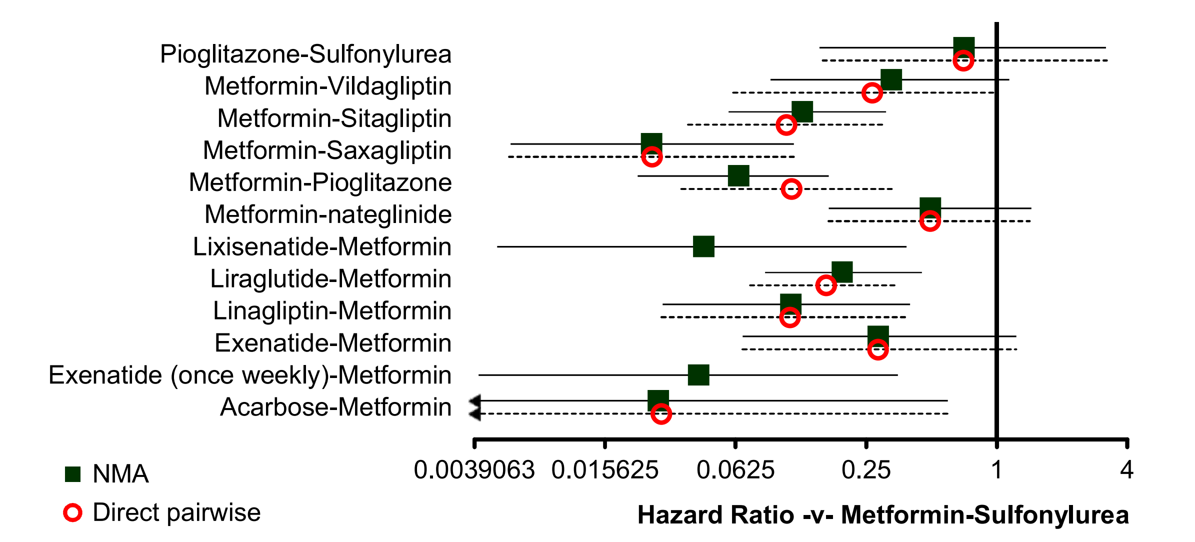
8.4.8.4 Hypoglycaemia at study end point

Results of the NMA are summarised below for the 11 treatment combinations that were compared with metformin-sulfonylurea. In general, all treatment combinations were more effective at preventing hypoglycaemic events than metformin-sulfonylurea which had the lowest ranking (median rank 12 [10 to 12]), followed by pioglitazone-sulfonylurea (median rank 11 [6 to 12]). Metformin-acarbose (median rank 2 [1 to 10]), metformin-lixisenatide (median rank 2 [1 to 7]) and metformin-saxagliptin (median rank 2 [1 to 6]) shared the highest ranking position, though metformin-saxagliptin had the narrowest credible intervals.



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 35: Network meta-analysis of hypoglycaemic events (study end point) – evidence network



Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 36: Network meta-analysis of hypoglycaemic events (study end point) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

Table 68: Network meta-analysis of hypoglycaemic events (study end point) – rankings for each comparator

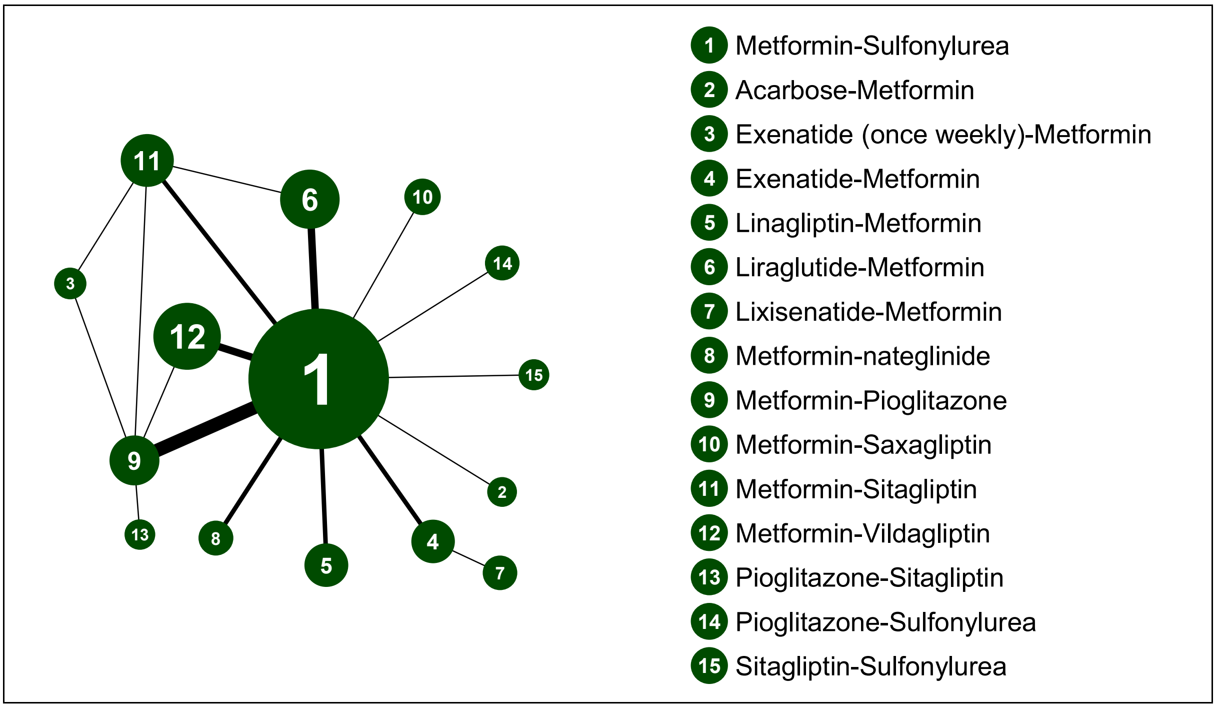
	Probability best	Median rank (95%CrI)
Metformin-Sulfonylurea	0.000	13 (11, 13)
Acarbose-Metformin	0.401	2 (1, 11)
Exenatide (once weekly)-Metformin	0.167	3 (1, 10)
Exenatide-Metformin	0.000	9 (5, 13)
Linagliptin-Metformin	0.009	6 (2, 10)
Liraglutide-Metformin	0.000	8 (5, 11)
Lixisenatide-Metformin	0.140	3 (1, 9)
Metformin-nateglinide	0.000	11 (7, 13)
Metformin-Pioglitazone	0.016	4 (2, 7)
Metformin-Saxagliptin	0.267	2 (1, 6)
Metformin-Sitagliptin	0.000	6 (4, 9)
Metformin-Vildagliptin	0.000	10 (5, 13)
Pioglitazone-Sulfonylurea	0.000	12 (7, 13)

8.4.8.5 Adverse events at study end point

Results of the 3 NMAs are summarised below. For dropouts due to adverse events and total dropouts, 12 treatment combinations were compared with metformin-sulfonylurea, while 7 treatment combinations were compared with metformin-sulfonylurea for nausea.

There is reasonable agreement between the NMA evidence and direct pairwise treatment effect estimates, as demonstrated by the substantial overlap between the credible/confidence intervals. In general, across all 3 measures, there were wide credible intervals which crossed the line of no effect. However, for all 3 measures, there was a trend for metformin-GLP1 mimetics (exenatide, liraglutide and lixisenatide) to be less effective at preventing attrition and nausea than metformin-sulfonylurea.

Pioglitazone-sitagliptin (median rank 3 [1 to 12]), metformin-nateglinide (median rank 2 [1 to 10]) and metformin-pioglitazone or sulfonylurea (median rank 2 [1 to 5] or median rank 2 [1 to 4] respectively) were associated with the highest rankings for dropouts due to adverse events, total dropouts and nausea respectively but the associated credible intervals were generally appreciably wide.


1
2
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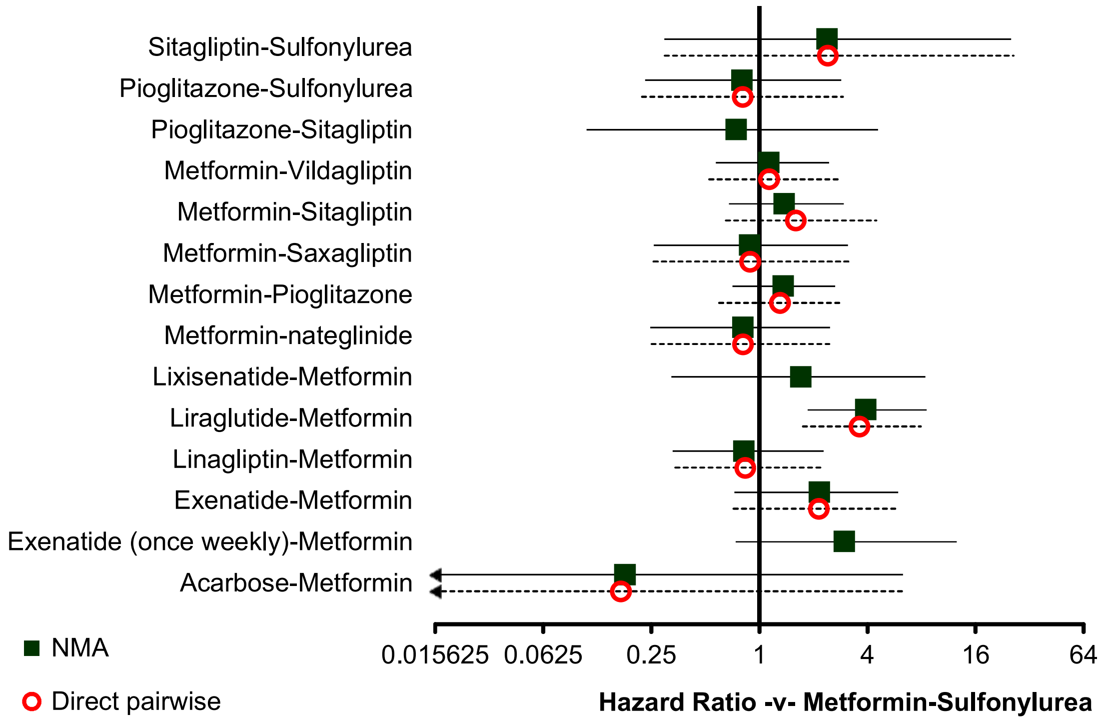
7
8
9
10
11
12
13
14
15
1 Metformin-Sulfonylurea
2 Acarbose-Metformin
3 Exenatide (once weekly)-Metformin
4 Exenatide-Metformin
5 Linagliptin-Metformin
6 Liraglutide-Metformin
7 Lixisenatide-Metformin
8 Metformin-nateglinide
9 Metformin-Pioglitazone
10 Metformin-Saxagliptin
11 Metformin-Sitagliptin
12 Metformin-Vildagliptin
13 Pioglitazone-Sitagliptin
14 Pioglitazone-Sulfonylurea
15 Sitagliptin-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 37: Network meta-analysis of dropouts due to adverse events (study end point) – evidence network



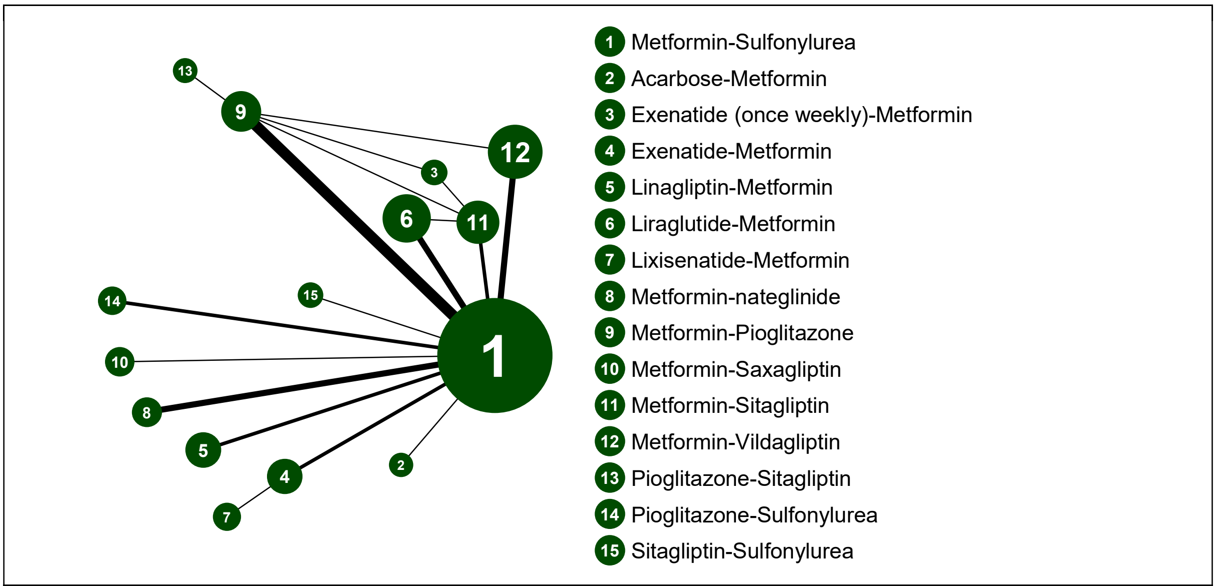
Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 38: Network meta-analysis of dropouts due to adverse events (study end point) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

Table 69: Network meta-analysis of dropouts due to adverse events (study end point) – rankings for each comparator

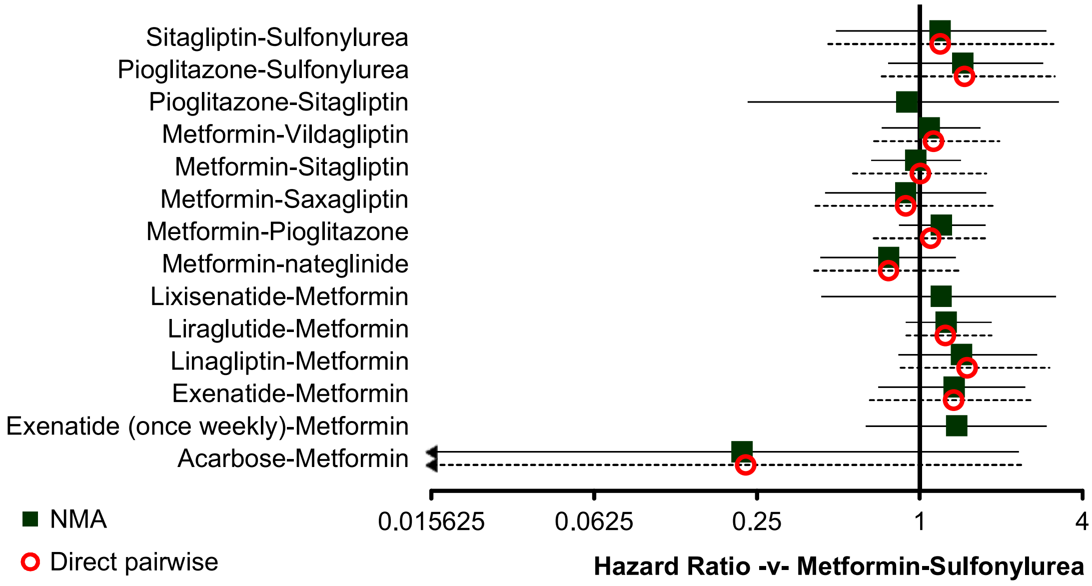
	Probability best	Median rank (95%CrI)
Metformin-Sulfonylurea	0.000	6 (3, 9)
Acarbose-Metformin	0.638	1 (1, 15)
Exenatide (once weekly)-Metformin	0.001	13 (4, 15)
Exenatide-Metformin	0.001	12 (4, 15)
Linagliptin-Metformin	0.036	5 (1, 12)
Liraglutide-Metformin	0.000	14 (11, 15)
Lixisenatide-Metformin	0.017	11 (2, 15)
Metformin-nateglinide	0.054	5 (1, 13)
Metformin-Pioglitazone	0.000	9 (4, 13)
Metformin-Saxagliptin	0.043	5 (1, 13)
Metformin-Sitagliptin	0.001	9 (3, 13)
Metformin-Vildagliptin	0.003	7 (3, 13)

	Probability best	Median rank (95%CrI)
Pioglitazone-Sitagliptin	0.124	4 (1, 14)
Pioglitazone-Sulfonylurea	0.060	5 (1, 13)
Sitagliptin-Sulfonylurea	0.020	12 (2, 15)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 39: Network meta-analysis of total dropouts (study end point) – evidence network

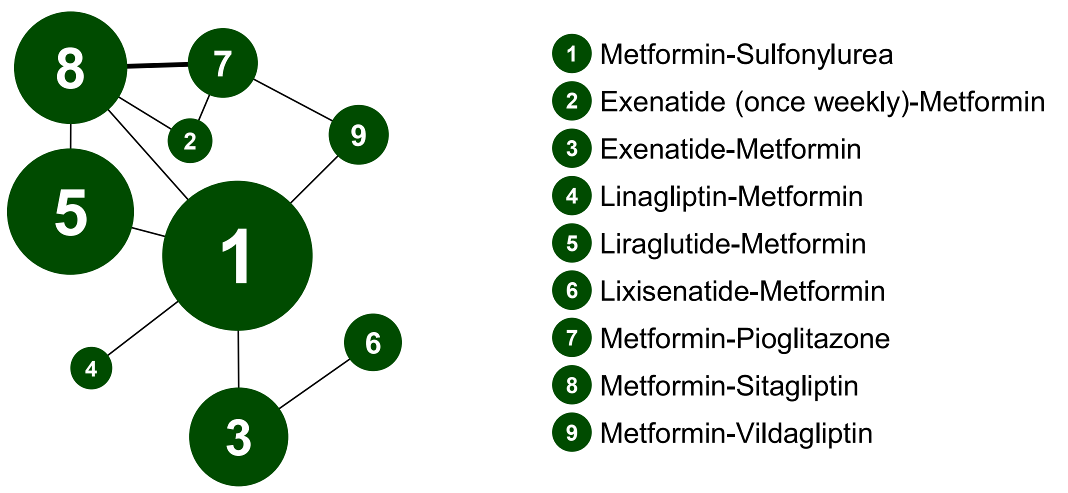


Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 40: Network meta-analysis of total dropouts (study end point) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

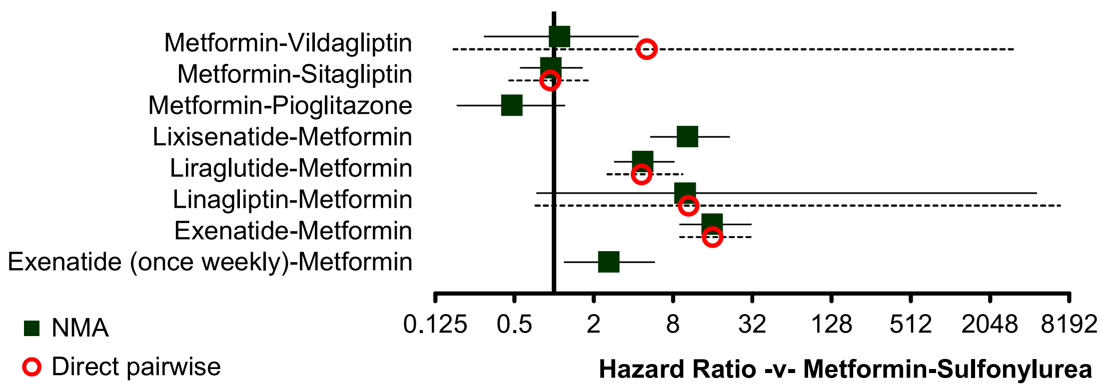
Table 70: Network meta-analysis of total dropouts (study end point) – rankings for each comparator

	Probability best	Median rank (95%Crl)
Metformin-Sulfonylurea	0.000	6 (3, 10)
Acarbose-Metformin	0.754	1 (1, 15)
Exenatide (once weekly)-Metformin	0.006	11 (2, 15)
Exenatide-Metformin	0.001	11 (3, 15)
Linagliptin-Metformin	0.001	12 (4, 15)
Liraglutide-Metformin	0.000	10 (5, 14)
Lixisenatide-Metformin	0.022	10 (2, 15)
Metformin-nateglinide	0.059	3 (1, 12)
Metformin-Pioglitazone	0.000	10 (4, 14)
Metformin-Saxagliptin	0.034	5 (1, 14)
Metformin-Sitagliptin	0.006	6 (2, 12)
Metformin-Vildagliptin	0.002	8 (3, 14)
Pioglitazone-Sitagliptin	0.096	5 (1, 15)
Pioglitazone-Sulfonylurea	0.001	12 (3, 15)
Sitagliptin-Sulfonylurea	0.018	9 (2, 15)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 41: Network meta-analysis of nausea (study end point) – evidence network



Values greater than 1 favour metformin-sulfonylurea; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 42: Network meta-analysis of nausea (study end point) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

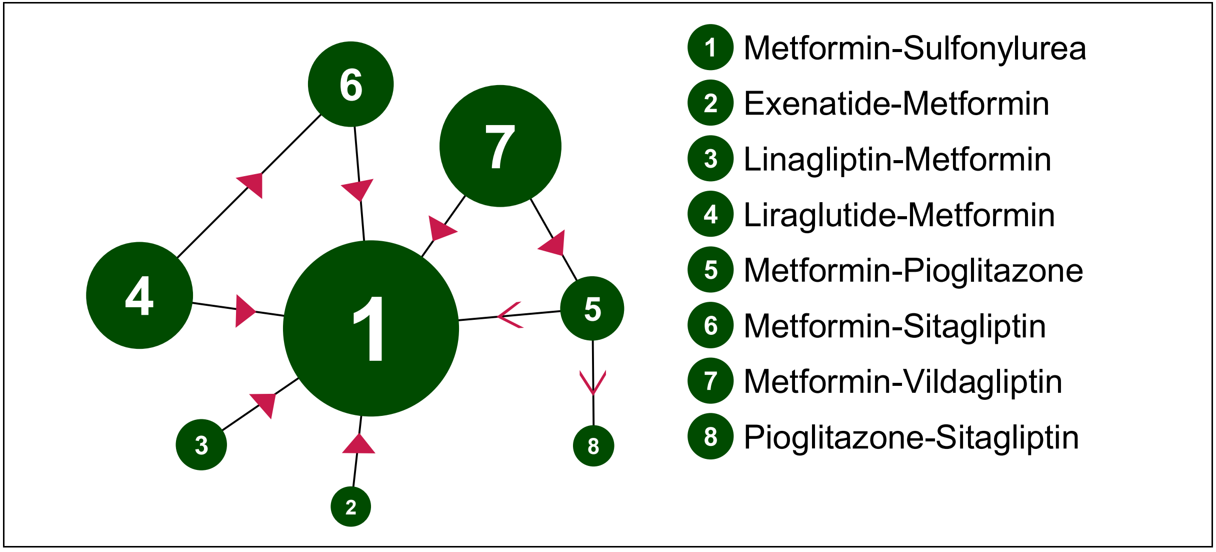
Table 71: Network meta-analysis of nausea (study end point) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-Sulfonylurea	0.048	3 (1, 4)
Exenatide (once weekly)-Metformin	0.000	5 (4, 6)
Exenatide-Metformin	0.000	9 (8, 9)
Linagliptin-Metformin	0.014	7 (2, 9)
Liraglutide-Metformin	0.000	6 (5, 7)
Lixisenatide-Metformin	0.000	7 (6, 8)
Metformin-Pioglitazone	0.863	1 (1, 3)
Metformin-Sitagliptin	0.023	3 (2, 4)
Metformin-Vildagliptin	0.053	4 (1, 6)

8.4.8.6 Change in body weight at 12 and 24 months

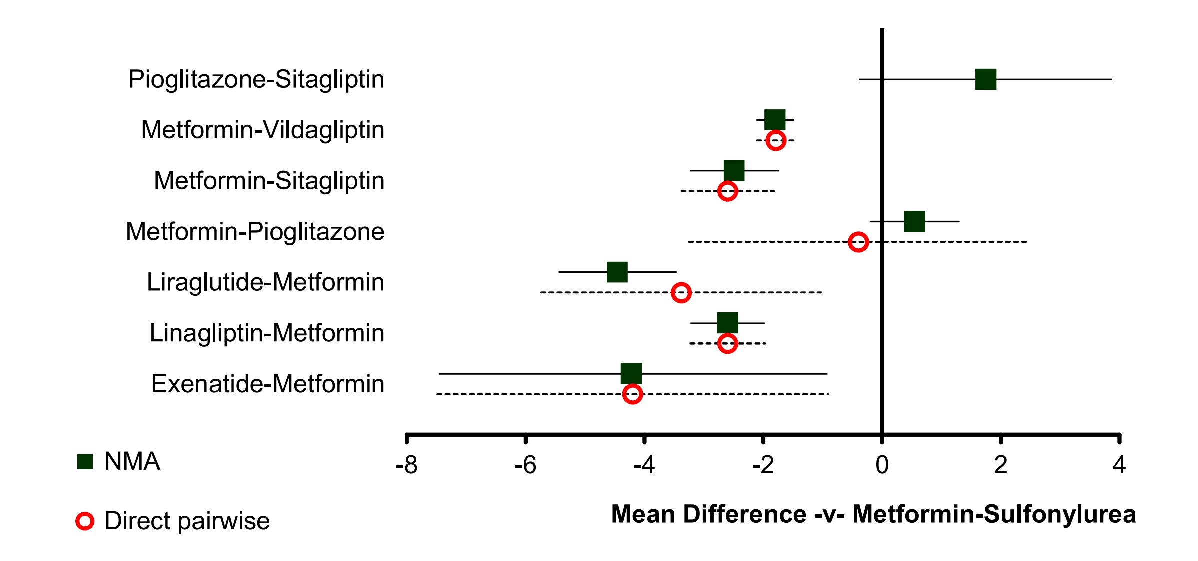
Results of the 2 NMAs are summarised below for the 7 and 8 treatment combinations that were compared with metformin-sulfonylurea at 12 and 24 months respectively. There was reasonable agreement in the NMA evidence and direct pairwise treatment effect estimates, with substantial overlap between the credible/confidence intervals.

In general, metformin combined with a DPP-4 inhibitor (linagliptin, sitagliptin and vildagliptin) or a GLP-1 mimetic (exenatide and liraglutide) were effective at weight loss when compared to metformin-sulfonylurea at 12 and 24 months. Metformin-exenatide and metformin-liraglutide had the highest ranking position at 12 months (median rank 2 [1 to 6] and median rank 2 [1 to 4] respectively) while metformin-liraglutide and metformin-linagliptin had the highest ranking position at 24 months (median rank 2 [1 to 5] and median rank 2 [1 to 6] respectively). Pioglitazone combined with sitagliptin or metformin at 12 months (median rank 8 [5 to 8] or median rank 7[5 to 8] respectively) and pioglitazone combined with sulfonylurea at 24 months (median rank 9 [9 to 9]) had the lowest ranking, suggesting weight gain.



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 43: Network meta-analysis of change in body weight (12 months) – evidence network

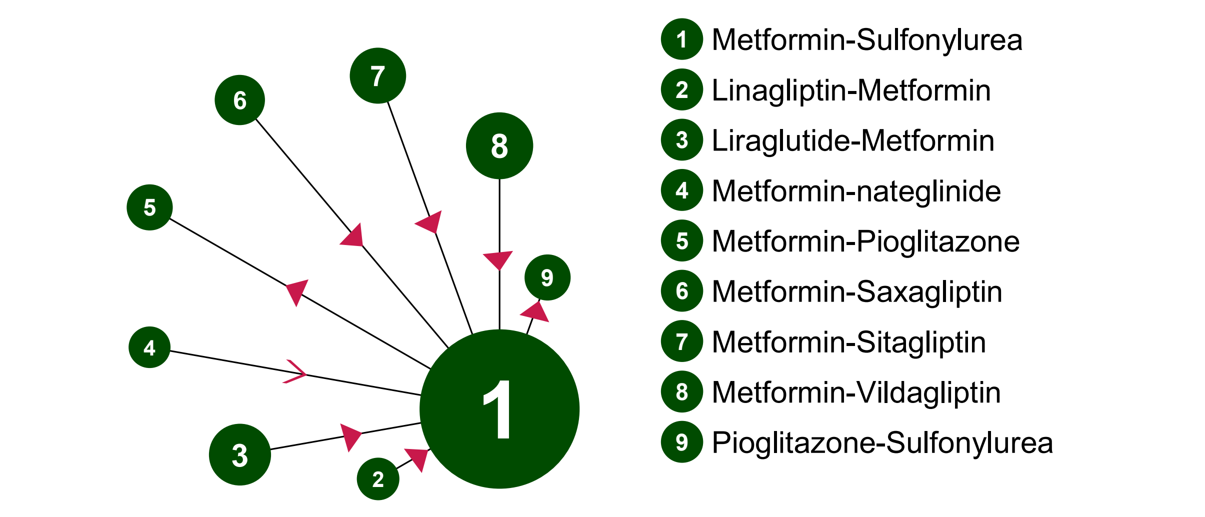


Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 44: Network meta-analysis of change in body weight (12 months) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

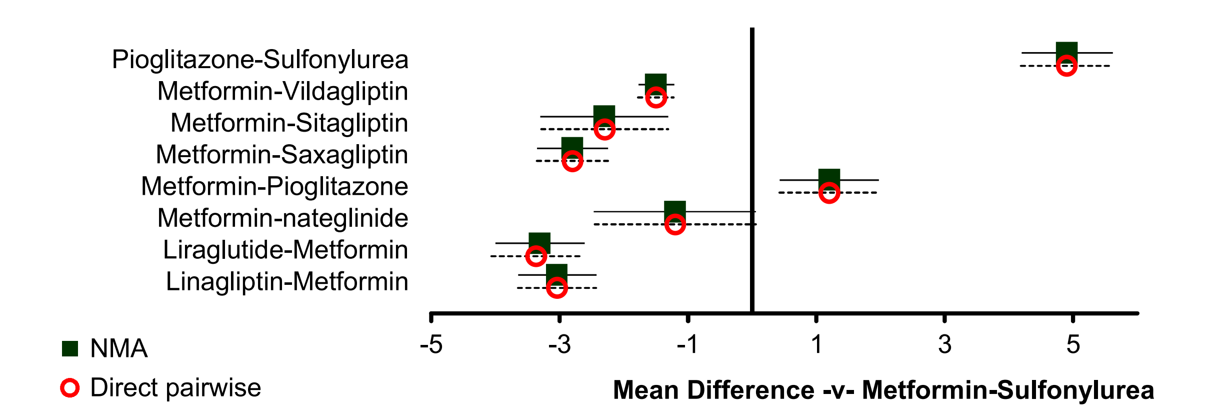
Table 72: Network meta-analysis of change in body weight (12 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-Sulfonylurea	0.000	6 (6, 7)
Exenatide-Metformin	0.445	2 (1, 5)
Linagliptin-Metformin	0.000	3 (2, 4)
Liraglutide-Metformin	0.555	1 (1, 2)
Metformin-Pioglitazone	0.000	7 (6, 8)
Metformin-Sitagliptin	0.000	4 (2, 5)
Metformin-Vildagliptin	0.000	5 (4, 5)
Pioglitazone-Sitagliptin	0.000	8 (6, 8)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 45: Network meta-analysis of change in body weight (24 months) – evidence network



Values greater than 0 favour metformin-sulfonylurea; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 46: Network meta-analysis of change in body weight (24 months) – relative effect of all options compared with common comparator (metformin-sulfonylurea)

Table 73: Network meta-analysis of change in body weight (24 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-Sulfonylurea	0.000	7 (6, 7)
Linagliptin-Metformin	0.249	2 (1, 4)
Liraglutide-Metformin	0.652	1 (1, 3)
Metformin-nateglinide	0.001	6 (4, 7)

	Probability best	Median rank (95%CrI)
Metformin-Pioglitazone	0.000	8 (8, 8)
Metformin-Saxagliptin	0.068	3 (1, 4)
Metformin-Sitagliptin	0.030	4 (1, 5)
Metformin-Vildagliptin	0.000	5 (4, 6)
Pioglitazone-Sulfonylurea	0.000	9 (9, 9)

8.4.9 Health economic evidence for first intensification

8.4.9.1 Systematic review of published cost–utility analyses

For first intensification, 2 UK studies were included covering 3 comparisons (Davies et al. 2012; Schwartz et al. 2008). Davies et al. (2012) found liraglutide-metformin to be cost effective compared with both metformin-sulfonylurea (liraglutide 1.2mg ICER £9400 per QALY, liraglutide 1.8mg ICER £16,500 per QALY) and metformin-sitagliptin (liraglutide 1.2mg ICER £9900 per QALY, liraglutide 1.8mg ICER £10,500 per QALY). Schwartz et al. (2008) found metformin-sitagliptin to be cost effective compared with metformin-sulfonylurea in Scotland (ICER €11,600 per QALY). Both papers included treatment effects for systolic blood pressure and cholesterol (as well as HbA1c, weight and hypoglycaemia). Some assumptions and data sources used in these CUAs were unclear. Both used relatively large utility decrements for weight gain and hypoglycaemia.

As no directly applicable studies with only minor limitations were found that covered all the comparators under consideration for each sub-question for this guideline, an original economic analysis was undertaken.

8.4.9.2 Original health economic analysis

For first intensification, 7 treatments could be modelled – all the modelled combinations contained metformin and none contained a meglitinide. People accrued an average of 16.3 undiscounted life years, of which 3.7 years were spent on first intensification therapy. As for initial therapy, there was little difference in lifetime complication rates as the differences in HbA1c treatment effects were even smaller.

People accumulated an average of 8.2 lifetime discounted QALYs, with most losses and differences coming from weight profiles and some from hypoglycaemic episodes. Treatment-related costs accounted for most variation in lifetime discounted costs.

First intensification therapy with metformin-pioglitazone had the lowest lifetime discounted costs and was the most cost-effective treatment option (see table 74). All DPP4 inhibitor-metformin combinations produced very similar lifetime discounted QALYs and costs and the GDG were happy to consider the 3 combinations to be equivalent, particularly if people could not take metformin-pioglitazone and metformin-sulfonylurea (see figure 47).

Table 74: Mean lifetime incremental cost–utility results for first intensification therapy

	Lifetime discounted		Incremental		
Therapy	Costs	QALYs	Costs	QALYs	ICER
Metformin-pioglitazone -> Met-I(NPH)	£20,390	8.217			
Metformin-sulfonylurea -> Met-I(NPH)	£20,522	8.213	£132	-0.004	Dominated
Metformin-vildagliptin -> Met-I(NPH)	£21,569	8.249	£1179	0.031	Ext. dom.
Linagliptin-metformin -> Met-I(NPH)	£21,654	8.252	£1264	0.034	£36,788
Metformin-sitagliptin -> Met-I(NPH)	£21,685	8.243	£31	-0.009	Dominated
Exenatide-metformin -> Met-I(NPH)	£23,213	8.255	£1560	0.003	Ext. dom.

Therapy	Lifetime discounted		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Liraglutide-metformin -> Met-I(NPH)	£23,614	8.284	£1960	0.032	£61,381

(a) Met-I(NPH) = Metformin-NPH insulin
(b) Ext. dom. = extendedly dominated

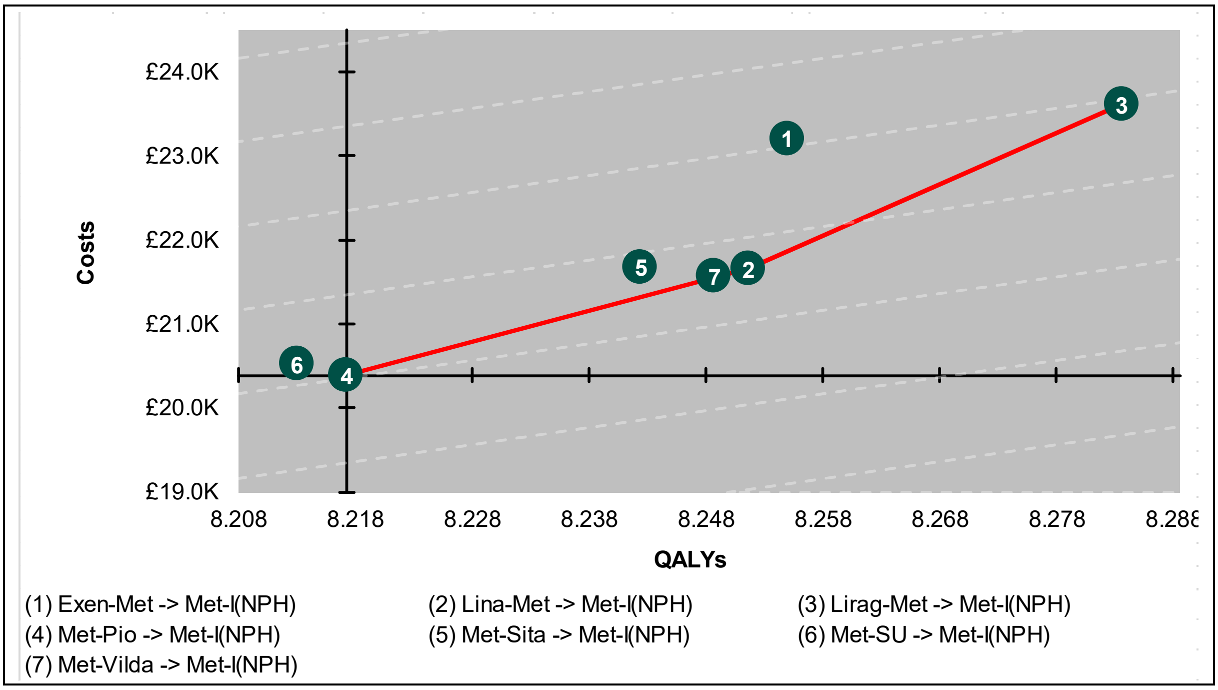


Figure 47: Cost–utility plane for first intensification

At first intensification, metformin-pioglitazone was the most cost-effective treatment combination at a maximum acceptable ICER of £20,000 per QALY in 48% of iterations (see figure 48). While metformin-pioglitazone and metformin-sulfonylurea showed only small incremental differences in the base case (see table 74), the superiority of metformin-pioglitazone was maintained in most probabilistic iterations.

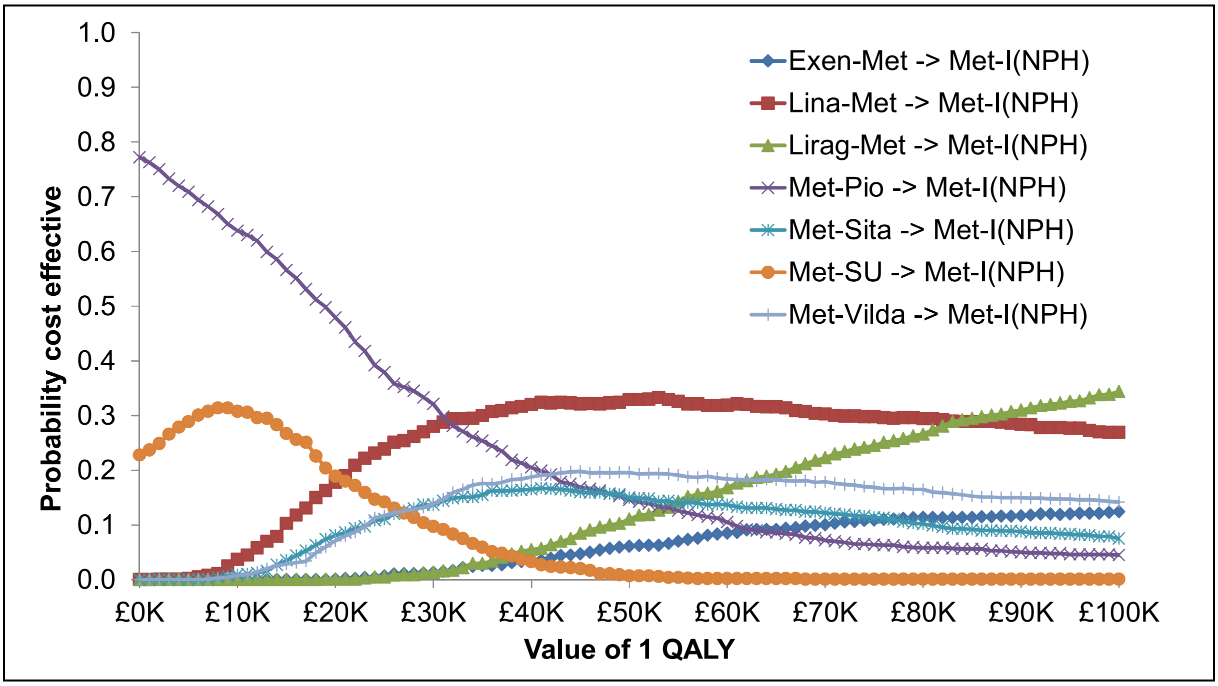


Figure 48: Cost-effectiveness acceptability curve for first intensification (class level)

8.4.10 Evidence statements for first intensification

8.4.10.1 Clinical evidence

8.4.10.1.1 Change in blood glucose

Evidence from 4 network meta-analyses including data from 20, 22, 16 and 6 RCTs at 3, 6, 12 and 24 months respectively for HbA1c levels showed that metformin-based combinations were generally associated with higher rankings at all 4 follow-up timepoints. At 3 and 6 months, metformin combined with a GLP-1 mimetic (exenatide, liraglutide) was most effective in reducing HbA1c levels, while metformin combined with nateglinide or pioglitazone were shown to be most effective at 12 and 24 months respectively. In general, the credible intervals surrounding these ranking were considerably wide, except at 6 months where there was greater certainty in the data. The quality of the evidence was moderate.

8.4.10.1.2 Hypoglycaemia at study end point

Evidence from a single network meta-analysis including data from 21 RCTs showed that sulfonylurea combined with metformin (median rank 12 [10 to 12]) or pioglitazone (median rank 11 [6 to 12]) were least effective in preventing hypoglycaemic events. Metformin-saxagliptin, metformin-lixisenatide and metformin-acarbose had the highest ranking suggesting these treatment combinations are effective in preventing hypoglycaemic events. The quality of the evidence was low.

8.4.10.1.3 Adverse events at study end point

Evidence from 3 network meta-analyses including data from 27, 29 and 11 RCTs for dropouts due to adverse events, total dropouts and nausea respectively showed that in general, metformin combined with a GLP-1 mimetic (exenatide, liraglutide and lixisenatide) is less effective in preventing dropouts and nausea compared to metformin-sulfonylurea. Metformin combined with pioglitazone or sulfonylurea were shown to most effective at preventing nausea. There was generally some uncertainty around the results demonstrated by wide credible intervals which in the main crossed the line of no effect. The quality of the evidence was moderate to low.

8.4.10.1.4 Change in body weight

Evidence from 2 network meta-analyses including data from 8 RCTs at 12 and 24 months showed that metformin combined with a DPP-4 inhibitor (linagliptin) or GLP-1 mimetic (exenatide and liraglutide) were most effective at promoting weight loss at 12 and 24 months. Whereas, pioglitazone combined with sitagliptin and metformin or sulfonylurea were associated with weight gain at 12 and 24 months respectively. The quality of the evidence was low.

8.4.10.2 Health economic evidence

A directly applicable health economic model with potentially serious limitations found that a combination of metformin–pioglitazone was the most cost-effective modelled option for first intensification therapy.

8.4.11 Evidence to recommendations for first intensification

Table 75: Linking evidence to recommendations

Relative value of different outcomes	The following outcomes were considered critical to decision making; glycaemic control (change in HbA1c), hypoglycaemic events and adverse events. Change in body weight was considered important to decision making. The GDG noted that glycaemic control was important in mitigating the increased risk of microvascular and macrovascular complications associated with increased levels of hyperglycaemia, necessitating intensification of drug therapy. However, the GDG acknowledged that tight glycaemic control may be associated with an increased risk of hypoglycaemia, which may negatively affect quality of life. Drug tolerability and change in body weight were considered important in determining the acceptability of treatment to the patient. The relative importance of each outcome variesaccording to several factors: • Short-term (3 and 6 months) versus long-term (12 and 24 months) evaluation. For example, adverse events and change in body weight are reflected at longer time points (12 and 24 months). • Severity of hyperglycaemia. • Individual circumstances, such as comorbidities.
Trade-off between benefits and harms	The GDG acknowledged that there was generally less evidence for this treatment level, resulting in sparser networks. The GDG noted that there was greater uncertainty in the evidence at this intensification level as demonstrated by the wide credible intervals that surrounded many of the point estimates across all outcomes. Moreover, the GDG recognised that the current evidence base was biased towards metformin-based combinations because, of the 14 available treatment options, only 3 did not include metformin (pioglitazone plus sitagliptin, pioglitazone plus sulfonylurea and sitagliptin plus sulfonylurea). Of the 14 treatment combinations, 7 included data for all required outcomes in the health economic model. The 7 interventions that were not included in the main health economic model were 4 metformin-based combinations (metformin–acarbose, metformin–lixisenatide, metformin–nateglinide and metformin–saxagliptin) and the 3 previously mentioned combinations that did not include metformin. The GDG considered the evidence surrounding the intensification options for people whose diabetes was inadequately controlled by metformin alone. The GDG agreed that, while metformin combined with a DPP-4 inhibitor (linagliptin, saxagliptin sitagliptin or vildagliptin) was moderately effective in controlling blood glucose levels, this treatment combination was associated with fewer hypoglycaemic events and weight loss. The GDG discussed the evidence surrounding the use of metformin in combination with pioglitazone and noted that it was most effective at reducing HbA1c levels at 24 months and preventing nausea, but was associated with weight gain.

	The GDG discussed the long-term safety concerns associated with the use of pioglitazone and DPP-4 inhibitors, and agreed that Medicines and Healthcare products Regulatory Agency (MHRA) guidance and patient suitability should be considered. For example, pioglitazone is not recommended for people with active bladder cancer, a history of bladder cancer or uninvestigated haematuria, or people with heart failure or who are at risk of osteoporosis. The GDG noted that there was limited information on long-term safety of DPP-4 inhibitors. The GDG agreed that there was tentative evidence that metformin–sulfonylurea was moderately effective in reducing HbA1c levels, but this treatment combination was strongly associated with more hypoglycaemic events. However, the GDG noted that the point estimates were associated with large credible intervals, indicating some measure of uncertainty around the data. The GDG recognised that there was evidence to indicate that metformin combined with a GLP-1 mimetic (exenatide or liraglutide [evidence base included 1.2 and 1.8mg]) may be effective in reducing HbA1c levels in the short term (up to 6 months), preventing hypoglycaemic events and promoting weight loss. The GDG discussed the long-term safety risks associated with the use of GLP-1 mimetics and the evidence from the health economic model, which they considered were important in the decision-making. The GDG considered that there was strong evidence from the health economic model that showed that this treatment combination was not cost effective and agreed not to recommend this option routinely. The GDG noted that where all other dual therapy options were not appropriate, individuals would naturally progress to second intensification where GLP-1s would become an option. The GDG recognised that there was limited evidence for treatment intensification options for people for whom metformin is contraindicated or not tolerated. The GDG noted that sitagliptin–sulfonylurea was associated with high rankings in change in HbA1c at 6 months, whereas pioglitazone–sulfonylurea was associated with weight gain at 24 months.
Consideration of health benefits and resource use	Economic model results showed a clustering of treatments, with all 3 modelled DPP-4 inhibitor–metformin combinations showing similar lifetime discounted costs and quality-adjusted life years (QALYs). In the base case, linagliptin–metformin produced an incremental cost-effectiveness ratio (ICER) of £36,800 per QALY compared with metformin–pioglitazone. In the probabilistic sensitivity analysis (PSA), metformin–pioglitazone had a 48% chance of being the most cost-effective treatment option. Metformin–pioglitazone and metformin–sulfonylurea showed similar lifetime discounted costs and QALYs. However, metformin–pioglitazone provided better value for money than metformin–sulfonylurea in most iterations of the PSA, meaning that, while the differences may be small, the superiority of metformin–pioglitazone appears to be a relatively robust finding. However, the GDG was concerned that for a number of people with type 2 diabetes, pioglitazone would be contraindicated, not tolerated or the person would be at high risk of the adverse effects

	of pioglitazone. Also, while changes in body weight were incorporated within the health economic modelling, the GDG agreed there would be some people with type 2 diabetes for whom the treatment-related weight gain associated with pioglitazone and sulfonylureas would not be acceptable. Therefore, the GDG considered it would be appropriate to recommend that people with type 2 diabetes could have the option to individualise their care by selecting DPP-4 inhibitor–metformin treatment options. Given the differences in lifetime discounted costs were mainly in treatment costs, the GDG recommended the DPP-4 inhibitor–metformin treatment options with the lowest DPP-4 inhibitor acquisition cost. The GDG noted that other factors should additionally be considered for example, licensed combinations/indications, but agreed that where 2 drugs in the same class are appropriate, the option with the lowest acquisition cost should be selected. Differences between drugs at first intensification were small, partly because of the normalising effect of future intensification in the economic model – patients were only on their first intensification therapies for an average of 3.7 years. QALY differences were driven by ifferences in weight gained; cost differences were predominantly because of the costs of the drugs themselves. The GDG noted that the economic model was not able to take account of the stopping rules from NICE guidance CG87 for GLP-1 combinations. The treatment effects for HbA1c and weight from the current guideline analysis were substantially less than those required by the CG87 stopping rules. The base-case economic model did not provide any evidence for combinations that did not contain metformin. As the economic results were driven primarily by body weight and hypoglycaemia, the GDG considered that it was highly unlikely combinations including pioglitazone and/or sulfonylurea for patients not taking metformin would appear cost effective compared with metformin-based combinations. However, it was unclear which combinations would be cost effective in a decision space that only contained non-metformin combinations. The GDG noted this would be a small subgroup of patients.
Quality of the evidence	The GDG agreed that the overall quality of the evidence for first intensification was moderate to low.
Other considerations	When defining the decision problem for this question, the GDG preferred not to make an *a priori* assumption of class effect across DPP-4 inhibitors. Therefore, each individual option for which evidence was available was analysed separately. Having reviewed the assembled evidence for each phase of treatment, the GDG noted that it was difficult to judge whether the different DPP-4 inhibitors could, in fact, be considered interchangeable: • In a few areas, a case could be made for the superiority of 1 option over another (for example, at initial therapy, sitagliptin seemed to have somewhat superior benefits to vildagliptin at similar net costs). • In other areas, all the DPP-4 inhibitors for which evidence was available appeared to have very similar benefits, harms and costs (for example, in combination with metformin at first intensification). • Elsewhere in the treatment pathway, evidence was extremely limited (for example, sitagliptin–metformin–sulfonylurea was the only treatment combination for which evidence was available at

	second intensification) or absent (for example, at first intensification, there was no evidence that could be used to assess the relative clinical effectiveness and cost effectiveness of DPP-4 inhibitors in combination with pioglitazone or sulfonylureas). Having considered these different situations, the GDG concluded that the most helpful recommendations would be ones that treated DPP-4 inhibitors as a class. Had it been presented with evidence that suggested that 1 or more of the options was superior to others across all phases of treatment, the GDG would clearly have been inclined to favour such option(s) in its recommendations. However, the picture that had emerged was much more sporadic, and the GDG was not confident that any apparent dissimilarities between options represented real differences that would be expected in clinical practice. Moreover, the GDG was mindful that a series of recommendations that alternated between treating DPP-4 inhibitors as a class, in some parts of the treatment pathway, and focusing on individual options in others would be confusing to readers of the guideline, even if those recommendations could be directly allied with the available evidence. For all of these reasons, the GDG took the view that recommendations should consistently refer to DPP-4 inhibitors as a class. It was a natural extension of this principle that prescribers should be encouraged to select the individual DPP-4 inhibitor with the lowest acquisition cost available to them where all other factors are equal for example, licensed indications/combinations. Recommendations in this section that cover glucagon-like peptide 1 mimetics (GLP-1s) refer to these drugs at a class level because based on the evaluated evidence, the GDG was not convinced of the purported material differences between the various preparations. The GDG noted that the mean age in the included studies was about 57 years and agreed that these trials are biased towards younger and fitter participants, who are less likely to experience significant comorbidities than the majority of people with type 2 diabetes seen in clinical practice. The GDG considered that the treatment effects observed in trials are likely to generalise to a population facing more comorbidities and other challenges to effective management of their disease. However, the GDG agreed that the balance of benefits and harms may be different in such cases, and there are specific issues based on clinical experience that may require particular attention that should be highlighted in the recommendations. It was noted that reporting of hypoglycaemia differed across the included studies. All categories of hypoglycaemia (for example, confirmed hypoglycaemia) were generally a subset of ‘any hypoglycaemia’, which was the most commonly reported category of hypoglycaemia across the included studies. The GDG discussed the risk of bias associated with reported hypoglycaemia and noted that self-reported hypoglycaemia may not be a reliable measure because a person’s perception of hypoglycaemia varies at different glucose levels. The GDG noted that the results from the sensitivity analyses of people who had previous experience of using 1 oral antidiabetic medicine were similar to the full dataset which included studies of

	mixed populations of people who were drug naïve, or on 1 or more oral antidiabetic medicines at screening. The GDG discussed the multiple factors that should be considered when selecting drug treatments. The GDG agreed that the benefits and risks should be discussed with the person and selecting specific drugs should involve an assessment of the effectiveness of the medicine(s) (in terms of metabolic response), safety (MHRA guidance) and tolerability of the medicine(s), person's clinical circumstances (for example, comorbidities, polypharmacy), person's preferences and needs, licensed indications or combinations and costs (where 2 medicines in the same class are appropriate, the option with the lowest acquisition cost should be selected). The GDG discussed the rationale for recommending premixed insulin in individuals with an HbA1c level above 75mmol/mol (9.0%). NPH insulin once or twice daily is helpful for people with a degree of residual endogenous insulin production. When insulin production is much reduced, this will be reflected in a relatively high HbA1c initially, and a disappointing response to NPH insulin alone. Such individuals also need some additional short-acting insulin. This can be given as separate injections but at the same time as NPH insulin. Or the two insulins can be used combined in a pre-mixed formulation.

8.4.12 Clinical evidence review for second intensification

In total 17,037 references were found for the main review question and 45 papers were included for second intensification which relate to 42 trials.

This review question addressed which treatment combination is most effective when people with type 2 diabetes who are treated with diet and a combination of 2 non-insulin based therapies have inadequate blood glucose control. The GDG agreed that both triple non-insulin based therapies and insulin based medicines are potential treatment options at second intensification. Because of the large volume of evidence relating to insulin therapy, the GDG prioritised the drug comparisons listed in Table 43 for second intensification, which were of particular clinical interest:

- 3 non-insulin based therapies versus 3 non-insulin based therapies
- Insulin versus 3 non-insulin based therapies
- Insulin + 1 non-insulin based therapy versus 3 non-insulin based therapies
- Insulin + 2 non-insulin based therapies versus 3 non-insulin based therapies
- Insulin versus insulin + 1 non-insulin based therapy
- Insulin versus insulin + 2 non-insulin based therapies
- Insulin + 1 non-insulin based therapy versus insulin + 1 non-insulin based therapy
- Insulin + 2 non-insulin based therapies versus insulin + 2 non-insulin based therapies
- Insulin + 1 non-insulin based therapy versus insulin + 2 non-insulin based therapies

RCTs of at least 12 week treatment duration examining the drug comparisons above were included. In contrast to initial therapy, it was assumed that most patients would be titrated to the maximal tolerated doses of previous oral therapy before starting a trial. Therefore, trials that did not report specific doses of continued previous therapy were still included (see section 8.4.2 for the main exclusion criteria).

8.4.12.1 Description of included studies for second intensification

A total of 10,170 participants from 39 RCTs were included. The majority of studies were carried out in multiple centres across different countries. The mean age ranged from 52.6 to 64.8 years. Mean HbA1c levels at baseline ranged from 62 to 97 mmol/mol (7.8% to 11%). The mean BMI ranged from 24.7 to 36.08 kg/m^2. Mean duration of diabetes ranged from 3.5 to 13.7 years, with 2 studies not reporting this information. Follow-up periods ranged from 12 weeks to 104 weeks. For full details of the included studies, see Appendix E.

8.4.12.2 Network meta-analyses for second intensification

To facilitate comparison across all available treatment options, 6 network meta-analyses were performed for all 3 critical and 1 important outcomes – change in HbA1c up to 12 months, hypoglycaemia at study end point, adverse events (that is, dropouts due to adverse events, total dropouts and nausea) at study end point and change in body weight up to 12 months. Where available, metformin-neutral protamine Hagedorn (NPH) insulin was selected as the reference treatment option as this combination was considered to reflect current standard clinical practice. For nausea only, metformin-biphasic insulin aspart was used as the reference treatment as no studies included metformin-NPH insulin. Full details of methods and additional NMA outputs are provided in Appendix J.

For continuous outcomes, measurements up to 1 year follow-up form each study were included in the NMA. This is related to the way in which HbA1c levels varies as type 2 diabetes progresses. Specifically, although initial reductions in HbA1c levels are observed following treatment, these levels will eventually drift back up over time. Further exploration of the included HbA1c data showed that there was little difference between measurements at 6 months and 12 months. Furthermore, as 3-month measurements were likely to be more conservative (that is, not bias in favour of the intervention) because of the J-shaped curve, pooling of these timepoints was considered appropriate. Where included trials reported more than one timepoint between 12 weeks and 1 year, only the latest timepoint was included in synthesis. A sparse connected network was produced for change in HbA1c levels. Only 1 trial (Gram et al. 2011, Holman et al. 1999) reported outcomes at 2 years follow-up and over. These results have not been presented because this did not form a network.

On the whole, the quality of the evidence was low as many of the connections were limited to single trials, the majority of studies were open label and some included RCTs may not have been representative of UK clinical population with type 2 diabetes who require second intensification of drug therapy. It was noted that random-effects models tended to estimate a fairly large inter-study heterogeneity term, which will reduce the precision of effect estimates.

Table 76: GRADE profile for network meta-analyses for second intensification

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Change in blood glucose (HbA1c)						
Up to 12 months	37	serious[1]	not serious[2]	not serious[3]	not serious	Moderate
Hypoglycaemia at study end point						
Study end point	34	serious[1]	not serious[2]	not serious[3]	serious[4]	Low
Adverse events at study end point						
Dropouts due to adverse events	25	serious[1]	serious[5]	not serious[3]	serious[4]	Low[6]
Total dropouts	25	serious[1]	not serious[2]	not serious[3]	serious[4]	Low

Assessment time points/ Measure	Number of RCTs	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Nausea	4	serious[1]	serious[5]	not serious[3]	serious[4]	Low[6]
Change in body weight						
Up to 12 months	27	serious[1]	not serious[2]	not serious[3]	serious[4]	Low

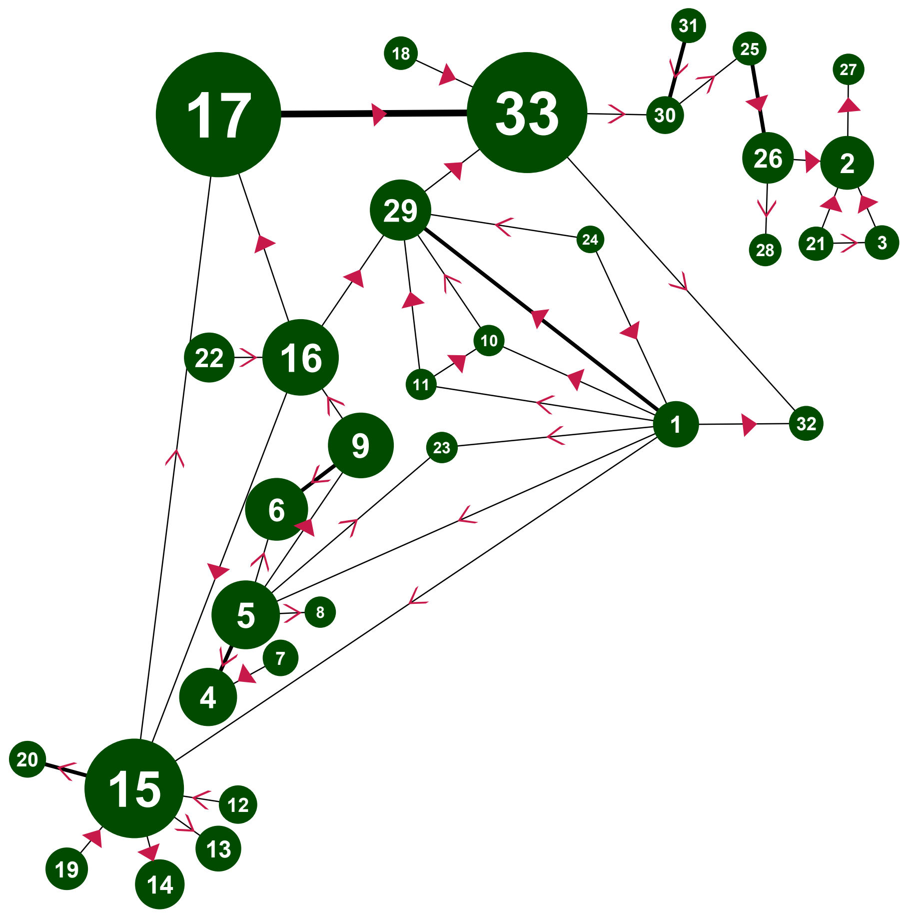
[1]Downgrade 1 level: baseline HbA1c ranged from 7.8 to 11%
[2]Assessed based on residual deviance, deviance information criterion and tau^2 (tau^2<0.5)
[3]Considered not serious as population, interventions, comparator and outcomes are as defined in protocol
[4]Downgrade 1 level: no interventions had probability of being best and worse ≥0.5
[5]Downgrade 1 level: tau^2≥0.5
[6]Maximum downgrade by 2 levels

8.4.12.3 Change in blood glucose (HbA1c) up to 12 months

Results of the NMA are summarised below for the 32 treatment combinations that were compared with metformin-NPH insulin up to 12 months. Of the 32 treatment combinations, 6 were 3 non-insulin based drug combinations, 6 were insulin only, 16 were insulin + 1 non-insulin based drug combinations and 4 were insulin + 2 non-insulin based drug combinations.

Where available, there is reasonable agreement between the NMA evidence and direct pairwise treatment effect estimates as demonstrated by the substantial overlap between the credible/confidence intervals. Overall, credible intervals crossed the line of no effect.

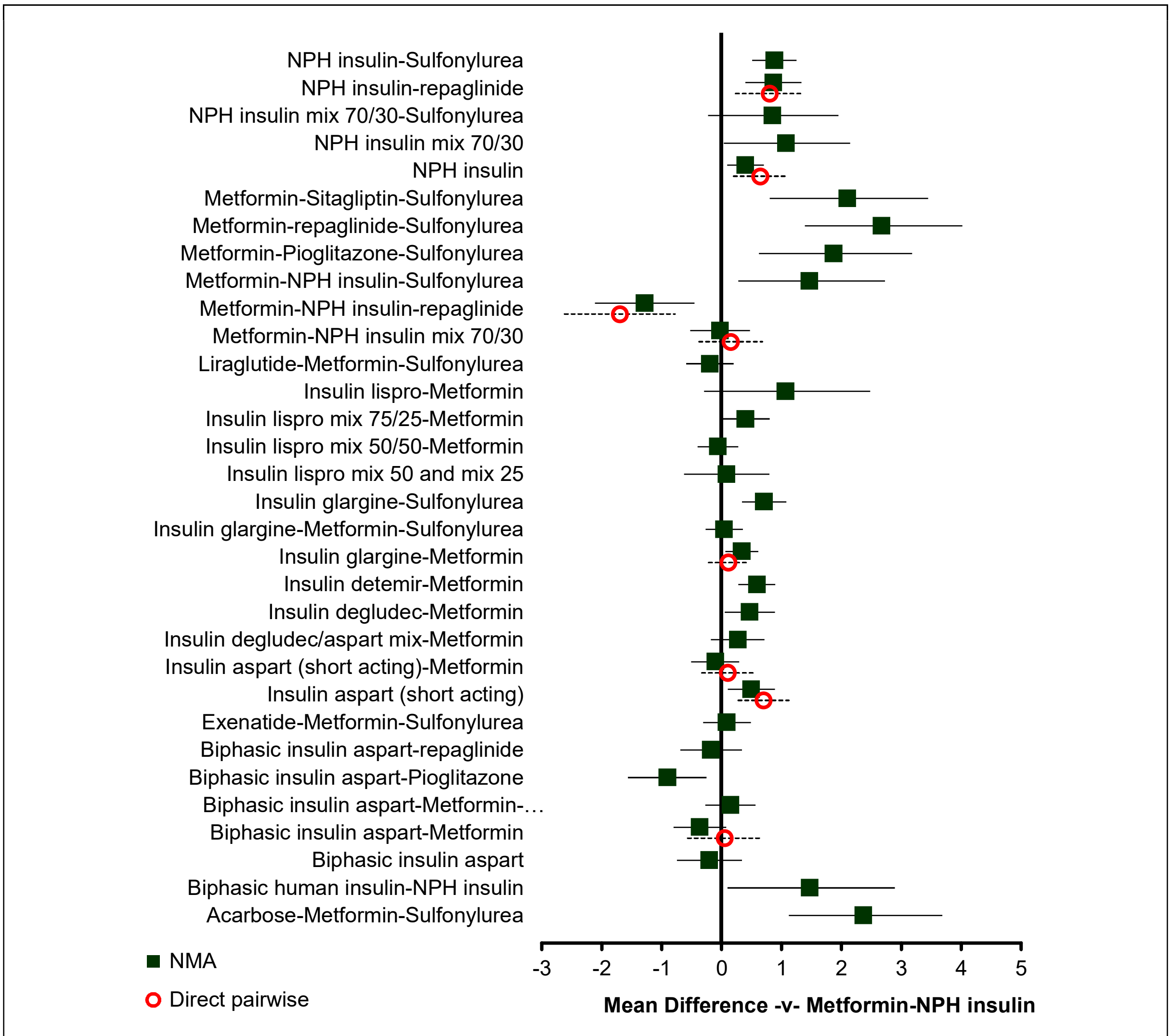
However, in general, compared to metformin-NPH insulin, 3 non-insulin based drug combinations, insulin only and insulin + 1 non-insulin based drug were shown to be less effective in reducing HbA1c levels. Of the 4 insulin + 2 non-insulin based drug combinations, only NPH insulin-metformin-repaglinide were shown to be more effective in reducing HbA1c levels than metformin-NPH insulin. This treatment combination had the highest ranking (median rank 1 [95% credible interval 1 to 7)], whereas metformin-repaglinide-sulfonylurea had the lowest ranking (median rank 33 [26 to 33]). The combination with the second highest ranking was biphasic insulin aspart-pioglitazone (median rank 2 [1 to 15]).



1 Metformin-NPH insulin
2 Acarbose-Metformin-Sulfonylurea
3 Biphasic human insulin-NPH insulin
4 Biphasic insulin aspart
5 Biphasic insulin aspart-Metformin
6 Biphasic insulin aspart-Metformin-Sulfonylurea
7 Biphasic insulin aspart-Pioglitazone
8 Biphasic insulin aspart-repaglinide
9 Exenatide-Metformin-Sulfonylurea
10 Insulin aspart (short acting)
11 Insulin aspart (short acting)-Metformin
12 Insulin degludec/aspart mix-Metformin
13 Insulin degludec-Metformin
14 Insulin detemir-Metformin
15 Insulin glargine-Metformin
16 Insulin glargine-Metformin-Sulfonylurea
17 Insulin glargine-Sulfonylurea
18 Insulin lispro mix 50 and mix 25
19 Insulin lispro mix 50/50-Metformin
20 Insulin lispro mix 75/25-Metformin
21 Insulin lispro-Metformin
22 Liraglutide-Metformin-Sulfonylurea
23 Metformin-NPH insulin mix 70/30
24 Metformin-NPH insulin-repaglinide
25 Metformin-NPH insulin-Sulfonylurea
26 Metformin-Pioglitazone-Sulfonylurea
27 Metformin-repaglinide-Sulfonylurea
28 Metformin-Sitagliptin-Sulfonylurea
29 NPH insulin
30 NPH insulin mix 70/30
31 NPH insulin mix 70/30-Sulfonylurea
32 NPH insulin-repaglinide
33 NPH insulin-Sulfonylurea

Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 49: Network meta-analysis of change in HbA1c (up to 12 months) – evidence network



Values greater than 0 favour metformin-NPH insulin; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 50: Network meta-analysis of change in HbA1c (up to 12 months) – relative effect of all options compared with common comparator (metformin-NPH insulin)

Table 77: Network meta-analysis of change in HbA1c (up to 12 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-NPH insulin	0.000	10 (5, 15)
Acarbose-Metformin-Sulfonylurea	0.000	32 (31, 32)
Biphasic human insulin-NPH insulin	0.000	28 (14, 30)
Biphasic insulin aspart	0.000	6 (3, 16)
Biphasic insulin aspart-Metformin	0.000	4 (3, 9)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.000	13 (7, 21)
Biphasic insulin aspart-Pioglitazone	0.236	2 (1, 3)
Biphasic insulin aspart-repaglinide	0.000	6 (3, 16)
Exenatide-Metformin-Sulfonylurea	0.000	12 (6, 18)
Insulin aspart (short acting)	0.000	20 (12, 27)
Insulin aspart (short acting)-Metformin	0.000	8 (3, 16)
Insulin degludec/aspart mix-Metformin	0.000	15 (7, 23)
Insulin degludec-Metformin	0.000	19 (12, 26)
Insulin detemir-Metformin	0.000	21 (17, 27)
Insulin glargine-Metformin	0.000	17 (12, 21)
Insulin glargine-Metformin-Sulfonylurea	0.000	11 (6, 16)
Insulin glargine-Sulfonylurea	0.000	22 (18, 28)
Insulin lispro mix 50 and mix 25	0.001	12 (3, 23)
Insulin lispro mix 50/50-Metformin	0.000	8 (3, 15)
Insulin lispro mix 75/25-Metformin	0.000	18 (10, 25)
Insulin lispro-Metformin	0.001	26 (5, 28)
Liraglutide-Metformin-Sulfonylurea	0.000	6 (3, 12)
Metformin-NPH insulin mix 70/30	0.000	9 (3, 20)
Metformin-NPH insulin-repaglinide	0.761	1 (1, 3)
Metformin-NPH insulin-Sulfonylurea	0.000	28 (19, 29)
Metformin-Pioglitazone-Sulfonylurea	0.000	30 (26, 31)
Metformin-repaglinide-Sulfonylurea	0.000	33 (32, 33)
Metformin-Sitagliptin-Sulfonylurea	0.000	31 (29, 32)
NPH insulin	0.000	18 (13, 23)
NPH insulin mix 70/30	0.000	26 (13, 29)
NPH insulin mix 70/30-Sulfonylurea	0.000	24 (6, 27)
NPH insulin-repaglinide	0.000	24 (18, 31)
NPH insulin-Sulfonylurea	0.000	24 (22, 30)

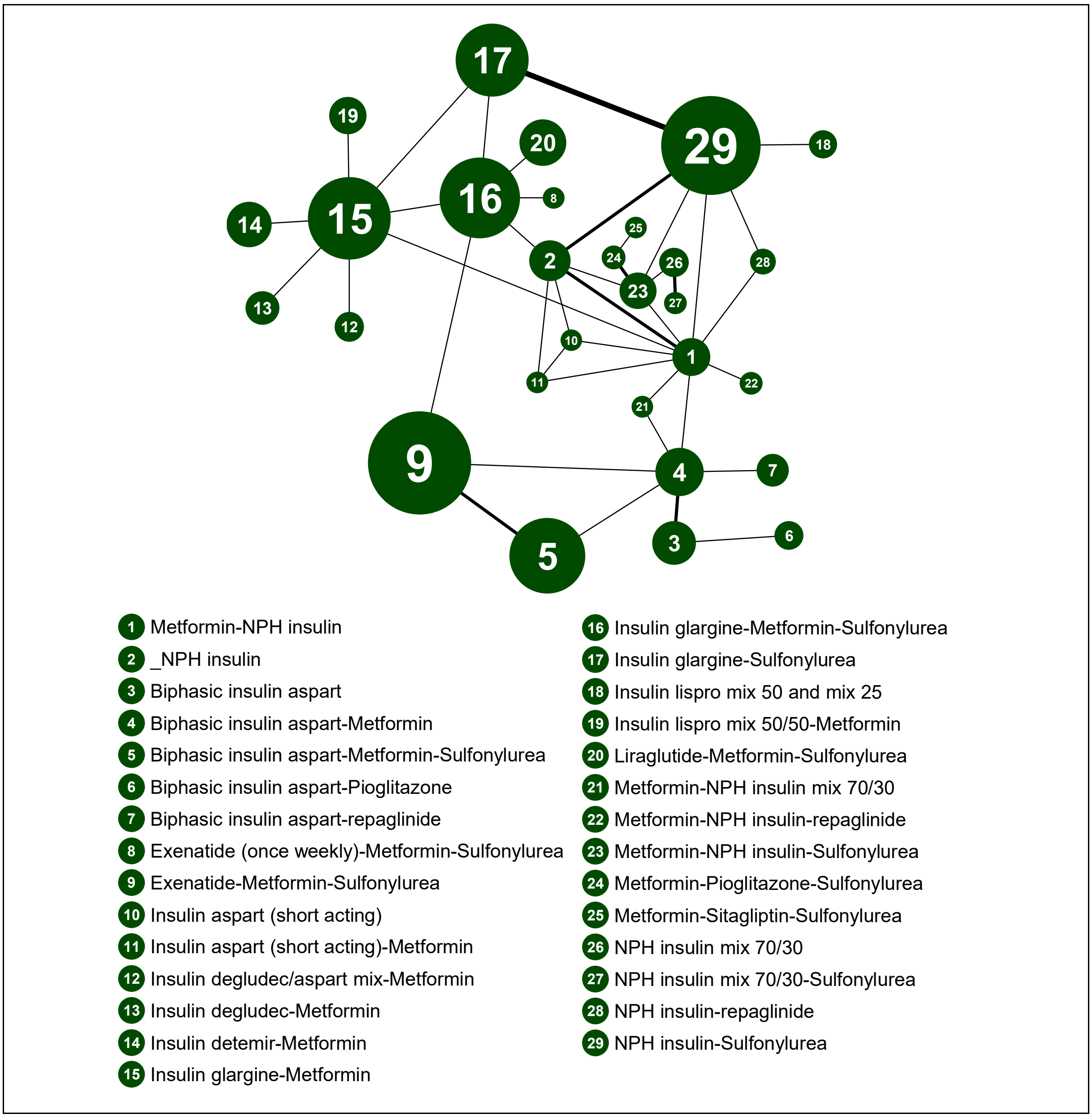
8.4.12.4 Hypoglycaemia at study end point

Results of the NMA are summarised below for the 28 treatment combinations that were compared with metformin-NPH insulin. Of the 28 treatment combinations, 5 were 3 non-insulin based drug combinations, 5 were insulin only, 14 were insulin + 1 non-insulin based drug combinations and 4 were insulin + 2 non-insulin based drug combinations.

There is reasonable agreement between the NMA evidence and direct pairwise treatment effect estimates as demonstrated by the substantial overlap between the credible/confidence intervals. In the main, credible intervals were wide and crossed the line of no effect.

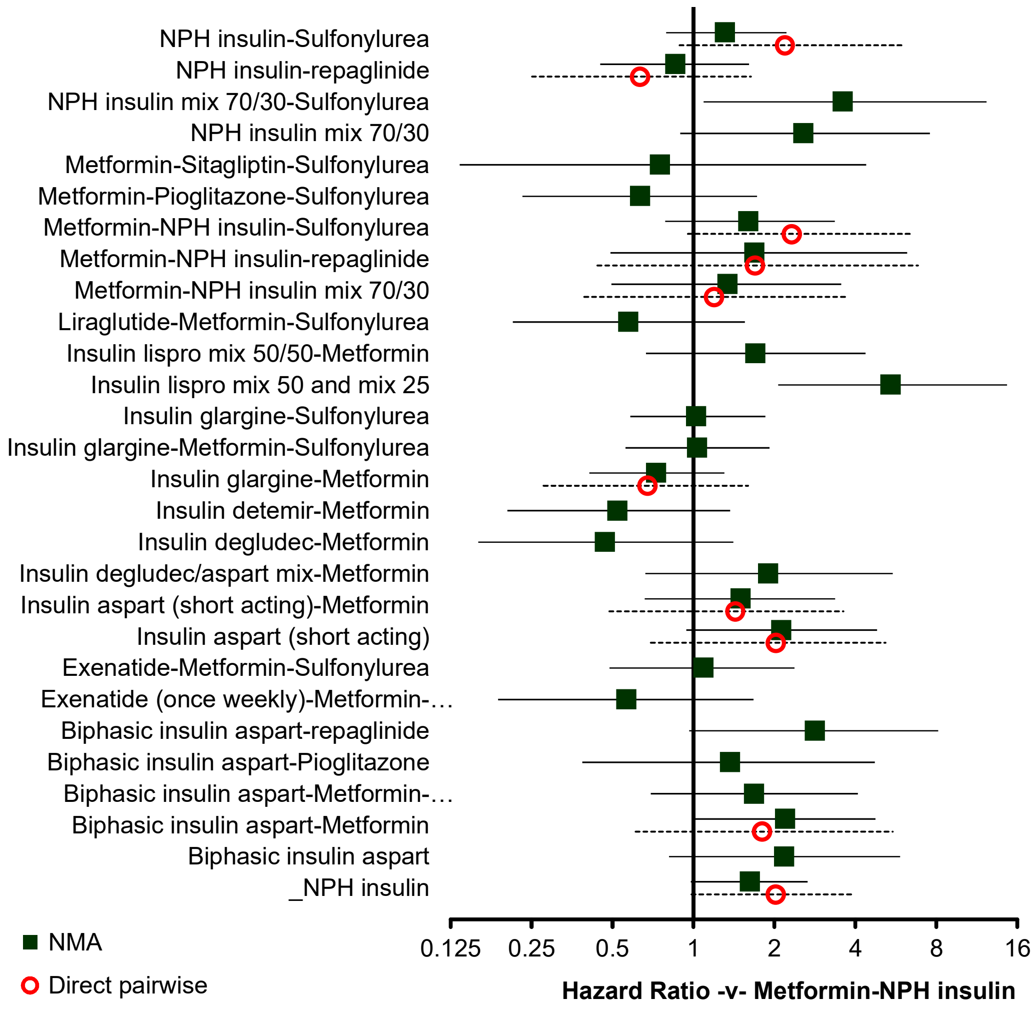
However, in general, compared to metformin-NPH insulin, insulin only and insulin + 2 non-insulin based drug combinations were shown to be associated with greater hypoglycaemic events, whereas, 3 non-insulin based drug combinations were generally associated with less hypoglycaemic events. Insulin + 1 non-insulin based drug combination were generally associated with greater hypoglycaemic events when compared to metformin-NPH insulin except for metformin combined with insulin glargine, detemir or degludec and NPH-insulin combined with repaglinide.

The treatment combinations with the highest ranking were metformin-insulin degludec (median rank 3 [95% credible interval 1 to 16)] and metformin-insulin detemir (median rank 3 [1 to 15]) though the associated credible intervals were wide. Insulin lispro mix 50 and mix 25 was associated with the lowest ranking (median rank 29 [22 to 29]).



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 51: Network meta-analysis of hypoglycaemic events (study end point) – evidence network



Values greater than 1 favour metformin-NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 52: Network meta-analysis of hypoglycaemic events (study end point) – relative effect of all options compared with common comparator (metformin-NPH insulin)

Table 78: Network meta-analysis of hypoglycaemic events (study end point) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-NPH insulin	0.000	10 (5, 17)
Biphasic insulin aspart	0.000	23 (9, 28)
Biphasic insulin aspart-Metformin	0.000	23 (13, 27)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.000	19 (8, 27)
Biphasic insulin aspart-Pioglitazone	0.015	16 (2, 27)
Biphasic insulin aspart-repaglinide	0.000	26 (12, 29)
Exenatide (once weekly)-Metformin-Sulfonylurea	0.156	4 (1, 17)
Exenatide-Metformin-Sulfonylurea	0.001	12 (4, 21)
Insulin aspart (short acting)	0.000	22 (10, 28)
Insulin aspart (short acting)-Metformin	0.001	17 (5, 27)
Insulin degludec/aspart mix-Metformin	0.000	21 (7, 28)
Insulin degludec-Metformin	0.284	3 (1, 16)
Insulin detemir-Metformin	0.157	3 (1, 15)
Insulin glargine-Metformin	0.001	6 (3, 14)
Insulin glargine-Metformin-Sulfonylurea	0.000	11 (5, 19)
Insulin glargine-Sulfonylurea	0.000	11 (5, 19)
Insulin lispro mix 50 and mix 25	0.000	29 (22, 29)
Insulin lispro mix 50/50-Metformin	0.000	19 (7, 28)
Liraglutide-Metformin-Sulfonylurea	0.120	4 (1, 16)
Metformin-NPH insulin mix 70/30	0.005	15 (3, 26)
Metformin-NPH insulin-repaglinide	0.009	19 (3, 29)
Metformin-NPH insulin-Sulfonylurea	0.000	18 (8, 26)
Metformin-Pioglitazone-Sulfonylurea	0.075	5 (1, 18)
Metformin-Sitagliptin-Sulfonylurea	0.164	7 (1, 27)
NPH insulin	0.000	19 (12, 25)
NPH insulin mix 70/30	0.000	24 (10, 28)
NPH insulin mix 70/30-Sulfonylurea	0.000	27 (14, 29)
NPH insulin-repaglinide	0.009	8 (2, 19)
NPH insulin-Sulfonylurea	0.000	15 (9, 22)

8.4.12.5 Adverse events at study end point

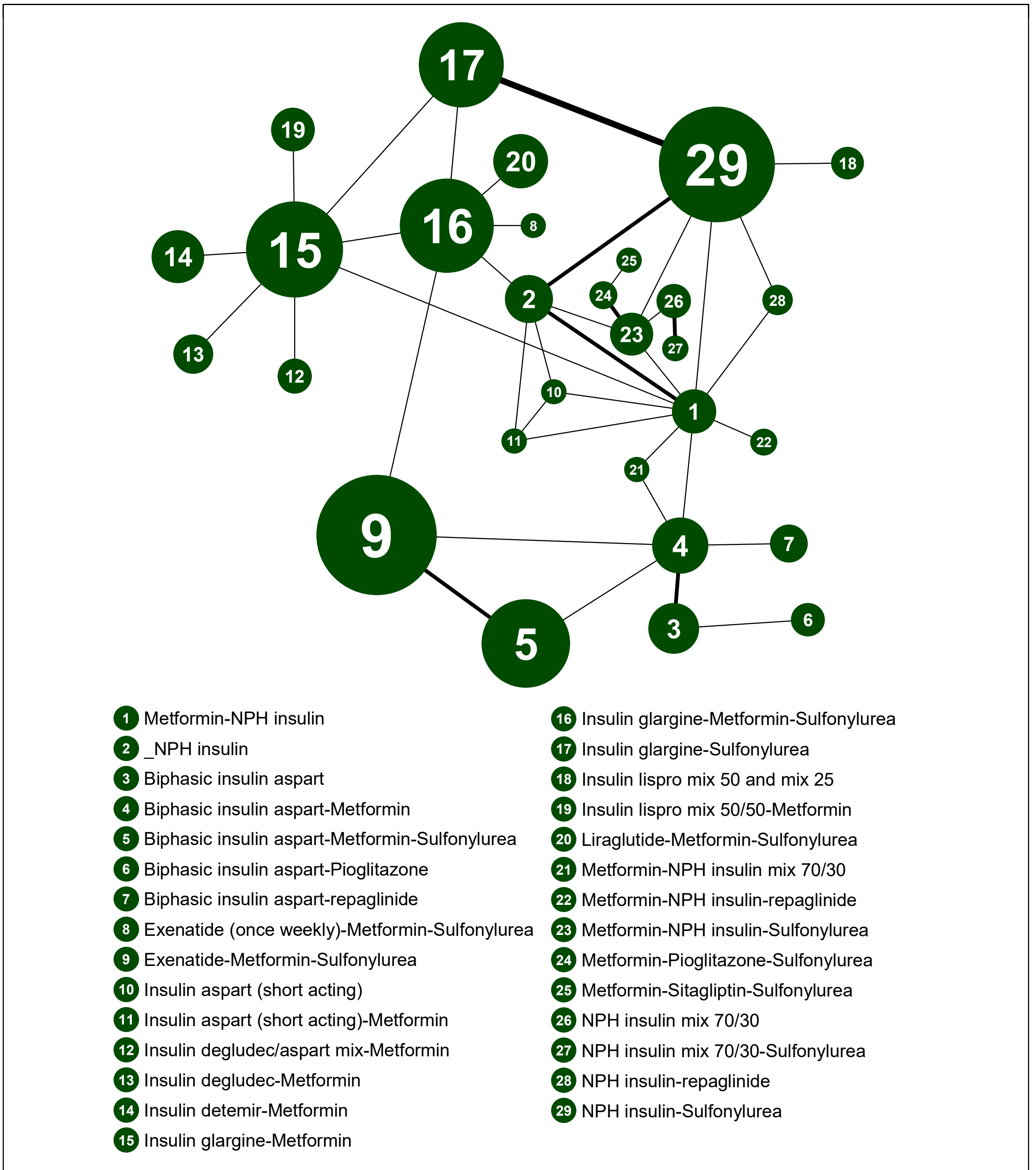
Results of the 3 NMAs are summarised below. For dropouts due to adverse events and total dropouts, 26 and 25 treatment combinations were compared with metformin-NPH insulin respectively, while 4 treatment combinations were compared with metformin-biphasic insulin aspart for nausea.

In general, there is reasonable agreement between the NMA evidence and direct pairwise treatment effect estimates, with substantial overlap between the credible/confidence intervals. However, there is substantial uncertainty in the data as the relative estimates are associated with considerably wide credible intervals with all crossing the line of no effect.

Insulin lispro mix 50 and mix 25 had the highest ranking (median rank 4 [1 to 19]) for dropouts due to adverse events, whereas a 3 non-insulin based drug combination (metformin-repaglinide-sulfonylurea) had the highest ranking for total dropouts (median rank 1 [1 to 23]) and 3 of the insulin combinations shared the highest ranking for nausea;

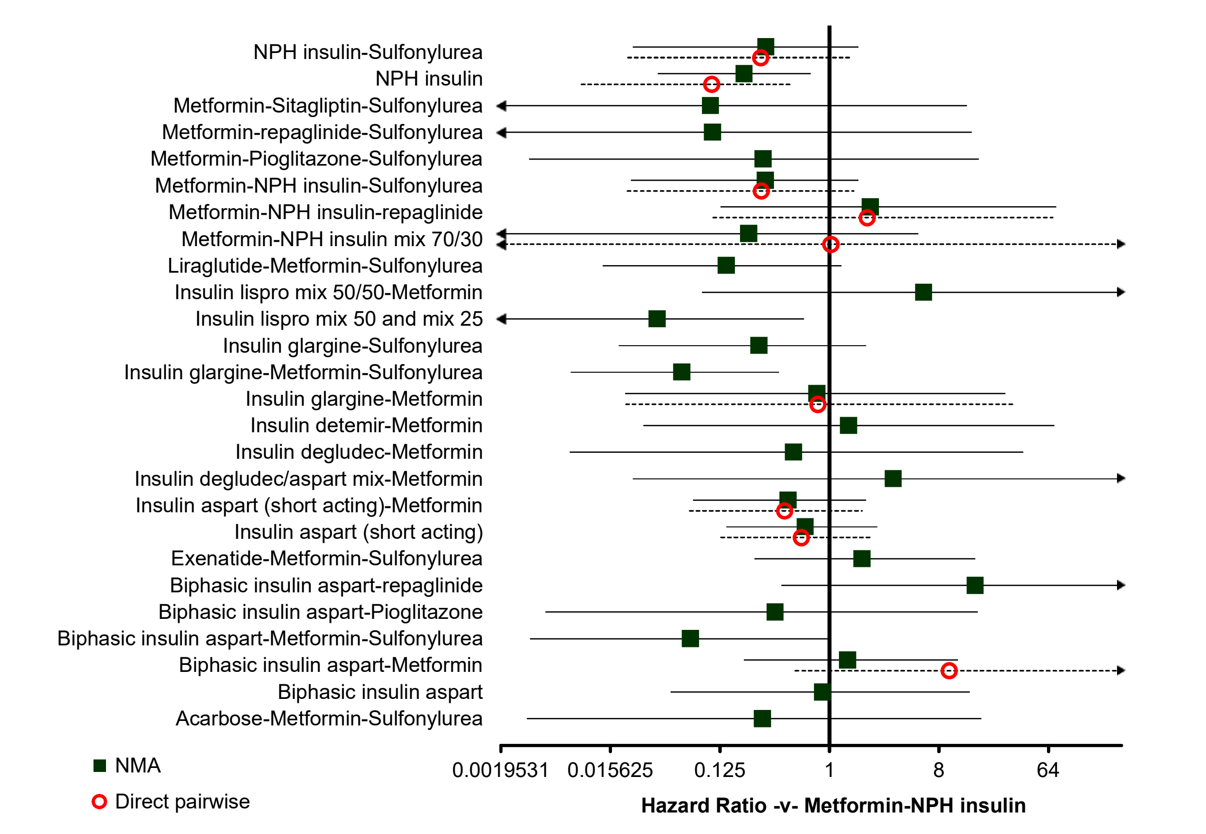
metformin-biphasic insulin aspart (median rank 2 [1 to 5]), metformin-sulfonylurea-biphasic insulin aspart (median rank 2 [1 to 5]) and metformin-sulfonylurea-insulin glargine (median rank 2 [1 to 5]).

Biphasic insulin aspart-repaglinide (median rank 26 [12 to 27]) and insulin aspart (short acting) (median rank 25 [13 to 26]) were ranked lowest for dropouts due to adverse events and total dropouts respectively.



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 53: Network meta-analysis of dropouts due to adverse events (study end point) – evidence network

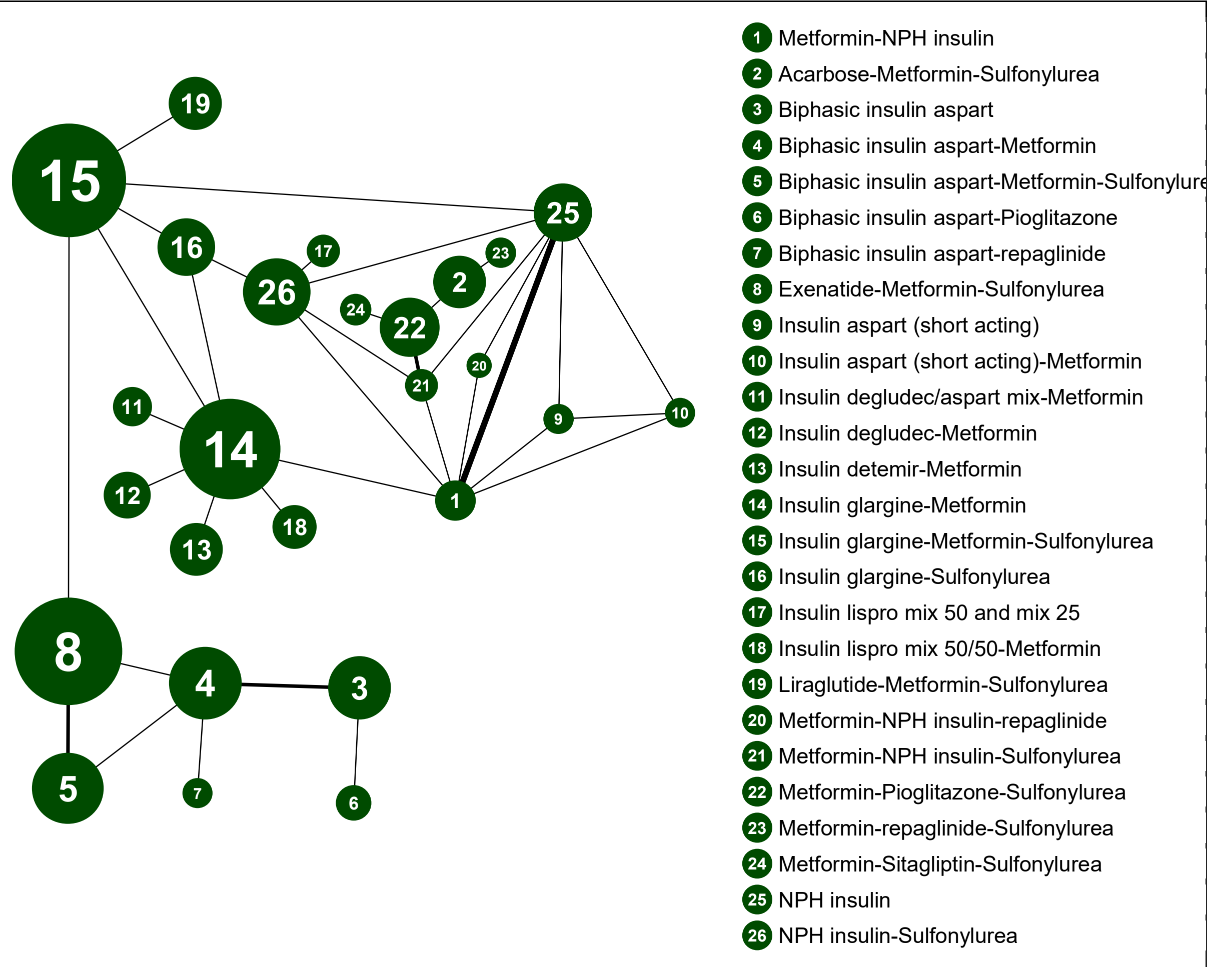


Values greater than 1 favour metformin-NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 54: Network meta-analysis of dropouts due to adverse events (study end point) – relative effect of all options compared with common comparator (metformin-NPH insulin)

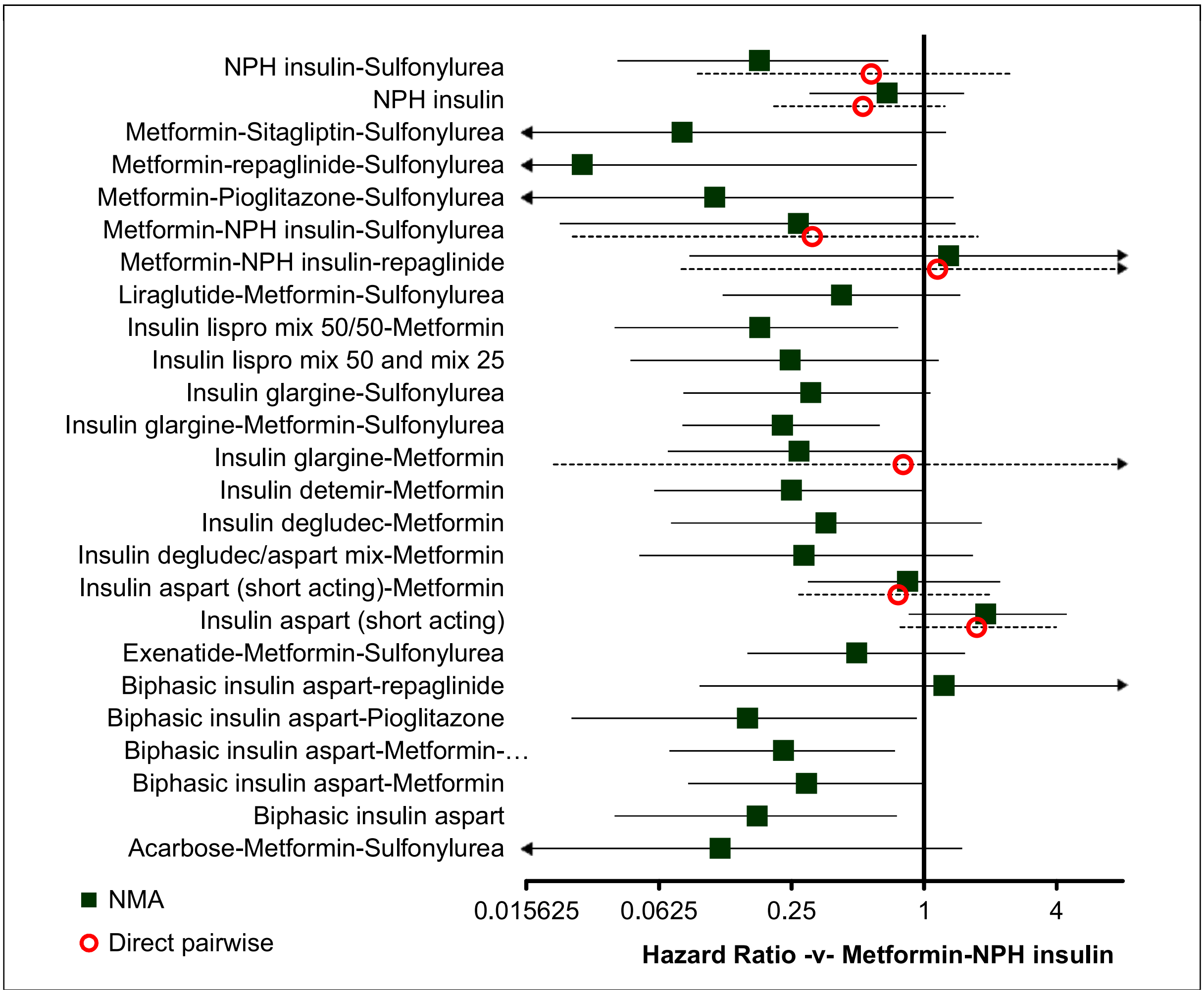
Table 79: Network meta-analysis of dropouts due to adverse events (study end point) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-NPH insulin	0.000	19 (12, 24)
Acarbose-Metformin-Sulfonylurea	0.004	12 (2, 26)
Biphasic insulin aspart	0.000	18 (5, 26)
Biphasic insulin aspart-Metformin	0.000	20 (10, 25)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.114	5 (1, 17)
Biphasic insulin aspart-Pioglitazone	0.050	13 (1, 26)
Biphasic insulin aspart-repaglinide	0.000	26 (14, 27)
Exenatide-Metformin-Sulfonylurea	0.000	22 (12, 26)
Insulin aspart (short acting)	0.000	16 (6, 24)
Insulin aspart (short acting)-Metformin	0.003	14 (4, 23)
Insulin degludec/aspart mix-Metformin	0.008	23 (3, 27)
Insulin degludec-Metformin	0.036	14 (1, 26)
Insulin detemir-Metformin	0.003	20 (4, 26)
Insulin glargine-Metformin	0.004	17 (3, 24)
Insulin glargine-Metformin-Sulfonylurea	0.082	4 (1, 12)
Insulin glargine-Sulfonylurea	0.003	11 (2, 22)
Insulin lispro mix 50 and mix 25	0.268	3 (1, 15)
Insulin lispro mix 50/50-Metformin	0.000	25 (8, 27)
Liraglutide-Metformin-Sulfonylurea	0.006	8 (2, 19)
Metformin-NPH insulin mix 70/30	0.119	10 (1, 25)
Metformin-NPH insulin-repaglinide	0.002	22 (7, 27)
Metformin-NPH insulin-Sulfonylurea	0.005	12 (3, 21)
Metformin-Pioglitazone-Sulfonylurea	0.003	12 (3, 26)
Metformin-repaglinide-Sulfonylurea	0.146	7 (1, 26)
Metformin-Sitagliptin-Sulfonylurea	0.143	6 (1, 25)
NPH insulin	0.001	9 (3, 17)
NPH insulin-Sulfonylurea	0.000	12 (3, 22)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 55: Network meta-analysis of total dropouts (study end point) – evidence network

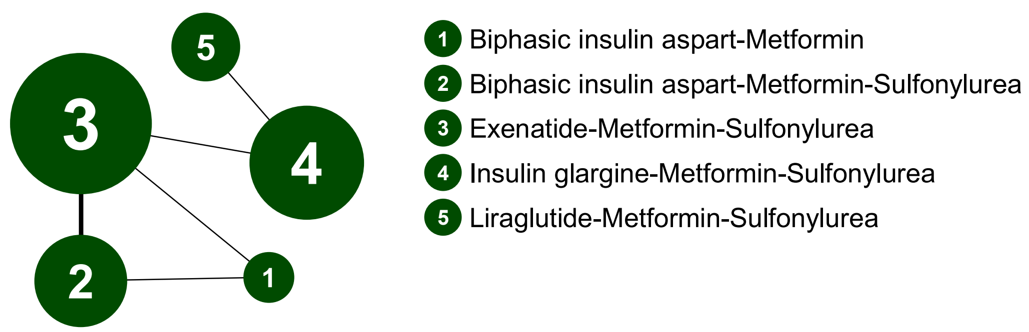


Values greater than 1 favour metformin- NPH insulin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 56: Network meta-analysis of total dropouts (study end point) – relative effect of all options compared with common comparator (metformin-NPH insulin)

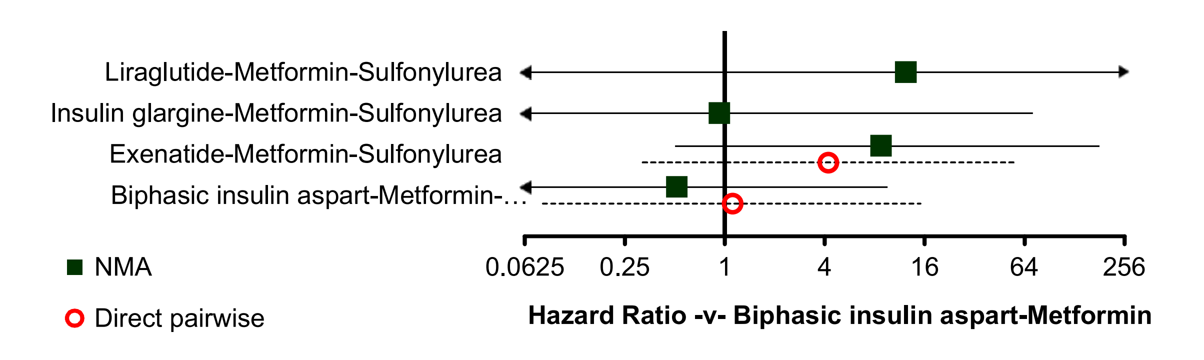
Table 80: Network meta-analysis of total dropouts (study end point) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-NPH insulin	0.000	23 (17, 25)
Acarbose-Metformin-Sulfonylurea	0.009	5 (2, 24)
Biphasic insulin aspart	0.025	8 (2, 18)
Biphasic insulin aspart-Metformin	0.000	14 (5, 20)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.003	10 (3, 18)
Biphasic insulin aspart-Pioglitazone	0.081	7 (1, 21)
Biphasic insulin aspart-repaglinide	0.005	24 (5, 26)
Exenatide-Metformin-Sulfonylurea	0.000	19 (11, 24)
Insulin aspart (short acting)	0.000	25 (22, 26)
Insulin aspart (short acting)-Metformin	0.000	22 (11, 25)
Insulin degludec/aspart mix-Metformin	0.014	13 (2, 24)
Insulin degludec-Metformin	0.003	16 (4, 25)
Insulin detemir-Metformin	0.003	11 (3, 21)
Insulin glargine-Metformin	0.000	13 (4, 20)
Insulin glargine-Metformin-Sulfonylurea	0.002	10 (4, 17)
Insulin glargine-Sulfonylurea	0.001	14 (5, 22)
Insulin lispro mix 50 and mix 25	0.015	11 (2, 23)
Insulin lispro mix 50/50-Metformin	0.038	8 (1, 18)
Liraglutide-Metformin-Sulfonylurea	0.000	17 (7, 24)
Metformin-NPH insulin-repaglinide	0.010	24 (3, 26)
Metformin-NPH insulin-Sulfonylurea	0.005	12 (3, 24)
Metformin-Pioglitazone-Sulfonylurea	0.013	4 (2, 23)
Metformin-repaglinide-Sulfonylurea	0.610	1 (1, 21)
Metformin-Sitagliptin-Sulfonylurea	0.130	3 (1, 22)
NPH insulin	0.000	21 (14, 24)
NPH insulin-Sulfonylurea	0.033	8 (1, 18)



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available.

Figure 57: Network meta-analysis of nausea (study end point) – evidence network



Values greater than 1 favour Biphasic insulin aspart-metformin; values less than 1 favour the comparator treatment. Direct pairwise evidence is drawn from inconsistency model. Solid and dashed error bars are 95% credible intervals.

Figure 58: Network meta-analysis of nausea (study end point) – relative effect of all options compared with common comparator (metformin-biphasic insulin aspart)

Table 81: Network meta-analysis of Nausea (study end point) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Biphasic insulin aspart-Metformin	0.222	2 (1, 5)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.460	2 (1, 4)
Exenatide-Metformin-Sulfonylurea	0.000	4 (3, 5)
Insulin glargine-Metformin-Sulfonylurea	0.292	2 (1, 4)
Liraglutide-Metformin-Sulfonylurea	0.025	5 (1, 5)

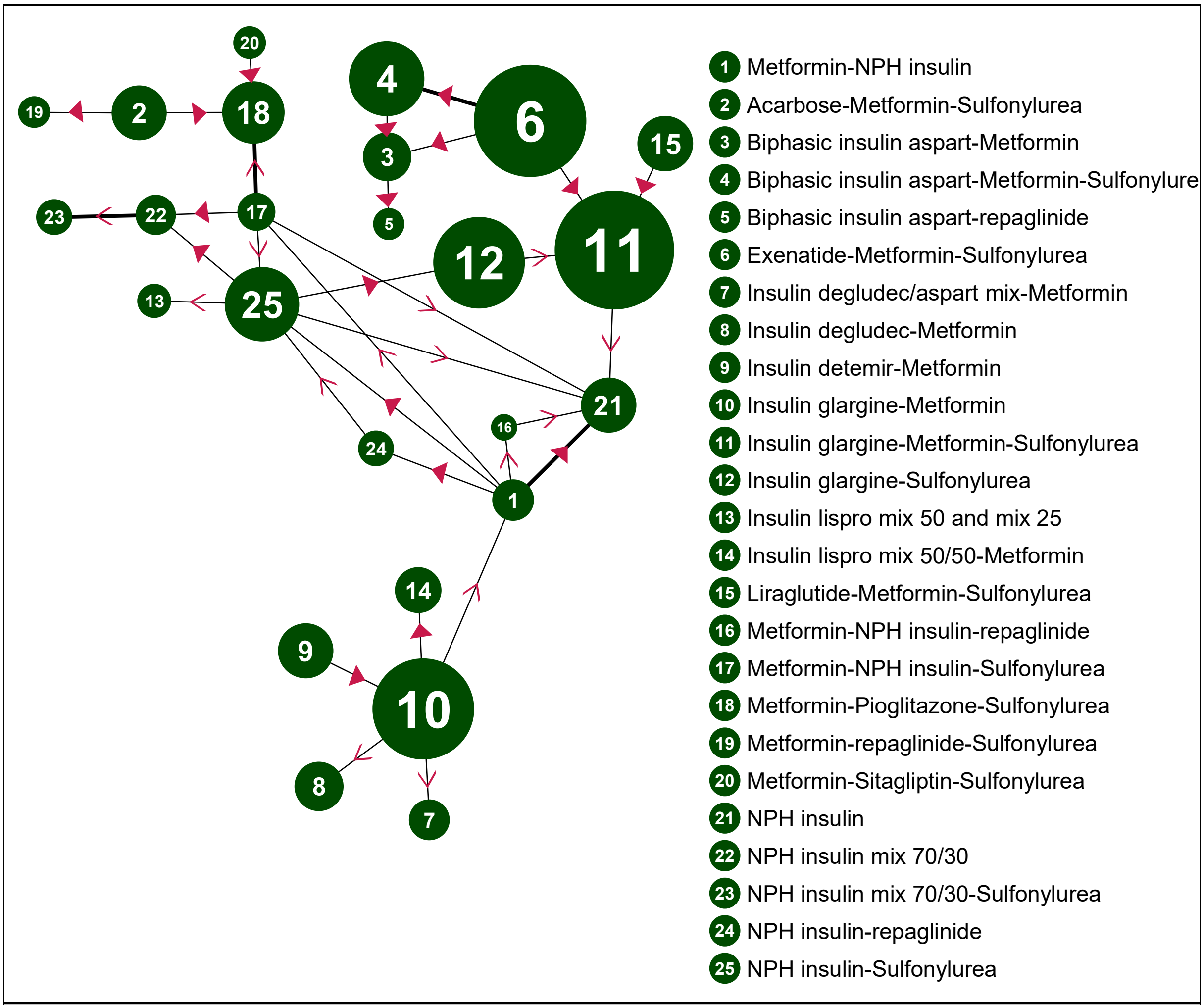
8.4.12.6 Change in body weight up to 12 months

Results of the NMA are summarised below for the 24 treatment combinations that were compared with metformin-NPH insulin. Of the 24 treatment combinations, 6 were 3 non-insulin based drug combinations, 3 were insulin only, 11 were insulin + 1 non-insulin based drug combinations and 4 were insulin + 2 non-insulin based drug combinations.

There is reasonable agreement between the NMA evidence and direct pairwise treatment effect estimates as demonstrated by the substantial overlap between the credible/confidence intervals.

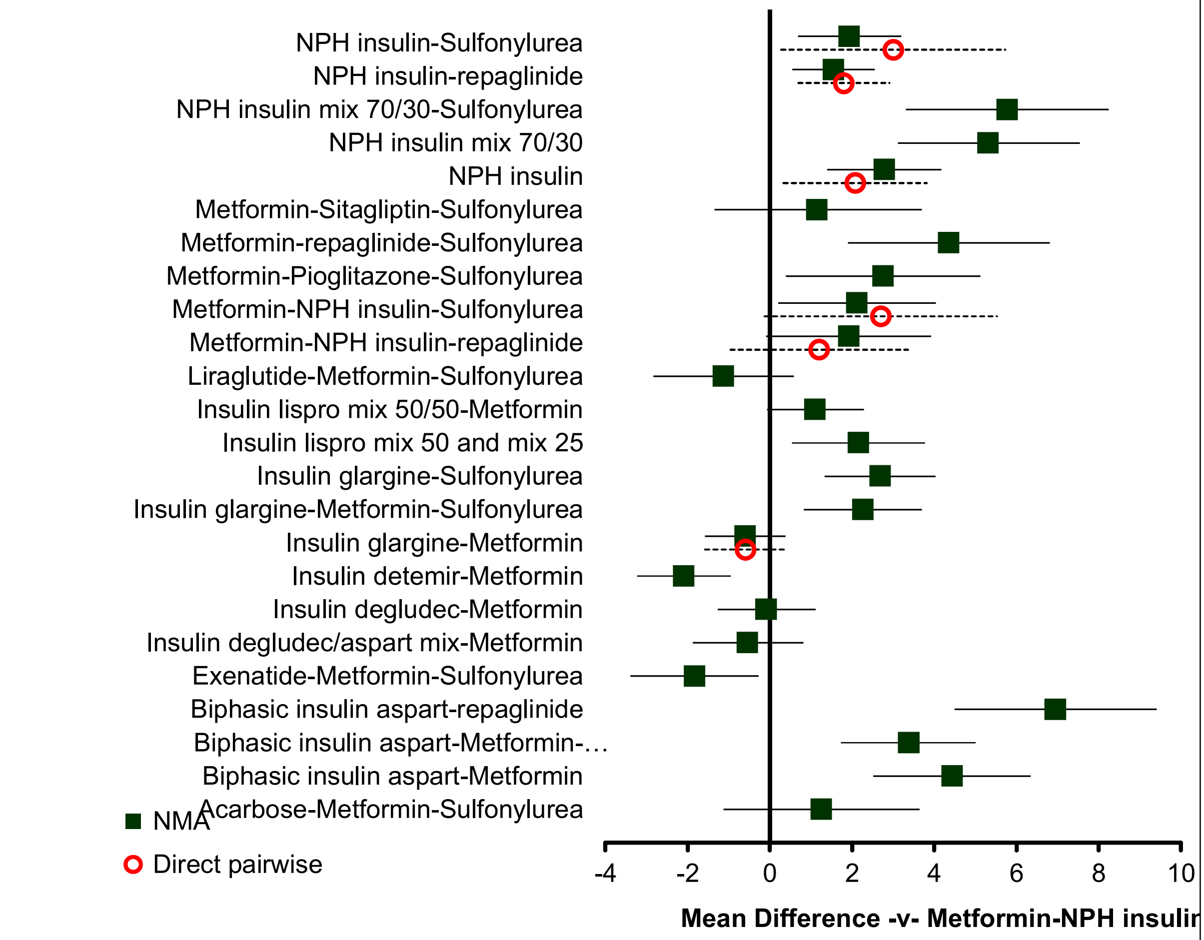
In general, compared to metformin-NPH insulin, insulin only and insulin + 2 non-insulin based drug combination were shown to be associated with weight gain. Combinations of 3 non-insulin based drug combinations were generally associated with weight gain except for combinations with GLP-1 mimetics (exenatide, liraglutide) with metformin and sulfonylurea which showed a trend for weight loss compared to metformin-NPH insulin, though credible intervals crossed the line of no effect. Insulin + 1 non-insulin based drug combinations were generally associated with weight gain, except for metformin-insulin detemir which was associated with weight loss.

The treatment combinations with the highest ranking were exenatide-metformin-sulfonylurea (median rank 2 [1 to 7]) and metformin-insulin detemir (median rank 2 [1 to 4]). Biphasic insulin aspart-repaglinide was associated with the lowest ranking (median rank 25 [22 to 25]).



Size of nodes is proportional to total number of participants randomised to receive the treatment in question across the evidence-base. Width of connecting lines is proportional to number of trial-level comparisons available. Arrowheads indicate direction of effect in pairwise data (a > b denotes a is more effective than b) – filled arrowheads show comparisons where one option is significantly superior (p<0.05); outlined arrowheads show direction of trend where effect does not reach statistical significance.

Figure 59: Network meta-analysis of change in body weight (up to 12 months) – evidence network



Values greater than 0 favour metformin-NPH insulin; values less than 0 favour the comparator treatment. Solid error bars are 95% credible intervals; dashed error bars are 95% confidence interval.

Figure 60: Network meta-analysis of change in body weight (up to 12 months) – relative effect of all options compared with common comparator (metformin-NPH insulin)

Table 82: Network meta-analysis of change in body weight (12 months) – rankings for each comparator

	Probability best	Median rank (95%CrI)
Metformin-NPH insulin	0.000	7 (4, 9)
Acarbose-Metformin-Sulfonylurea	0.001	10 (4, 18)
Biphasic insulin aspart-Metformin	0.000	22 (19, 24)
Biphasic insulin aspart-Metformin-Sulfonylurea	0.000	20 (14, 22)
Biphasic insulin aspart-repaglinide	0.000	25 (22, 25)
Exenatide-Metformin-Sulfonylurea	0.366	2 (1, 5)
Insulin degludec/aspart mix-Metformin	0.001	5 (2, 9)
Insulin degludec-Metformin	0.000	6 (3, 10)
Insulin detemir-Metformin	0.589	1 (1, 3)
Insulin glargine-Metformin	0.000	4 (2, 7)
Insulin glargine-Metformin-Sulfonylurea	0.000	15 (9, 19)
Insulin glargine-Sulfonylurea	0.000	17 (12, 20)
Insulin lispro mix 50 and mix 25	0.000	14 (8, 20)
Insulin lispro mix 50/50-Metformin	0.000	10 (7, 17)
Liraglutide-Metformin-Sulfonylurea	0.041	3 (1, 8)
Metformin-NPH insulin-repaglinide	0.000	13 (7, 21)
Metformin-NPH insulin-Sulfonylurea	0.000	14 (9, 20)
Metformin-Pioglitazone-Sulfonylurea	0.000	18 (10, 21)
Metformin-repaglinide-Sulfonylurea	0.000	22 (16, 24)
Metformin-Sitagliptin-Sulfonylurea	0.003	10 (3, 18)
NPH insulin	0.000	18 (12, 20)
NPH insulin mix 70/30	0.000	23 (20, 25)
NPH insulin mix 70/30-Sulfonylurea	0.000	24 (21, 25)
NPH insulin-repaglinide	0.000	11 (8, 17)
NPH insulin-Sulfonylurea	0.000	13 (9, 17)

8.4.13 Health economic evidence for second intensification

8.4.13.1 Systematic review of published cost–utility analyses

For second intensification, 7 UK studies were included covering 4 broad comparisons (Beaudet et al. 2011; McEwan et al. 2007; Pollock et al. 2012; Ray et al. 2007; Valentine et al. 2005; Waugh et al. 2010; Woehl et al. 2008), none of which covered all the comparators included in this guideline. Ray et al. (2007), Waugh et al. (2010) and Woehl et al. (2008) all compared exenatide with insulin glargine. All were based on the same RCT evidence (Heine et al. 2005) but found different results, because of differing treatment effect assumptions, drug price assumptions and weight loss utilities/profiles. Ray et al. (2007) thought exenatide-metformin-sulfonylurea was cost-effective compared to insulin glargine-metformin-sulfonylurea (ICER £22,400 per QALY); Waugh et al. (2010) found similar ICERs (ICERs 19,900 per QALY for males and £18,400 for females). Woehl et al. (2008) found insulin glargine-metformin-sulfonylurea dominated exenatide-metformin-sulfonylurea. Beaudet et al. (2011) compared exenatide once weekly with insulin glargine twice daily and found exenatide to be cost effective (ICER £10,600 per QALY), but did not model treatment withdrawals.

Two studies compared different biphasic insulins with insulin glargine. Pollock et al. (2012) found insulin lispro 50/50 to be dominant compared with insulin glargine, but assumed people were not taking concomitant oral medications and did not list their cost and utility sources. Valentine et al. (2005) found insulin aspart 70/30 to be cost effective compared with insulin glargine (ICER £7000 per QALY), but used a non-UK population and did not appear to model hypoglycaemia.

Two studies compared NPH insulin with insulin glargine, but came to opposing conclusions. McEwan et al. (2007) modelled either HbA1c or hypoglycaemia using unpublished treatment effect data and found insulin glargine to be cost effective compared with NPH insulin (ICER £13,900 per QALY for HbA1c reduction only, £10,000 per QALY for hypoglycaemia reduction only). Waugh et al. (2010) found insulin glargine-metformin-sulfonylurea was not cost effective compared with metformin-NPH insulin-sulfonylurea (ICERs £281,300 per QALY for males and £178,000 per QALY for females). Waugh et al. (2010) also found insulin detemir was not cost-effective compared with NPH insulin (ICER £187,700 per QALY for males and £102,000 per QALY for females), but their analysis did not cover all the comparators included in this guideline.

As no directly applicable studies with only minor limitations were found that covered all the comparators under consideration for each sub-question for this guideline, an original economic analysis was undertaken.

8.4.13.2 Original health economic analysis

For second intensification, 20 treatments could be modelled. People accrued an average of 13.9 undiscounted life years. Because of slightly greater differences in HbA1c treatment effects and a lack of further intensification, second intensification showed larger differences in lifetime complication rates than initial therapy and first intensification.

People accumulated between 6.8 and 7.4 lifetime discounted QALYs, with losses because of weight changes of between 0.3 and 0.5 QALYs and losses because of hypoglycaemic episodes of between 0.2 and 0.6 QALYs.

Second intensification therapy with metformin-pioglitazone-sulfonylurea had the lowest lifetime discounted costs and was the most cost-effective treatment option (see table 83). Compared with this option, all other treatment options were subject to dominance or extended dominance, with the exceptions of insulin detemir-metformin (ICER £40,800 per QALY) and liraglutide-metformin-sulfonylurea (ICER £172,900 per QALY compared with insulin detemir-metformin).

Table 83: Mean lifetime incremental cost–utility results for second intensification therapy

Therapy	Lifetime discounted		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Metformin-pioglitazone-sulfonylurea	£17,279	7.147			
NPH insulin-sulfonylurea	£21,636	7.097	£4358	-0.050	Dominated
Metformin-sitagliptin-sulfonylurea	£21,763	7.126	£4484	-0.021	Dominated
Metformin-NPH insulin-sulfonylurea	£22,000	7.020	£4721	-0.127	Dominated
Metformin-NPH insulin	£22,108	7.230	£4829	0.083	Ext. dom.
Biphasic insulin aspart-repaglinide	£22,738	6.979	£5460	-0.168	Dominated
Insulin glargine-metformin-sulfonylurea	£22,870	7.173	£5591	0.026	Dominated
NPH insulin	£22,896	7.060	£5617	-0.086	Dominated
Metformin-NPH insulin-repaglinide	£22,899	7.161	£5620	0.015	Dominated
Insulin glargine-sulfonylurea	£23,260	7.135	£5982	-0.011	Dominated
Insulin degludec/aspart mix-metformin	£23,263	7.134	£5984	-0.013	Dominated
Biphasic insulin aspart-metformin-sulfonylurea	£23,303	7.051	£6025	-0.096	Dominated
Insulin glargine-metformin	£23,716	7.270	£6437	0.123	Ext. dom.
Biphasic insulin aspart-metformin	£24,028	7.013	£6750	-0.134	Dominated
Insulin lispro mix 50/50-metformin	£24,136	7.126	£6858	-0.021	Dominated
Insulin detemir-metformin	£24,228	7.317	£6950	0.170	£40,778
Exenatide-metformin-sulfonylurea	£25,795	7.229	£1567	-0.088	Dominated
Insulin degludec-metformin	£26,097	7.320	£1869	0.003	Ext. dom.
Insulin lispro mix 50 and mix 25	£26,307	6.818	£2078	-0.499	Dominated
Liraglutide-metformin-sulfonylurea	£30,166	7.352	£5937	0.034	£172,890

(a) Ext. dom. = extendedly dominated

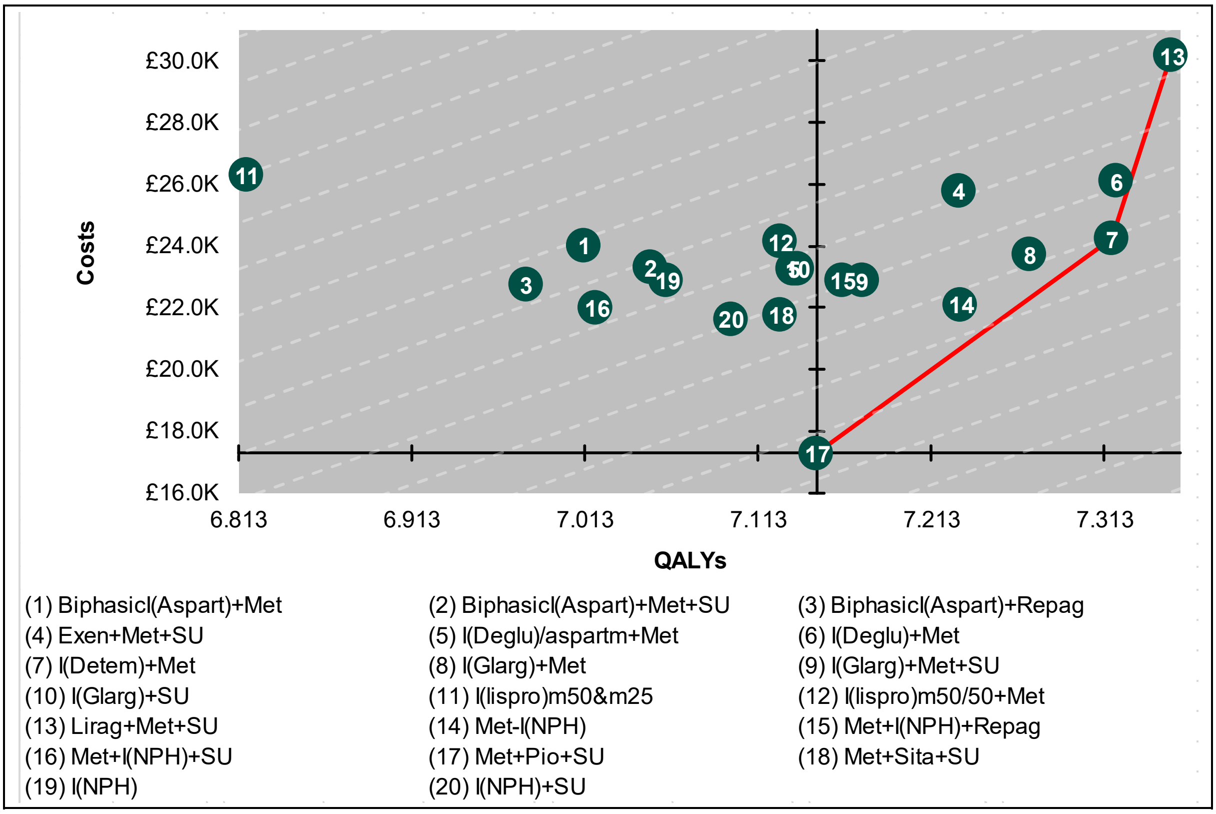


Figure 61: Cost–utility plane for 2nd intensification of therapy

There were a number of treatments with similar QALY gains and costs to insulin detemir-metformin (see figure 61). Of the group, insulin detemir-metformin gained the most QALYs because of its superior weight treatment effect, despite having the worst HbA1c/UKPDS QALYs of the group of treatment options. However, the GDG expressed concern as to whether such a weight change was achievable and sustainable in practice. In order to assess the sensitivity of the health economic model to the weight change assumptions, a sensitivity analysis was undertaken where the weight change assumptions were changed to both weight loss and weight gain only lasting for 1 year (as per the clinical evidence) – in the base case, weight loss only lasted 1 year but weight gained remained forever. In the sensitivity analysis, insulin detemir-metformin was dominated by metformin-pioglitazone-sulfonylurea and insulin degludec-metformin, indicating insulin detemir-metformin was highly sensitive to the weight profile assumptions applied (see figure 62).

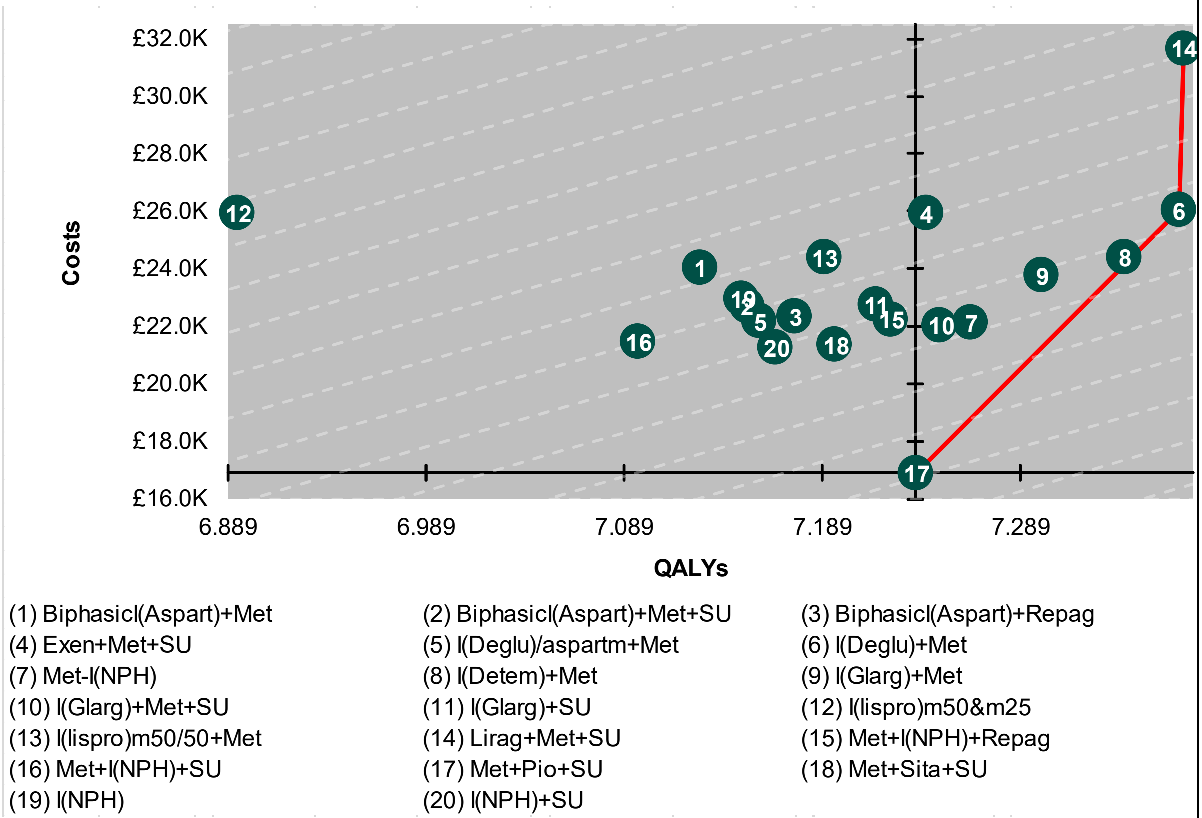


Figure 62: Cost–utility plane for 2nd intensification of therapy alternative weight profile sensitivity analysis

Given the many contraindications for prescribing pioglitazone, a further analysis was undertaken for a decision space without metformin-pioglitazone-sulfonylurea. In this analysis, Metformin-NPH insulin was a cost-effective option, resulting in QALY gains of 0.133 compared with the treatment option with the lowest lifetime discounted costs, NPH insulin-sulfonylurea, at an ICER of around £3600 per QALY gained. Insulin detemir-metformin was associated with an ICER of £24,300 per QALY when compared with metformin-NPH insulin (see table 86). Metformin-sitagliptin-sulfonylurea was extendedly dominated by NPH insulin-sulfonylurea and metformin-NPH insulin (see figure 63), but represented the only remaining non-injectable based treatment option.

Table 84: Mean lifetime incremental cost–utility results for second intensification therapy – when metformin-pioglitazone-sulfonylurea is not within the decision space

	Lifetime discounted		Incremental		
Therapy	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER**
NPH insulin-sulfonylurea	£21,636	7.097			
Metformin-sitagliptin-sulfonylurea	£21,763	7.126	£127	0.029	Ext. dom.
Metformin-NPH insulin-sulfonylurea	£22,000	7.020	£364	-0.077	Dominated
Metformin-NPH insulin	£22,108	7.230	£472	0.133	£3552
Biphasic insulin aspart-repaglinide	£22,738	6.979	£631	-0.251	Dominated
Insulin glargine-metformin-sulfonylurea	£22,870	7.173	£762	-0.057	Dominated
NPH insulin	£22,896	7.060	£788	-0.169	Dominated
Metformin-NPH insulin-repaglinide	£22,899	7.161	£791	-0.068	Dominated
Insulin glargine-sulfonylurea	£23,260	7.135	£1153	-0.094	Dominated
Insulin degludec/aspart mix-metformin	£23,263	7.134	£1155	-0.096	Dominated

Therapy	Lifetime discounted		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Biphasic insulin aspart-metformin-sulfonylurea	£23,303	7.051	£1196	-0.179	Dominated
Insulin glargine-metformin	£23,716	7.270	£1608	0.040	Ext. dom.
Biphasic insulin aspart-metformin	£24,028	7.013	£1921	-0.217	Dominated
Insulin lispro mix 50/50-metformin	£24,136	7.126	£2028	-0.104	Dominated
Insulin detemir-metformin	£24,228	7.317	£2121	0.087	£24,260
Exenatide-metformin-sulfonylurea	£25,795	7.229	£1567	-0.088	Dominated
Insulin degludec-metformin	£26,097	7.320	£1869	0.003	Ext. dom.
Insulin lispro mix 50 and mix 25	£26,307	6.818	£2078	-0.499	Dominated
Liraglutide-metformin-sulfonylurea	£30,166	7.352	£5937	0.034	£172,890

(a) Ext. dom. = extendedly dominated

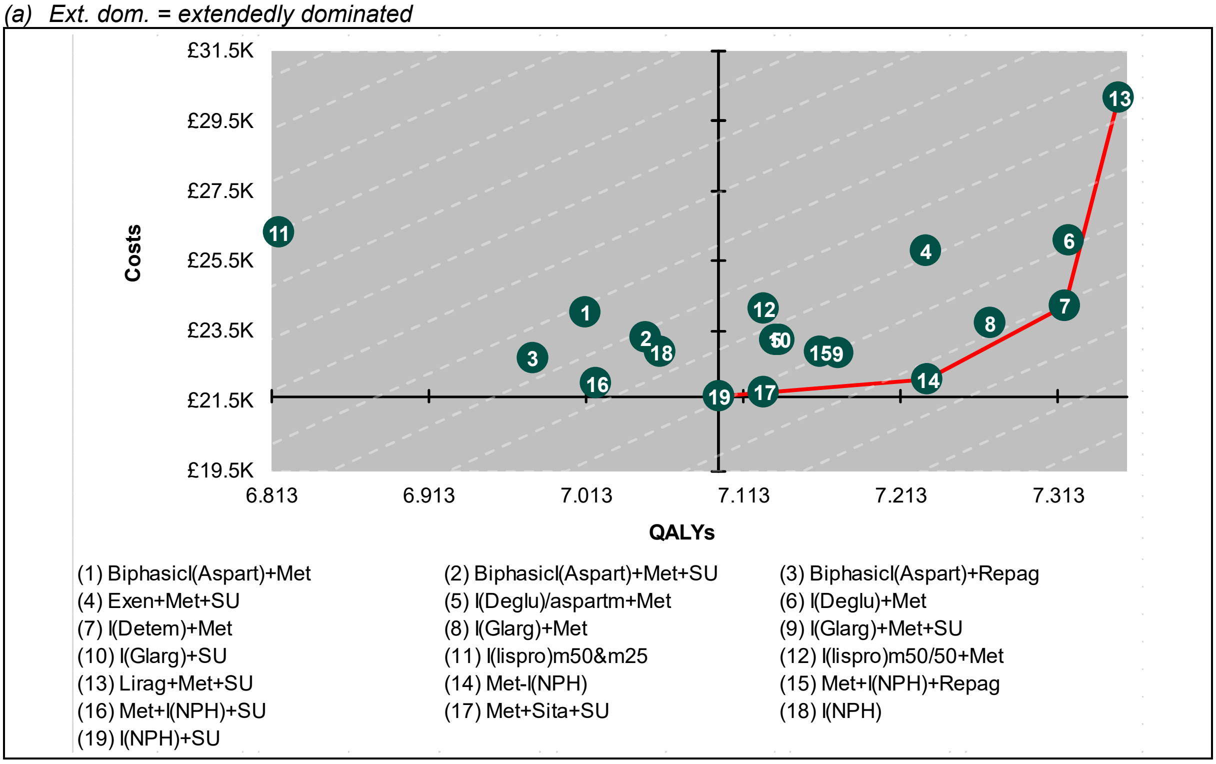


Figure 63: Cost–utility plane for 2nd intensification of therapy where metformin-pioglitazone-sulfonylurea is not a treatment option

If, following treatment with 3 oral anti-diabetic agents, NPH insulin-based treatment options fail to control a person's HbA1c, insulin glargine-metformin had an ICER of £8700 compared with insulin glargine-metformin-sulonylurea and insulin detemir-metformin had an ICER of £10,800/QALY compared with insulin glargine-metformin (see table 85 and figure 64).

Table 85: Mean lifetime incremental cost–utility results for second intensification of therapy when metformin-pioglitazone-sulfonylurea and NPH insulin is not a treatment option

Therapy	Lifetime Discounted		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Biphasic insulin aspart-repaglinide	£22,738	6.979			
Insulin glargine-metformin-sulfonylurea	£22,870	7.173	£132	0.194	£678
Insulin glargine-sulfonylurea	£23,260	7.135	£391	-0.038	Dominated
Insulin degludec/aspart mix-metformin	£23,263	7.134	£393	-0.039	Dominated

Therapy	Lifetime Discounted Costs	Lifetime Discounted QALYs	Incremental Costs	Incremental QALYs	ICER
Biphasic insulin aspart-metformin-sulfonylurea	£23,303	7.051	£434	-0.122	Dominated
Insulin glargine-metformin	£23,716	7.270	£846	0.097	£8,740
Biphasic insulin aspart-metformin	£24,028	7.013	£313	-0.257	Dominated
Insulin lispro mix 50/50-metformin	£24,136	7.126	£420	-0.144	Dominated
Insulin detemir-metformin	£24,228	7.317	£513	0.047	£10,795
Exenatide-metformin-sulfonylurea	£25,795	7.229	£1567	-0.088	Dominated
Insulin degludec-metformin	£26,097	7.320	£1869	0.003	Ext. dom.
Insulin lispro mix 50 and mix 25	£26,307	6.818	£2078	-0.499	Dominated
Liraglutide-metformin-sulfonylurea	£30,166	7.352	£5937	0.034	£172,890

(a) Ext. dom. = extendedly dominated

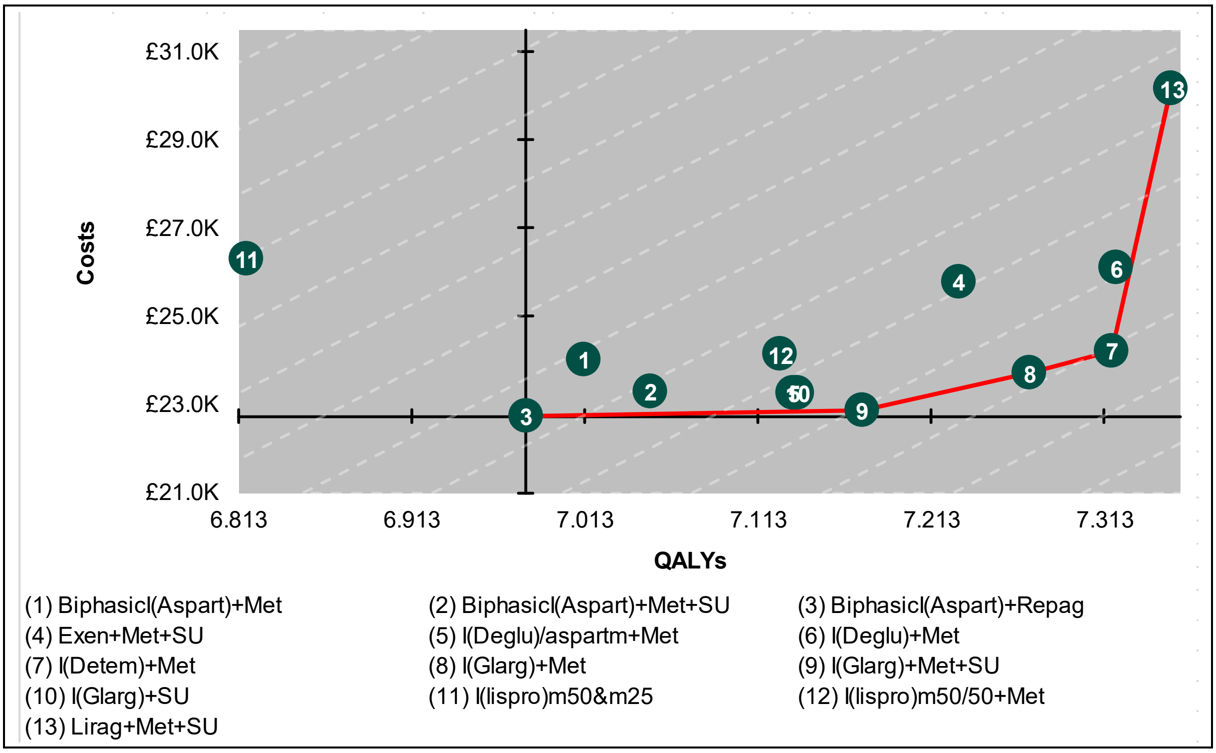


Figure 64: Cost–utility plane for 2nd intensification of therapy where 3 oral anti-diabetic agent treatment options followed by metformin-NPH insulin have failed to control HbA1c

For people who could not tolerate metformin, NPH insulin-sulfonylurea had the lowest lifetime discounted costs and was the most cost effective of the 5 treatment options (see table 86).

Table 86: Mean lifetime incremental cost–utility results for second intensification of therapy when metformin cannot be tolerated

Therapy	Lifetime Discounted Costs	Lifetime Discounted QALYs	Incremental Costs	Incremental QALYs	ICER
NPH insulin-sulfonylurea	£21,636	7.097			
Biphasic insulin aspart-repaglinide	£22,738	6.979	£1102	-0.118	Dominated
NPH insulin	£22,896	7.060	£1260	-0.037	Dominated

Therapy	Lifetime Discounted Costs	Lifetime Discounted QALYs	Incremental Costs	Incremental QALYs	ICER
Insulin glargine-sulfonylurea	£23,260	7.135	£1624	0.038	£42,369
Insulin lispro mix 50 and mix 25	£26,307	6.818	£3046	-0.317	Dominated

At second intensification, metformin-pioglitazone-sulfonylurea was the most cost-effective treatment option at a maximum acceptable ICER of £20,000 per QALY in 75% of iterations (see figure 65).

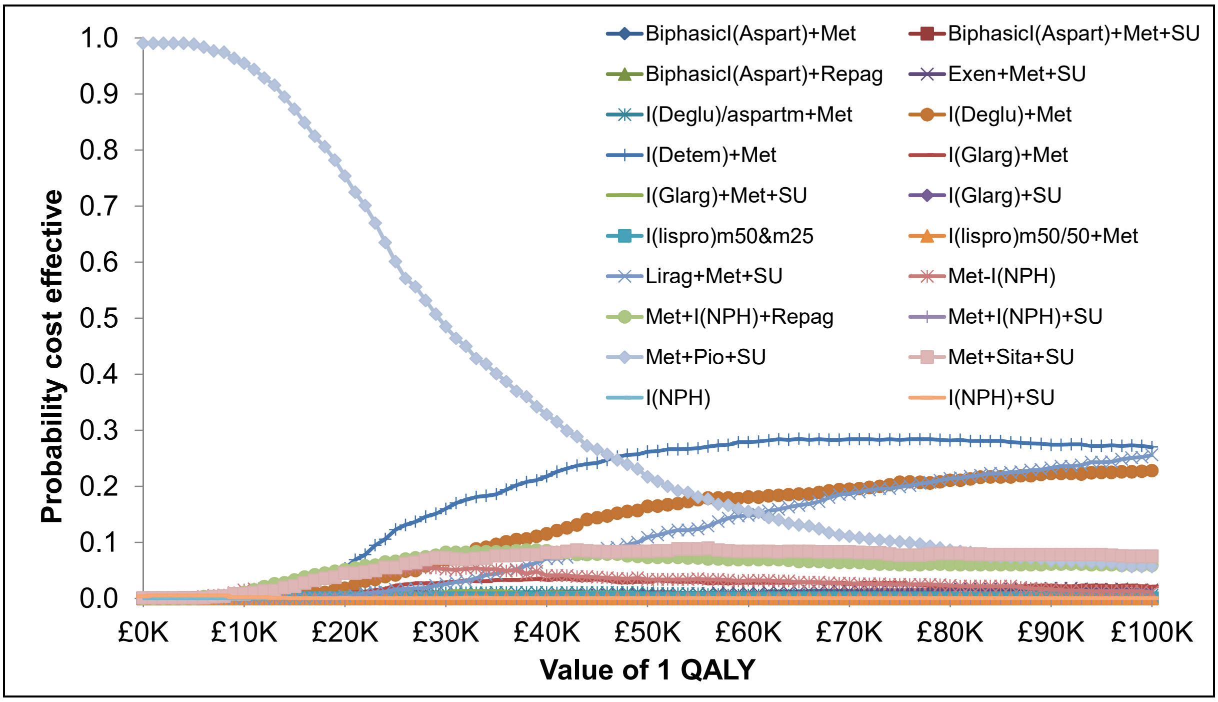


Figure 65: Cost-effectiveness acceptability curve for second intensification

8.4.14 Evidence statements for second intensification

8.4.14.1 Clinical evidence

8.4.14.1.1 Change in blood glucose up to 12 months

Evidence from a single network meta-analysis including data from 37 RCTs for HbA1c levels showed that NPH-insulin combined with metformin and repaglinide were most effective in blood glucose control, followed by biphasic insulin aspart-pioglitazone. Metformin-sulfonylurea-repaglinide was ranked lowest suggesting that this combination was least effective in decreasing HbA1c levels. The quality of the evidence was moderate.

8.4.14.1.2 Hypoglycaemia at study end point

Evidence from a single network meta-analysis including data from 34 RCTs showed that metformin combined with insulin degludec or insulin detemir were associated with high rankings (median rank 3 [1 to 16] and median rank 3 [1 to 15] respectively) indicating lower hypoglycaemic events. Insulin lispro mix 50 and mix 25 was associated with the lowest ranking suggesting higher hypoglycaemic events. However, there was greater uncertainty surrounding the evidence as the credible intervals were generally wide and crossed the line of no effect. The quality of the evidence was low.

8.4.14.1.3 Adverse events at study end point

Evidence from 3 network meta-analyses including data from 25, 25 and 4 RCTs for dropouts due to adverse events, total dropouts and nausea respectively, showed that insulin lispro 50 and 25 mix had highest ranking for dropouts due to adverse events, whereas a triple oral combination (metformin-sulfonylurea-repaglinide) had the highest ranking for total dropouts. Insulin combinations rather than triple non-insulin based drug combinations demonstrated comparatively higher rankings indicating lower nausea events (biphasic aspart-metformin, biphasic aspart-metformin-sulfonylurea and glargine-metformin-sulfonylurea). However, there was considerable uncertainty around the network meta-analyses demonstrated by wide credible intervals which in the main crossed the line of no effect. The quality of the evidence was low.

8.4.14.1.4 Change in body weight up to 12 months

Evidence from a single network meta-analysis including data from 27 RCTs showed that metformin-insulin detemir and a triple non-insulin based drug combination of metformin-sulfonylurea and a GLP-1 mimetic (exenatide, liraglutide) were associated with weight loss. Biphasic insulin aspart-repaglinide was associated with lowest ranking. The quality of the evidence was low.

8.4.14.2 Health economic evidence

A directly applicable health economic model with potentially serious limitations found metformin-pioglitazone-sulfonylurea was the most cost-effective modelled option for second intensification therapy. A further analysis found metformin-NPH insulin to be the most cost-effective treatment option when pioglitazone is not a treatment option. NPH insulin-sulfonylurea was the most cost-effective combination that did not contain metformin.

8.4.15 Evidence to recommendations for second intensification

Table 87: Linking evidence to recommendations

Relative value of different outcomes	The following outcomes were considered critical to decision-making: glycaemic control (HbA1c), hypoglycaemic events and adverse events. Change in body weight was considered important to decision-making. The GDG noted that glycaemic control was important in mitigating the much increased risk of microvascular and macrovascular complications associated with high levels of hyperglycaemia at this intensification level. However, the GDG acknowledged that tight glycaemic control may be associated with increased risk of hypoglycaemia, which may negatively affect quality of life. Drug tolerability and change in body weight were considered important in determining the acceptability of treatment to the person. The relative importance of each outcome varies according to several factors: • Severity of hyperglycaemia. • Individual circumstances such as comorbidities and body mass index.
Trade-off between benefits and harms	The GDG acknowledged that there was generally less evidence for this treatment level, resulting in sparser networks. The GDG noted that there was some uncertainty in the evidence at this

	intensification level as demonstrated by the wide credible intervals that surrounded many of the point estimates particularly related to adverse events. The GDG noted all 6 triple non-insulin based drug combinations included metformin. Of the 32 treatment combinations, 20 included data for all required outcomes in the health economic model. The 12 treatment combinations that were not included in the health economic model were 2 triple oral therapies (metformin–sulfonylurea–acarbose and metformin–sulfonylurea–repaglinide), 4 insulin-only combinations (biphasic insulin aspart, insulin aspart (short acting), NPH insulin 70/30 and biphasic insulin-NPH insulin) and 6 combinations of insulin + 1 oral antidiabetic drug (biphasic aspart–pioglitazone, insulin aspart–metformin, lispro 75/25–metformin, NPH 70/30–metformin, NPH 70/30–sulfonylurea and NPH insulin–repaglinide). The GDG noted that many of the triple oral antidiabetic drug combinations are not commonly used in clinical practice, such as acarbose and sulfonylurea–repaglinide which are both secretagogues that act by stimulating the pancreas. The GDG discussed that many patients are generally unwilling to start insulin therapy because of a fear of injections, hypoglycaemia and its potential impact on quality of life. The GDG discussed the evidence surrounding 3 non-insulin based drug combinations and noted that while they were not the most effective in decreasing HbA1c levels, they were associated with fewer hypoglycaemic events and, for some combinations, weight loss. The GDG discussed the evidence of combinations including GLP-1 mimetics and noted that while triple non-insulin based drug combinations including GLP-1 mimetics had better weight profiles, there was some uncertainty in the data. In addition, none of the GLP-1s triple combinations were shown to be significantly different in changes in HbA1c levels compared to metformin-NPH insulin. However, the GDG agreed that to facilitate a flexible approach to enable access for individuals most likely to benefit, this combination should be available to people for whom obesity is a concern (with due consideration given to different body mass index thresholds in ethnic minority groups), and only where other triple oral combinations are contraindicated or not effective. The GDG noted that there was a lack of evidence for combinations of GLP-1 mimetics and insulin, and therefore agreed that this option should only be offered in a specialist care setting. The GDG also noted that such treatment combinations are normally prescribed in complex cases and would therefore benefit from specialist care advice and ongoing support from a consultant-led multidisciplinary team, which may include a wide range of staff based in primary, secondary and community care. The GDG agreed that this group is likely to include a relatively small number of patients and therefore, it is unlikely to lead to a high volume of referrals even if there were no accredited GPs in the multidisciplinary team. The GDG discussed alternative options available if triple non-insulin based drug combinations failed to adequately control blood glucose levels. The GDG noted that metformin–NPH insulin was ranked in at least the top third for reducing HbA1c levels, hypoglycaemic events and change in body weight. The GDG recognised that there were other insulin–metformin combinations that had variable degrees of effectiveness across the 3 outcomes such as metformin–detemir ranked in the bottom third for change in HbA1c

	levels but highest third for hypoglycaemic events and change in body weight. The GDG discussed the evidence surrounding the relative benefit of weight loss compared with other treatments in the metformin–detemir combination, and noted that this was predominantly because of the comparative weight gain observed by all other insulin-based treatment combinations, rather than the marginal weight decrease in people receiving metformin–detemir observed in 1 trial (weight reduction of 0.5 kg). The GDG discussed intensification options for people in whom metformin is contraindicated or not tolerated, and noted that there was some evidence for sulfonylurea–insulin combinations and insulin only combinations. They noted that the evidence profile for NPH insulin–sulfonylurea, NPH insulin 70/30–sulfonylurea and insulin glargine–sulfonylurea were similar. The GDG discussed the value of using insulin to achieve rapid blood glucose control (rescue therapy) in clinical practice in patients who are symptomatically hyperglycaemic but agreed that treatment should be reviewed once blood glucose targets have been achieved.
Consideration of health benefits and resource use	Compared with earlier therapy levels, treatments at second intensification showed slightly greater differences in lifetime complication rates, because there were slightly greater HbA1c differences and no further intensifications of treatment. The economic model made explicit the trade-offs between the higher costs, benefits (HbA1c) and harms (hypoglycaemia and body weight) of insulin-based therapies against non-insulin based triple drug combinations, which are cheaper and associated with less harm but relatively ineffective at controlling HbA1c. Metformin–pioglitazone–sulfonylurea dominated all other treatment combinations, except for insulin detemir–metformin (incremental cost-effectivenes ratio [ICER] £40,800 per quality-adjusted life year [QALY]), and liraglutide–metformin–sulfonylurea (ICER £172,900 per QALY compared with insulin detemir–metformin). Insulin detemir–metformin showed a smaller QALY loss because of lower weight gain and lower hypoglycaemia rates than other treatments. The GDG expressed strong reservations as to whether these lower weight gains were seen in clinical practice and noted the very low quality of the clinical network supporting this evidence. It was also mindful that, in the base case, the model sustained the weight gains for other treatments for life and the GDG was unsure that a sustained weight difference between treatments would occur. The GDG considered that metformin–pioglitazone–sulfonylurea would be contraindicated for many people. The GDG considered a decision space without metformin–pioglitazone–sulfonylurea, which showed a cluster of longer-acting insulins combined with metformin to have similar lifetime discounted costs and QALYs. Compared with NPH insulin–sulfonylurea, metformin–NPH insulin produced an ICER of £3600 per QALY. Compared with metformin–NPH insulin, insulin detemir–metformin produced an ICER of £24,300 per QALY; the GDG was not convinced the lower weight gain associated with detemir–metformin was clinically realistic. Insulin glargine–metformin was extendedly dominated by metformin–NPH insulin

	and insulin detemir–metformin. However the GDG agreed there was value to people with type 2 diabetes in recommending a choice of insulin detemir–metformin or insulin glargine–metformin in certain circumstances. While metformin–sitagliptin–sulfonylurea was extendedly dominated by NPH insulin–sulfonylurea and metformin–NPH insulin, the GDG considered the dominance was marginal (the option was extremely close to the cost-effectiveness frontier) and there was value in recommending metformin–sitagliptin–sulfonylurea as an alternative to metformin–pioglitazone–sufonylurea and a non-injectable alternative to metformin–NPH insulin. The GDG noted there was no evidence for other DPP-4 inhibitor–metformin–sulfonylurea combinations. The GDG recognised a variety of factors would influence treatment option choice at second intensification, not just clinical and cost effectiveness and these would include the person's clinical circumstances, preferences and needs. While metformin–-pioglitazone–sulfonylurea and metformin–NPH insulin were the most cost-effective treatment options, the recommendations made allow people with type 2 diabetes to individualise their care. The GDG reviewed the insulin-based recommendations from NICE guidance CG87 and agreed that the updated evidence supported the use of insulin detemir and insulin glargine as alternatives to NPH insulin under certain circumstances. The GDG agreed that there was strong evidence to indicate that insulin degludec was not cost-effective and therefore was confident that this option should not be recommended. The GDG considered that GLP-1 mimetic combinations may be a cost-effective option for people with high BMIs who would require high doses (and therefore costs) of insulin or for whom other treatment options were not tolerated or were contraindicated. The GDG also considered that, in people for whom using insulin would have significant occupational implications, this could have a catastrophic impact on the person's quality of life. As a result, the health economic model might critically undervalue the benefits that would be associated with a treatment that forestalled the need for insulin. However, the GDG noted the high costs of these treatment options and their associated stopping rules that were designed to ensure they do not continue to be prescribed without substantial gains being achieved. For these reasons, the GDG chose to retain the GLP-1 mimetic combination options with their eligibility criteria and stopping rules from CG87. The GDG noted the ABCD audit which indicated that individuals on GLP-1s may show benefit from improvement in HbA1c levels and inadequate weight loss or inadequate improvement in HbA1c levels and adequate weight loss. However, the GDG agreed that, given the lack of cost effectiveness of GLP-1s demonstrated in the health economic modelling, the starting and stopping rules from CG87 should be retained. The GDG considered the small subset of modelled treatments that did not consider metformin. While NPH insulin and sulfonylurea was the most cost-effective option, the GDG noted it had little clinical experience of using this combination and considered that people might prefer to use NPH insulin alone.
Quality of the evidence	The GDG agreed that the overall quality of the evidence for second intensification was low. This was generally because the network was sparse with many connections limited to a single trial which led

	to some uncertainty around the results. In addition, for some outcomes, such as weight loss in 1 study, the results were not consistent with clinical experience. The GDG commented that the Derosa et al. (2013) trial was conducted in patients who were drug naïve at study baseline and may not be representative of the clinical population who require second intensification for glycaemic control. Therefore, this trial was excluded from the evidence base for second intensification. The GDG highlighted that outcomes, in particular hypoglycaemia, would be affected by the patients' stage of the condition. Specifically, it was suggested that patients with early type 2 diabetes will have relatively tight glycaemic control, are more likely to be using long-acting insulin and may be less likely to experience hypoglycaemia. In contrast, patients who are at a later stage of the condition may have higher glycaemic targets, are more likely to require biphasic insulin and are therefore more likely to experience hypoglycaemia.
Other considerations	When defining the decision problem for this question, the GDG preferred not to make an *a priori* assumption of class effect across DPP-4 inhibitors. Therefore, each individual option for which evidence was available was analysed separately. Having reviewed the assembled evidence for each phase of treatment, the GDG noted that it was difficult to judge whether the different DPP-4 inhibitors could, in fact, be considered interchangeable: • In a few areas, a case could be made for the superiority of 1 option over another (for example, at initial therapy, sitagliptin seemed to have somewhat superior benefits to vildagliptin at similar net costs). • In other areas, all the DPP-4 inhibitors for which evidence was available appeared to have very similar benefits, harms and costs (for example, in combination with metformin at first intensification). • Elsewhere in the treatment pathway, evidence was extremely limited (for example, sitagliptin–metformin–sulfonylurea was the only treatment combination for which evidence was available at second intensification) or absent (for example, at first intensification, there was no evidence that could be used to assess the relative clinical effectiveness and cost effectiveness of DPP-4 inhibitors in combination with pioglitazone or sulfonylureas). Having considered these different situations, the GDG concluded that the most helpful recommendations would be ones that treated DPP-4 inhibitors as a class. Had it been presented with evidence that suggested that 1 or more of the options was superior to others across all phases of treatment, the GDG would clearly have been inclined to favour such option(s) in its recommendations. However, the picture that had emerged was much more sporadic, and the GDG was not confident that any apparent dissimilarities between options represented real differences that would be expected in clinical practice. Moreover, the GDG was mindful that a series of recommendations that alternated between treating DPP-4 inhibitors as a class, in some parts of the treatment pathway, and focusing on individual options in others would be confusing to readers of the guideline, even if those recommendations could be directly allied with the available evidence. For all of these reasons, the GDG took the view that recommendations should consistently refer to DPP-4

	inhibitors as a class. It was a natural extension of this principle that prescribers should be encouraged to select the individual DPP-4 inhibitor with the lowest acquisition cost available to them, where all other factors are equal for example, licensed indications/combinations. Recommendations in this section that cover glucagon-like peptide 1 mimetics (GLP-1s) refer to these drugs at a class level because based on the evaluated evidence, the GDG was not convinced of the purported material differences between the various preparations. The GDG noted that the mean age in the included studies was about 57 years and agreed that these trials are biased towards younger and fitter participants, who are less likely to experience significant comorbidities than the majority of people with type 2 diabetes seen in clinical practice. The GDG considered that the treatment effects observed in trials are likely to generalise to a population facing more comorbidities and other challenges to effective management of their disease. However, the GDG agreed that the balance of benefits and harms may be different in such cases, and there are specific issues based on clinical experience that may require particular attention that should be highlighted in the recommendations. The GDG discussed that in clinical practice the use of triple non-insulin based drug combinations is preferred because patients are unwilling to start insulin therapy. The GDG noted that insulin therapy may not be appropriate for some patients. The GDG discussed that progress and individual care plans should be reassessed in people for whom insulin therapy may not be appropriate. Based on its clinical experience and expertise, the GDG agreed that this should be carried out after 6 months. This duration was agreed to maximise the accuracy of HbA1c measurements. Specifically, it was discussed that the accuracy of HbA1c measurements taken before 6 months may vary with some treatments taking longer to have an effect and missed doses having a larger impact. It was noted that reporting of hypoglycaemia differed across the included studies. All categories of hypoglycaemia (for example, confirmed hypoglycaemia) were generally a subset of ‘any hypoglycaemia’, which was the most commonly reported category of hypoglycaemia across the included studies. The GDG discussed the risk of bias associated with reported hypoglycaemia and noted that self-reported hypoglycaemia may not be a reliable measure because a person’s perception of hypoglycaemia varies at different glucose levels. The GDG noted that the results from the sensitivity analyses of people whose blood glucose levels had previously failed to be adequately controlled on 2 or more non-insulin based drug combinations were similar to the full dataset, which included studies of mixed populations of people whose treatment did not necessarily fail on/or who were previously exposed to 2 drugs, or studies of people whose treatment failed on 1 oral antidiabetic drug. Based on the health economic evidence of the associated cost-effectiveness of triple non-insulin based drug combinations, a

	strong 'offer' recommendation was made to intensify treatment by adding a sulfonylurea for people whose blood glucose levels on 2 non-insulin based drug combinations were not adequately controlled. This was assumed (as part of the overall structure of the pharmacological therapy review question) to provide better glycaemic control than dual therapy. However, it was agreed that this trial should be stopped if target HbA1c levels are not achieved. Where treatment has not been effective, a person's individual risks and benefits should be reassessed after 6 months and appropriate changes to their treatment plan should be made. This may involve discussing the risks and benefits associated with insulin-based therapy, ensuring any issues such as changes in employment are taken into account. The GDG discussed the multiple factors that should be considered when selecting drug treatments. The GDG agreed that the benefits and risks should be discussed with the person and selecting specific drugs should involve an assessment of the effectiveness of the medicine(s) (in terms of metabolic response), safety (MHRA guidance) and tolerability of the medicine(s), person's clinical circumstances (for example, comorbidities, polypharmacy), person's preferences and needs, licensed indications or combinations and costs (where 2 medicines in the same class are appropriate, the option with the lowest acquisition cost should be selected).

8.4.16 Evidence review for third intensification

In total 17,037 references were found for the main review question, but no trials were identified for inclusion for third intensification.

8.4.17 Recommendations

Recommendations in this section that cover dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) mimetics and sulfonylureas refer to each of these groups of drugs at a class level.

The current recommendations can be found at www.nice.org.uk/guidance/ng28

8.4.17.1 Rescue therapy at any phase of treatment

The current recommendations can be found at www.nice.org.uk/guidance/ng28

8.4.17.2 Initial drug treatment

The current recommendations can be found at www.nice.org.uk/guidance/ng28

8.4.17.3 First intensification of drug treatment

The current recommendations can be found at www.nice.org.uk/guidance/ng28

8.4.17.4 Second intensification of drug treatment

The current recommendations can be found at www.nice.org.uk/guidance/ng28

8.4.17.5 Insulin-based treatments

The current recommendations can be found at www.nice.org.uk/guidance/ng28

8.4.18 Research recommendations

6. **In adults with type 2 diabetes, what treatment combinations (for example, glucagon-like peptide-1 [GLP-1] mimetics and insulin, combination therapy with meglitinides) are most effective when initial drug treatment with non-metformin monotherapy fails to adequately control blood glucose levels?**

   Why this is important

   Although it is recognised that metformin therapy is suitable for most adults with type 2 diabetes, its use is contraindicated or not tolerated in approximately 15% of individuals. To date, research evidence has largely focused on metformin-based treatment combinations. Given the progressive nature of the condition, in which intensification of blood glucose lowering drug therapies are indicated over time, there is little evidence, for some adults, to guide management strategies on treatment combinations that do not include metformin. Randomised controlled trials are therefore needed to better understand the treatment choices that are available which improve blood glucose control and long-term risks of complications associated with diabetes.

7. **This research recommendation has been removed as part of the 2022 update.**

8. **This research recommendation was retained and refreshed as part of the 2022 update. When blood glucose levels are inadequately controlled by 3 oral antidiabetic drugs and/or insulin combinations, which blood glucose lowering therapies should be used to control blood glucose levels? [2015, amended 2022]**

   Why this is important

   As the incidence of type 2 diabetes increases in the younger population and as blood glucose control declines naturally over time, it is likely that further intensification of therapies would be needed. Currently, there is evidence up to second intensification of drug therapies, that is, when 2 or more non-insulin based treatment combinations fail to adequately control blood glucose levels. Randomised controlled trials are needed to improve understanding of alternative treatment options for adults at second intensification whose blood glucose is inadequately controlled with insulin and/or triple non-insulin based drug therapies.

9. **In adults with type 2 diabetes, what are the effects of stopping and/or switching drug treatments to control blood glucose levels, and what criteria should inform the decision?**

   Why this is important

There is a lack of evidence on the effects of stopping and/or switching drug treatments to control blood glucose levels. The current practice of 'stopping rules' is typically motivated by either inadequate blood glucose control (rising HbA1c levels) or intolerable side effects. There is limited understanding of the short- and long-term effects of stopping a therapy and switching to another in terms of diabetes control (HbA1c levels), hypoglycaemic risk, weight gain, and cardiovascular morbidity and mortality. In addition, there is limited understanding of how quickly consideration should be given to stopping and switching to another drug treatment and, if stopping and switching may be needed, what the optimal sequencing is of drug treatments. Randomised controlled trials examining these different issues would help to improve diabetes care.

10. **This research recommendation was stood down by the committee as part of the 2022 update.**

11. **This research recommendation has been removed as part of the 2022 update.**

12. **In adults with type 2 diabetes, what patient characteristics predict response or non-response to pharmacological blood glucose lowering therapies?**

    Why this is important

    There is little understanding of the prognostic characteristics that determine the likelihood that a person would benefit and respond or not respond to treatment. Increased understanding of important predictive criteria would better help clinicians target drug therapies and improve overall patient care. Prospective longitudinal cohort studies examining various types of prognostic factors such as demographic, disease-specific and comorbid are needed to identify characteristics that are likely to predict treatment response or non-response to blood glucose lowering therapies in adults with type 2 diabetes.

13. **In adults with type 2 diabetes and multimorbidity, what are the optimal blood glucose lowering treatment strategies?**

    Why this is important

    The evidence reviewed in this guideline commonly excluded participants with type 2 diabetes whose disease is complicated by significant coexisting conditions, although this is a common presentation in real-world practice. As a result, it is difficult to account for the impact of different comorbid conditions on the effectiveness of blood glucose lowering treatment strategies. A systematic review is needed to ascertain the optimal treatment strategies for blood glucose control in adults with type 2 diabetes and a range of comorbid conditions. Multimorbidity covers a wide range of conditions (for example, heart failure, chronic obstructive pulmonary disease and depression) and each would have different implications. Therefore, analyses should consider whether the optimal treatment strategies differ according to specific comorbid conditions.

8.5 Long-term serious adverse effects of blood glucose lowering drug treatments

This section was updated in 2015

8.5.1 Clinical introduction

The aim of this review is to provide supplementary information on the long-term serious adverse effects of the blood glucose lowering drug treatments that were assessed in section 8.4. For cohesiveness, included RCTs in section 8.4 that had relevant data at 2 or more years are reported in this review. In addition, this review links to the work undertaken by the Medicines and Healthcare products Regulatory Authority (MHRA) which has a role in ensuring that medicines such as those for controlling blood glucose are safe for use.

8.5.1.1 Long-term serious adverse effects of drug treatments in Clinical Guideline 66

CG66 did not cover the long-term serious adverse effects associated with blood glucose lowering drug treatments.

8.5.1.2 Long-term serious adverse effects of drug treatments in the update (2015)

This is a new question in this update and therefore searches have been carried out for this topic without any date restrictions (see Appendix C for update search strategies).

8.5.2 Evidence review

This section was updated in 2015

8.5.2.1 Review question

What are the serious adverse effects of long-term use of pharmacological interventions to control blood glucose in people with type 2 diabetes?

Table 88: PICO table

Population	Adults (18 years and over) with type 2 diabetes
Interventions	Acarbose Dipeptidyl peptidase-4 inhibitors (linagliptin, saxagliptin, sitagliptin and vildagliptin) Glucagon-like peptide-1 receptor agonists (conventional and prolonged release exenatide, liraglutide and lixisenatide) Insulin Meglitinides Metformin Sulfonylureas Thiazolidinediones (pioglitazone)
Comparators	Placebo/no treatment or other treatment (including combinations)
Outcomes	Cancer Cardiovascular disease (myocardial infarction, heart failure, stroke, ACS, TIA, revascularisation and stenting) Cognitive impairment Fracture Pancreatic disease Morbidity Mortality

Prospective, longitudinal, cohort studies focusing on the development of long-term safety issues such as renal failure, severe pancreatitis, cancer (for example bladder, thyroid), cardiac failure and other microvascular or macrovascular complications were considered. Studies were included if they had at least 200 participants and a minimum follow-up period of 2 years. Papers were excluded if they:

- were conference abstracts, letters, editorials and other non-prospective observational studies (evidence from registries and healthcare databases were considered to be retrospective)
- included a mixed population of people with type 1 and 2 diabetes and either did not report subgroup analyses, or less than 85% of the study population had type 2 diabetes
- included treatment groups that had mixed pharmacological interventions, for example intensive strategies
- included rosiglitazone as part of the drug treatment strategy
- did not include comparative data on the exposure to drug treatments
- did not report on the incidence of the safety outcomes.

For the full excluded list, see Appendix L. The detailed protocol is also available in Appendix C.

8.5.2.2 Clinical evidence

From the evidence review in section 8.4, 2 included RCTs (Gallwitz et al. 2012; Holman et al. 1999) provided long-term safety data and are reported here.

In total, 4669 references were found in the update searches and 5 prospective cohort studies were included (Aas et al. 2009; Bruno et al. 1999; Fisman et al 2001; Henricsson et al. 1997; Landman et al. 2010).

Studies focused on comparing glucose lowering therapies to each other (and/or dietary management), either in isolation or in combination with other pharmacological interventions, or to placebo. Evidence was available on acarbose (Holman et al. 1999), linagliptin (a dipeptidyl peptidase-4 (DPP-4) inhibitor; Gallwitz et al. 2012), insulin (Aas et al. 2009; Bruno et al. 1999; Henricsson et al. 1997), metformin (Fisman et al. 2001, Landman et al. 2010) and sulfonylurea (Bruno et al. 1999; Fisman et al. 2001). No relevant studies were identified for glucagon-like peptide-1 (GLP-1) receptor agonists, meglitinides and pioglitazone.

Pooling of data using meta-analysis was not possible because of differences in the reported outcomes and/or study designs. Cohort data were also adjusted for confounding factors, which were not consistent across the included studies. Therefore, results were presented in modified GRADE profiles, where individual studies rather than outcomes were assessed.

8.5.2.2.1 Description of included studies

Details of the included studies are found in the evidence tables (see Appendix E).

Acarbose

One 3-year RCT conducted in the UK including 1946 people (mean age 60 years; mean duration of diabetes 8 years; mean HbA1c at baseline 72 mmol/mol (8.7%); mean BMI not reported) provided data for acarbose compared to placebo (UKPDS; Holman et al. 1999).

Linagliptin (DPP-4 inhibitor)

One 2-year RCT conducted in multiple countries including 1552 people (mean age 59.8 years; mean HbA1c at baseline 61 mmol/mol (7.7%); mean BMI 30.3 kg/m^2), more than half of whom had diabetes for at least 5 years provided data for metformin compared to sulfonylurea (Gallwitz et al. 2012).

Insulin

A total of 4208 people (study size ranged from 865 to 1965) were included from 3 prospective cohort studies, carried out in Sweden (Henricsson et al. 1997) and in multiple countries (Aas et al. 2009; Bruno et al. 1999). The mean age ranged from 54 to 66. Mean duration of diabetes was reported in 2 studies as 8.5 years; the other study did not report this information (Aas et al .2009). Mean HbA1c at baseline was reported in 1 study ranging from 53 to 57 mmol/mol (ranged from 7% to 7.4%) in the different groups (Aas et al. 2009). No studies reported BMI. Follow-up periods ranged from 3 to 7 years.

Metformin

A total of 3628 people (study sizes 1353 and 2275) were included from 2 cohort studies, carried out in the Netherlands (ZODIAC; Landman et al. 2010) and Israel (Fisman et al. 2001). The mean ages were 67.8 and 60 years. The mean duration of diabetes was reported in 1 study as 6 years (Landman et al. 2010); the other study did not report this information. Mean HbA1c levels at baseline was 58 mmol/mol (7.5%) in 1 study (Landman et al. 2010); the other study did not report this information. Mean BMI was 28.9 and 27.5 kg/m^2. Follow-up periods were 7.7 and 10 years.

Sulfonylureas

A total of 4240 people (study sizes 1965 and 2275) were included from 2 cohort studies, carried out in Italy (Bruno et al. 1999) and Israel (Fisman et al. 2001). The mean ages were 66 and 60 years. The mean duration of diabetes was reported in 1 study as 8.5 years (Bruno et al. 1999); the other study did not report this information. Mean HbA1c levels at baseline were not reported in either study. Mean BMI was 27.5 kg/m^2 in 1 study (Fisman et al. 2001); the other study did not report this information. Follow-up periods were 7 and 7.7 years.

The summary GRADE tables are presented for this review question (see Appendix D for full GRADE tables).

Table 89: Summary GRADE profile for acarbose

Number of studies	Design	Effect (95% CI)		Quality
		Outcome	Estimate	
Acarbose plus existing therapy (n=973) compared to placebo plus existing therapy (n=973); mean 3 years follow-up; subgroup of the UKPDS study				
1 (Holman 1999) –UKPDS	RCT	Any diabetes related end point Microvascular disease	RR 1.00 (0.81 to 1.23) RR 0.91 (0.61 to 1.35)	Moderate
Abbreviations: CI confidence intervals; RR relative risk				

Table 90: Summary GRADE profile for linagliptin (dipeptidyl-peptidase 4 inhibitor)

Number of studies	Design	Effect (95% CI)		Quality
		Outcome	Estimate	
DPP-4 inhibitor (linagliptin) plus metformin (n=776) compared to sulfonylurea (glimepiride) plus metformin (n=775); mean 2 year follow-up; people with type 2 diabetes on a stable dose of metformin				
1 (Gallwitz 2012)	RCT	All-cause mortality Any cardiovascular event[Ŧ] Cardiovascular death Myocardial infarction Stroke Admission because of unstable angina	RR not significant RR 0.46 (0.23 to 0.91) RR 1.00 (0.14 to 7.07) RR 0.60 (0.22 to 1.64) RR 0.27 (0.08 to 0.97) RR 1.00 (0.20 to 4.93)	Moderate
Abbreviations: CI confidence intervals; RR relative risk; [Ŧ] Any cardiovascular event defined as cardiovascular death, myocardial infarction, stroke and admission because of unstable angina				

Table 91: Summary GRADE profile for insulin

Number of studies	Design	Effect (95% CI)		Quality
		Outcome	Estimate	
Insulin compared to diet alone (overall n=1941); mean 7 year follow-up; people with type 2 diabetes				
1 (Bruno 1999)	cohort	All-cause mortality Cardiovascular mortality	Adj RR 1.71 (1.18 to 2.48) Adj RR 1.35 (0.79 to 2.32)	Very low

Number of studies	Design	Effect (95% CI)		Quality
		Outcome	Estimate	
		Ischaemic heart mortality Cerebrovascular mortality Chronic renal failure	Adj RR 2.95 (1.07 to 8.10) Adj RR 1.00 (0.41 to 2.45) Adj RR 2.26 (0.82 to 6.19)	
Insulin (n=333) compared to oral antidiabetic medication (n=unclear, up to 1045); median 3.1 year follow-up; people with type 2 diabetes attending retinopathy screening				
1 (Henriccson 1997)	cohort	<u>People who changed from oral medication to insulin compared to those remaining on oral medication</u> - Blindness/visual impairment - Progression of retinopathy 3 or more levels	 Adj RR 2.7 (1.8 to 4.0) Adj RR 1.6 (1.3 to 1.9)	Very low
Diet alone (n=99) compared to oral antidiabetic drugs (n=250) compared to new insulin users (n=245) compared to existing insulin users (n=271); mean 3 year follow-up; people with type 2 diabetes and suspected myocardial infarction who took part in the DIGAMI RCT (24 hour insulin infusion compared to conventional management)				
1 (Aas 2009) – DIGAMI	cohort	<u>Existing insulin users compared to other groups</u> - cardiovascular death <u>New insulin users compared to other groups</u> - Reinfarction	 HR 2.38 (1.34 to 4.22) HR 2.49 (1.23 to 5.03)	Very low
Abbreviations: CI confidence intervals; HR hazard ratio; RR relative risk ; Adj RR adjusted relative risk – see evidence tables for details of individual adjustments that were applied				

Table 92: Summary GRADE profile for metformin

Number of studies	Design	Effect (95% CI)		Quality
		Outcome	Estimate	
Metformin (n=79) compared to diet alone (n=990); mean 7.7 year follow-up; people with type 2 diabetes and coronary artery disease				
1 (Fisman 2001)	cohort	All-cause mortality	Adj HR 1.19 (0.76 to 1.84)	Very low
Metformin plus existing diabetes therapy (n=289) compared to existing diabetes therapy alone (n=1064); mean 10 year follow-up; unclear population, part of ZODIAC study				
1 (Landman 2010) – ZODIAC	cohort	All-cause mortality Cancer mortality	Adj HR 0.94 (0.73 to 1.22) Adj HR 0.43 (0.23 to 0.80)	Very low

		Cardiovascular mortality	Adj HR 2.27 (1.36 to 3.78)	
Metformin plus sulfonylurea (glyburide) (n=253) compared to diet alone (n=990); mean 7.7 year follow-up mean; people with type 2 diabetes and coronary artery disease				
1 (Fisman 2001)	cohort	All-cause mortality	Adj HR 1.53 (1.20 to 1.96)	Very low
Abbreviations: CI confidence intervals; HR hazard ratio; RR relative risk ; Adj RR adjusted relative risk – see evidence tables for details of individual adjustments that were applied				

Table 93: Summary GRADE profile for sulfonylurea

Number of studies	Design	Effect (95% CI)		Quality
		Outcome	**Estimate**	
Sulfonylurea compared to diet alone (overall n=1941); mean 7 year follow-up; people with type 2 diabetes				
1 (Bruno 1999)	cohort	All-cause mortality Cardiovascular mortality Ischaemic heart mortality Cerebrovascular mortality	Adj RR 1.14 (0.82 to 1.58) Adj RR 1.02 (0.64 to 1.63) Adj RR 1.63 (0.64 to 1.14) Adj RR 1.09 (0.52 to 2.32)	Very low
Glyburide (n=953) compared to diet alone (n=990); mean 7.7 year follow up; people with type 2 diabetes and coronary artery disease				
1 (Fisman 2001)	cohort	All-cause mortality	Adj HR 1.21 (1.02 to 1.44)	Very low
Sulfonylurea plus biguanides compared to diet alone (overall n=1941); mean 7 year follow-up; people with type 2 diabetes				
1 (Bruno 1999)	cohort	All-cause mortality Cardiovascular mortality Ischaemic heart mortality Cerebrovascular mortality	Adj RR 1.13 (0.79 to 1.62) Adj RR 1.04 (0.62 to 1.75) Adj RR 2.49 (0.96 to 6.50) Adj RR 0.91 (0.39 to 2.12)	Very low
Abbreviations: CI confidence intervals; HR hazard ratio; RR relative risk				

8.5.2.3 Health economic evidence

This section was updated in 2015

No health economic evidence was found for this question. It was noted that most type 2 diabetes health economic analyses are based on projections of long-term outcomes from short-term clinical biomarkers, but these do not take account of long-term safety concerns.

8.5.3 Evidence statements

8.5.3.1 Clinical evidence

No relevant studies on glucagon-like peptide-1 receptor agonists, meglitinides and pioglitazone were identified.

Evidence on the long-term serious adverse effects associated with other blood glucose lowering medicines (acarbose, linagliptin, insulin, metformin and sulfonylurea) was provided by 7 studies (2 randomised controlled trials and 5 prospective cohort studies). The quality of the evidence ranged from high to very low.

The overall effects of the reviewed drug treatments on long-term safety outcomes were unclear. This is because studies were often underpowered to detect differences between the intervention and comparator groups; it is likely that confounding factors were present in the data and outcomes were not reported consistently across the included studies. Therefore, there is uncertainty in the results of the individual studies, and no conclusions can be drawn about the long-term serious adverse effects of the pharmacological interventions that were reviewed.

8.5.4 Evidence to recommendations

Table 94: Linking evidence to recommendations

Relative value of different outcomes	All long-term safety outcomes were considered critical to decision-making. Equal value was placed on all outcomes, since the risk of any serious adverse events was considered to be clinically important.
Trade-off between benefits and harms	People with type 2 diabetes are at risk of long-term microvascular and macrovascular complications. Blood glucose lowering drug treatments that aim to reduce the likelihood of these complications by improving glycaemic control are also associated with potential harms. Consideration of the balance between pharmacological benefits and harms against the long-term complications of diabetes is required. The review question only focused on the serious adverse effects caused by the long-term use of drug treatments. The relative benefits of the pharmacological interventions were reviewed in section 8.4 of this guideline, where the trade-off between benefits and harms was considered in more detail, along with the evidence from this question.
Consideration of health benefits and resource use	No health economic evidence was discussed for this question. The GDG noted that most type 2 diabetes health economic analyses are based on projections of long-term outcomes from short-term clinical biomarkers, but these do not take account of long-term safety concerns.
Quality of evidence	The GDG noted the limited amount of evidence that was identified in the review and discussed the possibility of expanding the study design criteria to include data from registries and databases that were set up to prospectively collect data. The GDG agreed that these designs do not

	address pre-specified hypotheses, have significant methodological limitations such as enrolment biases and are inherently retrospective because the study is developed once observations of interest have been made. Therefore, the GDG agreed that such evidence would not add to the review and should not be included. In addition, the GDG noted that the Medicines and Healthcare products Regulatory Agency (MHRA) whose specific remit is to examine the benefits and harms of pharmacological interventions and issue regulatory action when necessary, considers all available evidence such as those from databases and registries and therefore the inclusion of such evidence would also duplicate work already carried out. The GDG discussed the relative quality of randomised controlled trials (RCTs) and prospective cohort studies. The GDG agreed that the lack of randomisation in cohort studies means that results are likely to be confounded and need to be appropriately adjusted. Although all of the studies did adjust data to take identified confounding factors into consideration, the GDG considered that unidentified confounding factors were likely to be present in the evidence, which cannot be adjusted for by the studies. The GDG noted that confounding factors were adjusted inconsistently across the studies such that some adjusted for all known factors, but others only to varying degrees. Therefore, the GDG agreed that overall, it could not be confident of the findings of the studies derived from the cohort studies. The GDG noted that trials with appropriate randomisation methods are less likely to be affected by biases from confounding factors, since adequate randomisation should lead to an equal balance of known and unknown factors in the randomised arms. However, the GDG expressed concern regarding the reporting of outcomes from the included RCTs such that multiple variations of outcome combinations were used as composite outcomes, which undermines the credibility of the findings. The GDG noted that in most of the studies, the natural progression of diabetes to worsen over time was not addressed, such that it was not clear whether changes or augmentation of drug treatments were considered, which are likely to confound the results. The GDG agreed that overall, the quality of the evidence was low and noted the lack of studies on some pharmacological interventions. In particular, the GDG noted that the PROActive trial on pioglitazone was excluded but agreed that long-term serious adverse effects are identified in the MHRA safety alerts. The GDG noted the lack of evidence in some serious outcomes such as bone fracture and renal cancer which are new concerns for people using these drug treatments to control blood glucose levels. The GDG agreed that there was insufficient evidence to inform making recommendations regarding the long-term safety of the pharmacological interventions included in the review. The GDG considered that the MHRA, with its remit to look at the ongoing safety of pharmacological interventions, is able to provide the most up-to-date information in this area.
Other considerations	The GDG agreed that the evidence in this review would be considered with the findings on the benefits and shorter term adverse effects in the pharmacological review question in section 8.4, to develop the overall recommendations for these interventions.

8.5.5 Recommendations and research recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng28

9 Managing complications

9.1 Autonomic neuropathy

9.1.1 Clinical introduction

There are many manifestations of autonomic neuropathy as a complication of long-term hyperglycaemia. These include gastroparesis, diarrhoea, faecal incontinence, erectile dysfunction, bladder disturbance, orthostatic hypotension, gustatory and other sweating disorders, dry feet, and unexplained ankle oedema.

Gastroparesis can be one of the more devastating complications of autonomic neuropathy. While it can present as bloating, nausea and fullness on eating, severe intermittent hypoglycaemia can be a major problem for people on glucose lowering therapy, while vomiting may be intermittent and sudden or occasionally severe and protracted.

The clinical questions addressed include in whom to suspect gastroparesis might be present, what medications might help, and what other measures might be taken.

9.1.2 Methodological introduction

Eight studies were identified in this area all of which involved domperidone, metoclopramide or erythromycin. Two studies were excluded for methodological reasons.[381,382]

The remaining 6 studies comprised 4 RCTs of the drug against placebo; erythromycin vs placebo,[383] metoclopramide vs placebo,[384,385] domperidone vs placebo,[386] and 2 direct drug RCT comparisons; metoclopramide vs erythromycin,[387] and domperidone vs metoclopramide.[388]

There were methodological quality issues with these studies, which often involved small numbers of participants with a range of demographic and clinical details. Furthermore, although symptom scores were used as measures in 3 studies,[384,385,388] these were not based on a recognised or validated scale and were not consistent in the measures they recorded or in the scoring system allotted to the measures. The remaining 3 studies used the SF-36 health-related quality of life tool,[386] gastric emptying using a γ-camera[387] and scintigraphic studies.[383]

9.1.2.1 Health economic methodological introduction

No health economic papers were identified.

9.1.2.2 Evidence statements

9.1.2.3 Drug vs placebo

9.1.2.3.1 Erythromycin

One crossover study with 10 participants with diabetes and known prolonged gastric emptying were given 200 mg of IV erythromycin or IV placebo.[383] Ten age and sex matched health participants were also used as a comparator group. This study used scintigraphic studies and found that for 60 and 120 minutes IV erythromycin significantly increased gastric emptying, (measured as the mean percentage simultaneously ingested food retained in the stomach, for solids), compared with placebo (21±5 vs 85±7, $p<0.0005$ and 4±1 vs 63±9, $p<0.0005$ respectively).

For liquids the mean percentage retained was significantly lower for the IV erythromycin compared with placebo again at both 60 and 120 minutes (22±5 vs 54±5, $p<0.0005$ and 9±3 vs 32±4, $p<0.005$ respectively).

IV erythromycin was also found to have increased gastric emptying for solids at 60 minutes when compared with healthy subjects in the comparator group ($p<0.05$).

There were no AEs found with this study, this study had a further open-label phase with oral erythromycin, not reported here. **Level 1+**

9.1.2.3.2 Metoclopramide

Two studies,[384,385] one of which was a crossover study,[384] were identified comparing oral metoclopramide 10 mg QID and placebo, both studies used the diary recording of symptoms and though the scales used were broadly similar they were not identical, there were no major AEs identified in either study.

One study identified that the mean symptom scores for the 3-week treatment phase was significantly less for metoclopramide than for placebo; 26.5±3.7 vs 45.3±7.8, $p<0.01$. This study also found that the mean individual scores for 4/5 symptoms (fullness, pressure and bloating, nausea, vomiting, anorexia) showed that metoclopramide significantly reduced the symptoms compared with placebo ($p<0.05$).[385]

The crossover study found that symptom improvement was significantly greater for metoclopramide than placebo for nausea at weeks 1 and 3 ($p<0.05$). This was also found for fullness at weeks 2 and 3 ($p<0.05$). Changes found for other symptoms were not significantly improved for metoclopramide compared with placebo.[384] **Level 1+**

9.1.2.3.3 Domperidone

One study[386] considered domperidone vs placebo, this study combined a 4-week period where participants took 20 mg domperidone QID (single-blind phase) orally, followed by a 4-week period of 20 mg domperidone QID or placebo (double-blind phase). Entry into the second phase was dependent on a decrease on the baseline symptom score, those classed as responders, following completion of the single-blind phase.

Single-blind phase: significant symptomatic improvement was found at the end of the single-blind phase ($p<0.0001$). Improvements were also noted in the health-related quality of life measured on the SF-36 scale (all domains $p<0.001$, except physical functioning, $p<0.01$).

Double-blind phase: symptom severity increased with both domperidone and placebo, though they did not return to baseline levels, this increase in severity was greater for placebo compared with domperidone ($p<0.05$). AEs were not reported. **Level 1+**

9.1.2.4 Head-to-head comparisons

9.1.2.4.1 Metoclopramide vs erythromycin

One crossover study with 13 participants considered erythromycin 250 mg TID with metoclopramide 10 mg TID.

Gastric empting was considered at 60 and 90 minutes and while significant improvements were found for both drugs there was no significant difference found between the effects between erythromycin and metoclopramide.

The symptom score was significantly less for erythromycin; 2(0–5), than for metoclopramide; 3(0–11), $p<0.05$.

No serious AEs were noted, though N=2 of the patients did have weakness, sedation and leg cramps with metoclopramide. **Level 1+**

9.1.2.4.2 *Domperidone vs metoclopramide*

One study with 95 participants considered domperidone 20 mg QID with metoclopramide 10 mg QID. Gastroparetic symptoms and tolerability were assessed, it should be noted for tolerability assessment participants were specifically asked about central nervous system (CNS) associated side effects; these have previously been identified in association with metoclopramide.

Although significant reductions in symptoms were found with both domperidone and metoclopramide, there was no significant difference found between the 2 treatments.

For tolerability, at week 2 the severity of somnolence ($p<0.001$), akathisia ($p=0.03$), anxiety ($p=0.02$) and depression ($p=0.05$) were significantly greater for metoclopramide than for domperidone ($p<0.001$-0.05). While at week 4 this was found for severity of somnolence ($p=0.03$) and reduced mental acuity ($p=0.04$). **Level 1+**

9.1.3 Evidence to recommendations

The evidence reported had methodological limitations, notably studies of small sample sizes. The GDG agreed that there is a poor evidence base for the treatment of gastroparesis. Nevertheless they noted that the evidence reported suggested that the prokinetic drugs, metoclopramide, domperidone, along with erythromycin, were all effective in at least some people with gastroparesis resulting from autonomic neuropathy. On consideration of the evidence it was not possible to distinguish usefully between the prokinetic drugs. The group agreed that choice of initial therapy should be based on tolerability issues, including drug interactions. It was noted that differential diagnosis can be difficult, and the diagnostic tests not secure, while serious prolonged vomiting could become a medical emergency. Accordingly referral beyond diabetes services is sometimes indicated.

While the group gave priority to medication for the management of this condition, clinical experience suggested that non-pharmacological approaches including postural advice and timing of ingestion of fluids and solids could prove useful to some people.

The recommendation on the treatment of gastroparesis from clinical guideline 87 has been replaced by recommendations from the guideline update of type 1 diabetes which undertook a new evidence review on the management of gastroparesis in type 1 diabetes. It was agreed by the guideline committees for type 1 diabetes and for type 2 diabetes that the management of gastroparesis would be similar for people with diabetes. It was considered important to highlight the MHRA warning around the use of domperidone.

9.1.4 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng28

9.2 Nerve damage

9.2.1 Other aspects of autonomic neuropathy

9.2.1.1 Clinical introduction

Other aspects of autonomic neuropathy, including diarrhoea, faecal incontinence, bladder disturbance, orthostatic hypotension, gustatory and other sweating disorders, dry feet, and unexplained ankle oedema, can offer diagnostic and management problems, and on occasion be very disabling.

Alternatively symptoms may be vague and may present insidiously without realisation that they are diabetes-related, while nerve damage can be also be found in asymptomatic people. A mixed presentation is common, may be exacerbated by other drug therapy (e.g. tricyclic drugs), and may give troublesome hypoglycaemia. People with advanced autonomic neuropathy may also have advanced retinopathy, nephropathy, and somatic neuropathy.

9.2.1.2 Evidence to recommendations

The GDG reviewed the opinion-based recommendations made in the NICE type 1 diabetes guideline 2004.[26] They were found for the most part appropriate, and are reproduced with some editorial change only. It was recognised that these recommendations are for the most part identification and diagnostic issues, and that specialist management where required would often lie outside diabetes services.

9.2.1.3 Recommendations

9.2.1.3.1 Painful diabetic neuropathy

The current recommendations can be found at www.nice.org.uk/guidance/ng28

9.2.1.3.2 Autonomic neuropathy

The current recommendations can be found at www.nice.org.uk/guidance/ng28

9.2.1.3.3 Diabetic foot problems

The current recommendations can be found at www.nice.org.uk/guidance/ng28

9.2.1.3.4 Diabetic kidney disease

The current recommendations can be found at www.nice.org.uk/guidance/ng28

9.3 Erectile dysfunction

This section was updated in 2015

9.3.1 Clinical introduction

People with type 2 diabetes have an increased risk of microvascular complications, and damage to small blood vessels and autonomic nerves may affect sexual stimulation and response, leading to erectile dysfunction in men.

This section addressed whether pharmacological treatment (either alone or in combination) should be used to manage erectile dysfunction. This review also looked at whether the use of pharmacological treatments should be restricted to specific subgroups of the population and what adverse events are associated with their use.

9.3.1.1 Erectile dysfunction in Clinical Guideline 66

The pharmacological management of erectile dysfunction was originally covered as part of CG66 and included men with both type 1 and type 2 diabetes. The original searches were conducted from 2001 to 2007 (see Appendix G for search strategies from CG66). Update searches have been carried out for this topic with a date restriction of 2007 to June 2014 for phosphodiesterase 5 (PDE-5) inhibitors, and no date restrictions for alprostredil and testosterone therapy (see Appendix C for update search strategies) as these terms had not previously been searched. The evidence considered in this review question in CG66 included 1 systematic review and 9 RCTs.

9.3.1.2 Erectile dysfunction in the update (2015)

CG66 focused on the use of PDE-5 inhibitors for the management of erectile dysfunction. For this update, the review question has been expanded to cover the use of alprostredil and testosterone therapy (see Appendix C for full review protocols).

9.3.2 Evidence review

9.3.2.1 Review question

What pharmacological treatment should be used to manage erectile dysfunction in men with type 2 diabetes?

Table 95: PICO table

Population	Men (18 years and over) with diabetes (including type 1 and type 2)
Interventions	Testosterone therapy, phosphodiesterase 5 (PDE-5) inhibitors and alprostredil (alone or in combination)
Comparators	Placebo, standard care (or other treatment)
Outcomes	Erectile function (assessed using validated scale/measure such as International Index of Erectile Function; IIEF) Adverse events Health-related quality of life

Randomised controlled trials (RCTs) examining the use of alprostredil, PDE-5 inhibitors and testosterone therapy (alone or in combination) for the management of erectile dysfunction in men with diabetes were included. Papers were excluded if they:

- were non-randomised (including cohort, case-control and case series studies), narrative reviews, conference abstracts, letters and editorials

- focused on the diagnosis of erectile dysfunction
- assessed the use of testosterone therapy in men who did not have erectile dysfunction.

For the full excluded list, see Appendix L. The detailed protocol is also available in Appendix C.

The main outcomes for this review question were erectile function and adverse events. Erectile function was assessed using 4 main measures:

- Erectile function (EF) domain of the international index of erectile function (IIEF) questionnaire
- Question 2 from the sexual encounter profile (SEP-2) relating to success in penetration
- Question 3 from the sexual encounter profile (SEP-3) relating to success in intercourse
- Global efficacy question (GEQ) relating to whether treatment improved erections.

Where possible, studies were pooled using meta-analysis techniques (pairwise comparisons). The GDG agreed that it was not clinically appropriate to undertake a network meta-analysis for the available evidence on PDE-5 inhibitors because of the heterogeneity of the studies in terms of population, interventions, outcomes and quality.

9.3.2.2 Clinical evidence

The evidence that was originally included in CG66 was re-reviewed as part of the update, and all were found to be relevant. The Cochrane systematic review included in CG66 on PDE-5 inhibitors had not been updated (Vardi and Nini 2007). Full text papers of the relevant RCTs included in the Cochrane review were obtained and these were preferentially used. Data for Escobar-Jimenez (2002) was taken from the Cochrane systematic review.

In total, 349 references were found for this review question and 15 RCTs were included (Boulton et al. 2001; Buvat et al. 2006; Deyoung et al. 2012; Escobar-Jimenez 2002; Goldstein et al. 2003, 2012; Hackett et al. 2013; Hatzichristou et al. 2008; Ishii et al. 2006; Kamenov 2011; Rendell et al. 1999; Saenz de Tejada et al. 2002; Safarinejad 2004; Stuckey et al. 2003; Ziegler et al. 2006). One trial used a crossover design (Buvat et al. 2006). Four studies included people with type 2 diabetes only (Boulton et al. 2001; Deyoung et al. 2012; Escobar-Jimenez 2002; Hackett et al. 2013), 2 studies included people with type 1 diabetes only (Stuckey et al. 2003; Ziegler et al. 2006), 1 study did not report the proportion of people with type 1 and 2 diabetes (Ishii et al. 2006) and the remaining 8 studies included populations with type 2 diabetes ranging from 80% to 90.7%. All but 3 studies (Escobar-Jimenez 2002; Hackett et al. 2013; Kamenov 2004) specified in the inclusion criteria that participants should be heterosexual males or with a female partner. No relevant studies on alprostredil were identified.

The following comparisons were included as part of this review question:

- PDE-5 inhibitors versus placebo – 12 trials; 1 on avanafil (Goldstein et al. 2012), 6 on sildenafil (Boulton et al. 2001; Deyoung et al. 2012; Escobar-Jimenez 2002; Rendell et al. 1999; Safarinejad 2004; Stuckey et al. 2003), 2 on tadalafil (Hatzichristou et al. 2008; Saenz de Tejada et al. 2002) and 3 on vardenafil (Goldstein et al. 2003; Ishii et al. 2006; Ziegler et al. 2006)
- PDE-5 inhibitors versus PDE-5 inhibitors – 2 trials (Buvat et al. 2006; Kamenov 2011)
- Testosterone replacement therapy versus placebo – 1 trial (Hackett et al. 2013)

9.3.2.2.1 Description of included studies

Details of the included studies are found in the evidence tables (see Appendix E).

PDE-5 inhibitors versus placebo

A total of 3513 people (study size ranged from 24 to 778) were included from 12 RCTs, carried out in the USA (Goldstein et al. 2003, 2012; Rendell et al. 1999), Canada (Deyoung et al. 2012), Germany (Ziegler et al. 2006), Spain (Escobar-Jimenez 2002; Saenz de Tejada et al. 2002), Iran (Safarinejad 2004), Japan (Ishii et al. 2006) and multiple countries (Boulton et al. 2001; Hatzichristou et al. 2008); 1 study did not report this information (Stuckey et al. 2003). The mean age ranged from 46 to 59 years, with 1 study not reporting this information (Escobar-Jimenez 2002). The mean duration of diabetes in 4 studies ranged from 11 to 12 years, with the remaining 8 studies not reporting this information. Mean HbA1c levels at baseline were not reported by any studies. Mean BMI in 4 studies ranged from 27.1 to 30.7 kg/m^2, with 8 studies not reporting this information. Follow-up periods ranged from 10 to 16 weeks.

PDE-5 inhibitors versus PDE-5 inhibitors

A total of 811 people (study sizes 49 and 762) were included from 2 RCTs, carried out in the Bulgaria (Kamenov 2004) and in different countries (Buvat et al. 2006). The mean ages were 50 and 57 years. The mean duration of diabetes was 9.5 and 10.8 13 years. Mean HbA1c levels at baseline were not reported by either study. Mean BMI was 29.2 and 28.7 kg/m^2. A follow-up period of 12 weeks was reported by 1 study (Buvat et al. 2006), but this information was unclear in the other study. One trial compared different treatment regimens of the same drug (Buvat et al. 2006), while the other compared two different drugs (Kamenov 2004).

Testosterone replacement therapy versus placebo

One 30 week trial conducted in the UK including 199 people diagnosed with type 2 diabetes and hypogonadism (mean age 61.6 years; mean duration of diabetes and HbA1c levels not reported; mean BMI 32.7 kg/m^2), 84.% of whom were diagnosed with erectile dysfunction, compared intramuscular testosterone undecanoate with placebo (Hackett et al. 2013).

The summary GRADE tables are presented for this review question, the full versions can be found in Appendix D.

Table 96: Summary GRADE profile for PDE-5 inhibitors versus placebo

Number of RCTs	Number of people		Effect (95% CI)	Quality
	PDE-5 inhibitor	Placebo		
Erectile Function using the International Index of Erectile Function [IIEF] mean score on EF domain; 12 to 16 week follow-up				
11 (Boulton 2001; Escobar-Jimenez 2002; Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	2142	1174	MD 5.58 (4.48 to 6.68)	Low
Erectile function using the Sexual Encounter Profile mean scores of SEP Q2 (successful insertion); 12 week follow-up				
5 (Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Ziegler 2006)	1059/1559	274/616	RR 1.47 (1.33 to 1.61)	Low
Erectile function using the Sexual Encounter Profile mean scores of SEP Q3 (successful intercourse); 12 week follow-up				
5 (Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Ziegler 2006)	800/1551	160/618	RR 1.87 (1.61 to 2.16)	Low
Erectile function-using the Global Efficacy Question mean scores of GEQ (global improvement); 12 to 16 week follow-up				
8 (Boulton 2001; Escobar-Jimenez 2002; Goldstein 2003; Hatzichristou 2008; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003)	623/1064	116/743	RR 3.62 (2.57 to 5.09)	Moderate
Any adverse events; 12 to 16 week follow-up				
11 (Boulton 2001; Escobar-Jimenez 2002; Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	610/9064	115/5249	RR 2.69 (1.87 to 3.86)	Low
Headache; 12 to 16 week follow-up				
10 (Boulton 2001; Escobar-Jimenez 2002; Goldstein 2003, 2012; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	185/2065	43/1126	RR 3.08 (1.46 to 6.48)	Low
Flushing; 12 to 16 week follow-up				

Number of RCTs	Number of people		Effect (95% CI)	Quality
	PDE-5 inhibitor	Placebo		
10 (Boulton 2001; Escobar-Jimenez 2002; Goldstein 2003, 2012; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	191/2065	6/1126	RR 8.65 (4.5 to 16.66)	Low
Bronchitis; 12 to 16 week follow-up				
1 (Ziegler 2006)	3/163	4/155	RR 0.71 (0.16 to 3.14)	Moderate
Upper respiratory tract infections; 12 to 16 week follow-up				
7 (Goldstein 2003, 2012; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Ziegler 2006)	147/1814	43/875	RR 1.12 (0.57 to 2.2)	Low
Discontinuation due to adverse events; 12 to 16 week follow-up				
9 (Goldstein 2003, 2012; Hatzichristou 2008; Ishii 2006; Rendell 1999; Saenz de Tejada 2002; Safarinejad 2004; Stuckey 2003; Ziegler 2006)	46/2013	14/1167	RR 1.67 (0.89 to 3.13)	Low
Dyspepsia; 12 to 16 week follow-up				
4 (Boulton 2001; Goldstein 2012; Rendell 1999; Stuckey 2003)	26/601	2/465	RR 6.09 (1.77 to 20.94)	Moderate
Abnormal vision; 12 to 16 week follow-up				
3 (Boulton 2001; Rendell 1999; Stuckey 2003)	12/343	3/335	RR 2.92 (0.71 to 11.99)	Moderate
Abbreviations: 95%C, 95% confidence interval; IIEF International Index of Erectile Function questionnaire; EF Erectile function domain of IIEF; MD mean difference; SEP Sexual Encounter Profile (diary questions regarding sexual encounter); GEQ Global Efficacy Question; RR risk ratio				

Table 97: Summary GRADE profile of subgroup analyses by baseline HbA1c level for PDE-5 inhibitors versus placebo

Number of RCTs	Number of people		Measure of effect	Quality
	Intervention	Placebo		
Erectile Function (measured with International Index of Erectile Function [IIEF] mean score on EF domain				

Number of RCTs	Number of people		Measure of effect	Quality
	Intervention	Placebo		
Sildenafil versus placebo				
1 (Boulton 2001)	47	47	Mean change from baseline stratified by baseline HbA1c level: • <8.3%: 8.9* with sildenafil versus 0.6 with placebo • ≥8.3%: 8.2* with sildenafil versus -0.5 with placebo	Moderate
Vardenafil versus placebo				
1 (Zieglar 2006)	154	149	Mean end point stratified by baseline HbA1c level: • Good (<7%): 21* with vardenafil versus 15 with placebo • Moderate (7-8%): 21* with vardenafil versus 14 with placebo • Poor (>8%): 18* with vardenafil versus 16 with placebo Interaction term between treatment and level of glycaemic control was not statistically significant	Moderate
Tadalafil versus placebo				
2 (Hatzichristou 2008; Saenz de Tejada 2002)	339	169	Mean change from baseline stratified by baseline HbA1c level • Good (<7%): 3.8 (2.5 mg), 6.6 (5 mg) 9.7 (10 mg), 8.3 (20 mg) with tadalafil versus -1.0, 1.4 with placebo • Fair (7-9.5%): 7.3 (2.5 mg), 3.2 (5 mg), 6.0 (10 mg), 6.7 (20 mg) with tadalafil versus -0.9, 1.4 with placebo • Poor (>9.5%): 1.4 (2.5 mg), 4.7 (5 mg), 3.8 (10 mg), 8.3 (20 mg) with tadalafil versus 3.9, 0.5 with placebo	Very low
**p<0.0001 versus placebo*				

Table 98: Summary GRADE profile for PDE-5 inhibitor versus PDE-5 inhibitor

Number of RCTs	Number of people		Measure of effect	Quality
	Intervention	Comparator		
	Tadalafil on demand	Tadalafil 3 times per week		
Erectile Function-using the International Index of Erectile Function [IIEF] mean score on EF domain; 12 week follow-up				
1 (Buvat 2006)	762	762	Mean change from baseline 8.9 (SE 0.3) on demand versus 9.1 (SE 0.3) for 3 times per week	Low

Number of RCTs	Number of people		Measure of effect	Quality
	Intervention	Comparator		
Erectile function using the Sexual Encounter Profile mean scores of SEP Q2 (successful insertion); 12 week follow-up				
1 (Buvat 2006)	762	762	Percentage of people answering 'yes' at end point was 73.0% on demand versus 74.9% for 3 times per week (p<0.05)	Low
Erectile function using the Sexual Encounter Profile mean scores of SEP Q3 (successful intercourse); 12 week follow-up				
1 (Buvat 2006)	762	762	Percentage of people answering 'yes' at end point was 58.0% on demand and 60.5% for 3 times per week (p<0.05).	Low
Treatment emergent adverse events				
1 (Buvat 2006)	762	762	• Back pain: 2.5% on demand versus 2.1% 3 times per week • Dyspepsia: 5.9% on demand versus 5.8% 3 times per week • Flushing: 1.6% on demand versus 2.1% 3 times per week • Headache: 4.7% on demand versus 5.6% 3 times per week • Myalgia: 1.4% on demand versus 2% 3 times per week	Low
	Tadalafil	**Vardenafil**		
Any adverse events				
1(Kamenov 2004)	7/24	6/25	• Dyspepsia: 8.4% with tadalafil versus 4% with vardenafil • Flushing: 4.2% with tadalafil versus 8% with vardenafil • Headache: 8.3% with tadalafil versus 8% with vardenafil • Myalgia: 8.4% with tadalafil versus 0% with vardenafil • Nasal congestion: 0% with tadalafil versus 8% with vardenafil	Low

Table 99: Summary GRADE profile for testosterone therapy versus placebo

Number of RCTs	Number of people		Effect (95% CI)	Quality
	Testosterone	Placebo		
Erectile Function domain of IIEF questionnaire				
1 (Hackett 2013)	91	95	Mean difference 3.47 (0.40 to 6.54)	Low
Adverse event (total dropouts)				
1 (Hackett 2013)	4/97	5/102	Relative risk 0.84 (0.23 to 3.04)	Low

9.3.2.3 Health economic evidence

Literature searches were carried out to find any existing cost utility analyses (CUAs) of the pharmacological management of erectile dysfunction in people with type 2 diabetes (see appendix C for search strategies). In total 88 articles were returned, and 2 CUAs were retained (Smith and Roberts 2000; Stolk et al. 2000). However neither of these studies was specific to a diabetic population. The GDG considered it might be possible to extrapolate from the general erectile dysfunction population to the type 2 diabetes erectile dysfunction population, so the searches were re-run without the type 2 diabetes search terms. This produced a further 1 CUA which again was not specific to the type 2 diabetes population (Aspinall et al. 2011) but it did specify that no difference in clinical effectiveness by risk factor (including type 2 diabetes) had been found.

None of the 3 studies compared different pharmacological treatments for erectile dysfunction – 1 study compared sildenafil to no treatment (Smith and Roberts 2000), 1 study compared sildenafil to injection therapy (Stolk et al. 2000) and 1 study compared different doses of vardenafil (Aspinall et al. 2011). No studies included avanafil or tadalafil.

None of the 3 studies were specific to the UK setting; 2 studies were model based analyses (Smith and Roberts 2000), (Stolk et al. 2000) whilst the third study (Aspinall et al. 2011) was a decision tree based on an RCT.

Two of the studies (Smith and Roberts 2000), (Aspinall et al. 2011) used a 3% discount rate (instead of a 3.5% discount rate) and 1 study (Stolk et al. 2000) did not specify whether a discount rate was used.

All studies used similar utility decrements for the erectile dysfunction state. 1 study (Aspinall et al. 2011) used a utility decrement of 0.13 that was taken from another included study (Smith and Roberts 2000) which in turn was taken from an American time trade off study in the context of prostate cancer. 1 study (Stolk et al. 2000) undertook their own population based time trade off study which produced a utility decrement of 0.13. It is not known whether the utility decrement for erectile dysfunction in people with type 2 diabetes is likely to differ from that in the general population.

All 3 studies found that the new treatment (sildenafil (Smith and Roberts 2000), (Stolk et al. 2000) or vardenafil (Aspinall et al. 2011)) was cost effective compared to the alternative chosen, at the usually accepted thresholds. For sildenafil, Smith and Roberts (2000) reported incremental cost effectiveness ratios (ICERs) less than $12,000/QALY; Stolk et al. (2000) reported ICERs less than £4000/QALY. For vardenafil, Aspinall et al. (2011) reported ICERs below $6000/QALY. All 3 studies assessed the uncertainty in the ICERs and found that, whilst the results were sensitive to some inputs, the ICERs were likely to remain below conventional thresholds in the majority of cases.

This question was not prioritised by the GDG for de novo economic modelling.

Table 100: Economic evidence table for erectile dysfunction in the general population

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
Aspinall et al, 2011 Hypothetical cohort of USA male veterans aged 60 with ED Vardenafil compared 0 doses to 4, 6 or 8 doses per month **Partly applicable**[a,d,e] **Potentially serious limitations**[a,b,c]	Effects: Systematic review (PDE5s) Costs: VA pharmacy data ($, 2009) Utilities: Baseline and ED as Smith (2000); increased gain by dose assumed	Markov model with lifetime time horizon Systematic review found no difference in efficacy for diabetes Estimates of extra doses utilities were conservative No mortality effect, no loss of treatment effect AEs not modelled, states same rates as placebo	0/month $0 4/month $707.70 6/month $353.90 8/month $353.90	0/month 0 QALYs 4/month 1.23 6/month 0.14 8/month 0.07	0/month Not applicable 4/month $576 /QALY 6/month $2585 /QALY 8/month $5169 /QALY	Providing extra monthly doses of Vardenafil is cost effective compared with less monthly doses at $50,000/QALY threshold	ICER sensitive to utility for 6/8 month and drug cost. ICER remains < $50,000 if 6/8 month QALY gain > 0.001 (base case 0.01), drug cost < $15 (base case $2, UK equivalent £3.50). In PSA, 6 doses was favoured 84% and 8 doses 61% at $50,000/ QALY
Smith, 2000 Hypothetical cohort of USA males aged 60 with ED Sildenafil compared to no treatment **Partly applicable**[a,d,e,g] **Potentially serious limitations**[a,b,f]	Effects: RCTs Costs: US$ 1998; drugs wholesale price; AEs estimated Utilities: Baseline US TTO; ED from prostate cancer screening study; AEs estimated	Markov model with lifetime time horizon No treatment assumed to incur no costs AEs: assumed No external funding listed Supported by VA Centre for Medication Safety	Treated v not $3970[h] $3950[i]	Treated v not 0.3519[h] 0.351[i]	Treated v not $11,290/ QALY[h] $11,230/ QALY[i]	Sildenafil treatment is cost effective compared with no treatment at $50,000/ QALY threshold	Remains cost effective when assumptions biased against treatment[g]. If utility gain > 0.05 (base case 0.13), ICER remained < $50,000/ QALY[g] In PSA, sildenafil was favoured 98% of times at $50k/QALY[g]
Stolk et al. (2000) RCT (n=532) Sildenafil compared to usual treatment (injection therapy) **Partly applicable**[a,d,e] **Potentially serious limitations**[a,f,j]	Effects: RCT, expert opinion. Uptake assumed Costs: 1999, drugs data, resource use estimated Utilities: Dutch population TTO, assumed same both treatments	RCT based decision tree with 5 year time horizon Likely to under estimate utility gain because of RCT ITT and QoL assumptions Funded by industry	Year 1 £28,368 Year 5 £89,226	Year 1 7.79 QALYs Year 5 33.92	Year 1 £3639/ QALY Year 5 £2630/ QALY	Sildenafil is cost effective compared to usual care at £20,000/QALY threshold	ICER sensitive to dosing frequency (base case 1/week), utility gain and effectiveness. But in worst case scenario, ICER remains <£10k/QALY

Study, Population, Comparators and Quality	Data Sources	Other Comments	Incremental			Conclusions	Uncertainty
			Cost	Effect	ICER		
a Not UK based b Not 3.5% discount rate c No non-drug costs included d Does not compare relevant treatments e Not diabetes specific f Drug costs appear high g Analysis mainly from societal not NHS perspective h Societal perspective i Third party payer perspective j Potential conflict of interest							
AEs: adverse events ED: erectile dysfunction ICER: incremental cost effectiveness ratio PDE5s: QALY: quality-adjusted life year QoL: quality of life USA: United States of America VA: Veterans Association							

9.3.2.4 Evidence statements

9.3.2.5 Clinical evidence

No relevant studies on alprostredil were identified.

9.3.2.5.1 PDE-5 inhibitors versus placebo

Overall, evidence from 4 meta-analyses including data from up to 11 trials showed on 4 different assessment scales, a significant improvement in erectile function with PDE-5 inhibitors compared to placebo up to 16 weeks. The quality of the evidence ranged from moderate to low. Four RCTs showed no difference in erectile function outcomes based on baseline HbA1c levels. The quality of the evidence ranged from moderate to very low.

Evidence from 4 meta-analyses including data from up to 11 trials showed a significant increase in risk of any adverse events, dyspepsia, flushing and headache with PDE-5 inhibitors compared to placebo up to 16 weeks. The quality of the evidence ranged from moderate to low.

9.3.2.5.2 PDE-5 inhibitors versus PDE-5 inhibitors

Two small trials provided no conclusive findings regarding different regimens of tadalafil that is, on demand versus 3 times per week or different drugs that is, tadalafil versus vardenafil. The quality of the evidence was low.

9.3.2.5.3 Testosterone replacement therapy versus placebo

Evidence from a single RCT showed that the use of long-acting intramuscular testosterone therapy was associated with improvement in erectile function in people with type 2 diabetes diagnosed with hypogonadism. There is limited data on the associated adverse effects of testosterone therapy. The quality of the evidence was low.

9.3.2.6 Health economic evidence

No CUAs were found that directly compare the 4 PDE-inhibitor treatments under consideration and no CUAs were found that were specific to people with diabetes. Three CUAs found that 2 of the treatments (sildenafil and vardenafil) for erectile dysfunction are likely to be cost effective at the appropriate thresholds, but used different comparators (no treatment or injection therapy). No CUAs were found for tadalafil or avanafil. While none were undertaken in diabetic specific or UK populations, all the CUAs used similar utility gains for successful erectile dysfunction treatment and produced base case ICERs that are likely to be below the £20,000 per QALY threshold. All 3 CUAs contained assumptions that are conservative or biased towards the alternative treatment but under sensitivity analysis the treatment option remained likely to be cost effective.

9.3.3 Evidence to recommendations

Table 101: Linking evidence to recommendations

Relative value of different outcomes	Topic experts were invited to the GDG meeting to inform the clinical discussions before making recommendations. The Group agreed that the critical outcomes for decision-making were change in erectile function and adverse events, and that both outcomes were weighted equally. The GDG acknowledged that for PDE-5 inhibitors, adverse effect profiles may differ according to the specific drug, but agreed that it

	was not possible to weight the severity of the events as most side effects are mild and may be individualised.
Trade-off between benefits and harms	The GDG discussed the benefits associated with PDE-5 inhibitors in improving erectile function, self-esteem and quality of life for patients and their partners. The GDG noted that the use of PDE-5 inhibitors was associated with relatively mild side effects including headaches and flushing, which may reduce over time. The GDG agreed that it is unlikely that these reductions in adverse events would have been observed in the presented evidence because of the trials' short follow-up periods which ranged from 10 to 16 weeks. The GDG noted the different side effects that are associated with individual drugs, for example, tadalafil with backaches and sildenafil with blue-green vision, and agreed that it was not possible to differentiate between the severity of these generally mild adverse events and the associated impact on people, which may vary.
Consideration of health benefits and resource use	The 3 cost–utility analyses (CUAs) found did not meet the NICE reference case, but the GDG concluded they showed that effective treatments were likely to increase utility by an extent that would offset reasonable costs. Although no economic evidence was found for using PDE-5 inhibitors to treat erectile dysfunction in people with type 2 diabetes, the GDG considered that it was possible to extrapolate from evidence in the general population. The GDG noted that men with type 2 diabetes and erectile dysfunction are likely to be on the higher doses of PDE-5 inhibitor drugs but, even with this in mind, considered that the CUAs presented indicated that effective treatments were likely to increase utility by an extent that would offset reasonable costs.
Quality of evidence	The GDG discussed the overall quality of the evidence for the PDE-5 inhibitors and agreed that it was low to very low. The GDG discussed the characteristics of people who were included in the trials and noted that some studies excluded people who had cardiovascular disease, hypertension and vascular impairment. Therefore, the GDG agreed that the studies may not be representative of the clinical type 2 diabetes population. The GDG also noted that people taking nitrates (for example, for ischaemic heart disease) would not be able to participate because the use of PDE-5 inhibitors is specifically contraindicated in these individuals. The GDG discussed the inclusion of the 2 studies where all participants were men with type 1 diabetes and noted that these studies may also have underestimated treatment effects, because these patients were younger and may have had different baseline characteristics compared with people with type 2 diabetes. The GDG discussed the 2 trials examining testosterone therapy. One trial was considered to be very low-quality evidence because oral testosterone is not used in clinical practice, the small sample of men included in the study had symptoms of andropause or erectile dysfunction, and the trial was open label, with no treatment used as a comparison group rather than placebo. The GDG agreed that this trial should be excluded (Boyanov et al. 2003).

	The second placebo-controlled trial on intramuscular testosterone therapy was not considered to be generalisable to men with type 2 diabetes because the study included a specific subgroup of men who were purposely screened for hypogonadism. The GDG noted that there was little evidence on the safety issues associated with testosterone therapy. The GDG noted the lack of evidence on alprostredil.
Other considerations	The GDG also discussed contributory risk factors and generally agreed that this would include cardiovascular risk, so this was added to the existing recommendation about assessment and education. The GDG discussed the other recommendations that were included in NICE guidance CG66, and agreed that these were still relevant. The GDG noted that the majority of studies were conducted in heterosexual couples. The GDG considered that a research recommendation would be useful given that it is not clear from the limited evidence base whether the effectiveness of therapies would be similar for men with type 2 diabetes who are in same-sex relationships. When making recommendations for the use of testosterone therapy, the GDG considered the following points: • There were 2 low-quality trials that were not relevant to clinical practice and were associated with several methodological limitations. • Therefore, the GDG did not think that there was sufficient evidence to make any recommendations for the use of testosterone therapy. When making recommendations for the use of PDE-5 inhibitors, the GDG considered the following points: • Overall, it was agreed that the included evidence was of low quality and involved a heterogeneous population, which may not be representative of patients with type 2 diabetes. • Alternative treatment options were not considered as part of the evidence review. • Treatment of erectile dysfunction that patients consider to be problematic should be discussed with patients and be treated on an individual basis. Therefore, the GDG changed the wording of the recommendation from ‘offer’ to ‘consider’. Although they were confident that PDE-5 inhibitors will do more good than harm for most men with type 2 diabetes and are likely to be cost effective, it was also agreed that alternative options (which were not reviewed as part of this question) may be similarly cost effective. The GDG also added the word ‘initially’ to reflect that in clinical practice, drugs and doses are chosen but may be altered depending on the progress of the person. The GDG also agreed that there was a lack of evidence for the use of PDE-5 inhibitors in specific subgroups of the population and as a result no specific recommendations were made.

9.3.4 Recommendations and research recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng28

Research recommendations

14. **What is the optimal dosing of different phosphodiesterase-5 (PDE-5) inhibitors for people with type 2 diabetes and erectile dysfunction?**

    Why this is important

    Although phosphodiesterase-5 (PDE-5) inhibitors have been shown to be effective compared to placebo in improving erectile function in men with type 2 diabetes, there is little understanding of the optimal dosing strategies for the different drugs available in this class. Double-blind randomised controlled trials in this area could help inform clinical practice.

15. **What is the effectiveness of pharmacological treatment strategies for people with type 2 diabetes and erectile dysfunction who do not respond to phosphodiesterase-5 (PDE-5) inhibitors, for example PDE-5 inhibitor plus prostaglandins?**

    Why this is important

    There is limited understanding of alternative treatment strategies available to men who do not respond to phosphodiesterase-5 (PDE-5) inhibitors. Double-blind randomised controlled trials of combination therapies and other pharmacological treatments could help inform clinical practice.

16. **What is the effectiveness of treatment strategies (pharmacological and non-pharmacological) for sexual dysfunction related to type 2 diabetes in women?**

    Why this is important

    Sexual dysfunction affect women with type 2 diabetes and there is limited understanding of available effective treatment strategies. A systematic review is needed examining the clinical and cost-effectiveness of available treatment strategies for women with type 2 diabetes and sexual dysfunction.

17. **What is the effectiveness of treatment strategies (pharmacological and non-pharmacological) for sexual dysfunction in adults with type 2 diabetes in same-sex relationships?**

    Why this is important

    Sexual dysfunction in adults with type 2 diabetes in same-sex relationships is an important area, where there is a limited understanding about effective treatment strategies. A systematic review is needed examining the clinical and cost-effectiveness of available treatment strategies for adults with type 2 diabetes and sexual dysfunction in same-sex relationships.

9.4 Eye disease

Diabetes eye damage is the single largest cause of blindness before old age with a progressive incidence in people with type 2 diabetes.[346] 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.

Appropriate clinical questions 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, good blood pressure, and good blood lipid control can be useful in people with type 2 diabetes.

9.4.1 Methodological introduction

It was noted that management in this area was largely determined by practice for all people with diabetes and not just those with type 2 diabetes. Indeed retinopathy screening programmes to be provided on a local community basis were a key early target of the National Service Framework (NSF) for diabetes, and since that time the UK National Screening Programme has published and updated a workbook on ‘Essential elements in developing a diabetic retinopathy screening programme’ for the guidance of health authorities and primary care trusts in England.[347]

These observations, and a lack of awareness amongst experts of new publications that might affect recommendations on retinopathy screening, led to the conclusion that recommendations for people with type 2 diabetes should closely follow those for type 1 diabetes (NICE guideline 2004),[26] which themselves were largely based on generic evidence independent of type of diabetes.

Accordingly the recommendations of the type 1 diabetes guidelines, and the evidence statements underlying them were reviewed, together with the national screening document. There are no significant changes from the type 1 diabetes recommendations.

9.4.2 Recommendations

The current recommendations can be found at www.nice.org.uk/guidance/ng28

10 Reference

10.1 Reference for update sections in 2015 (2, 3, 7, 8 and 9.3)

Anon (1993) Efficacy and safety of two different dosages of acarbose in non-insulin dependent diabetic patients treated by diet alone. Diabetes, Nutrition & Metabolism - Clinical & Experimental 6(3): 147-54

Anon (1994) The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. Annals of Internal Medicine 1994; 121(12): 928-35

Anon (1996) Efficacy of acarbose monotherapy in patients with type 2 diabetes: A double-blind study conducted in general practice. Endocrinology & Metabolism; 3(4): 275-80

Anon (1997) Multicentric clinical trial to assess efficacy and tolerability of acarbose (BAY G 5421) in comparison to glibenclamide and placebo. Diabetologia Croatica 1997; 26(2): 83-9

Anon (2001) Comparison of acarbose and gliclazide as first-line agents in patients with type 2 diabetes. Current Medical Research and Opinion. 16(4): 296-306

Anon (2002) Improved Glycemic Control and Lipid Profile in a Randomized Study of Pioglitazone Compared with Acarbose in Patients with Type 2 Diabetes Mellitus. 1: 329-36

¤llsten K, Virtanen KA, ¶nnqvist F et al. (2002) Rosiglitazone but Not Metformin Enhances Insulin- and Exercise-Stimulated Skeletal Muscle Glucose Uptake in Patients With Newly Diagnosed Type 2 Diabetes. Diabetes 51: 3479-85

Aas AM, Ohrvik J, Malmberg K et al. (2009) Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. Diabetes, Obesity & Metabolism 11: 323-9

Abbatecola AM, Rizzo MR, Barbieri M et al. (2006) Postprandial plasma glucose excursions and cognitive functioning in aged type 2 diabetics. Neurology 67: 235-40

Adler AI, Neil HA, Manley SE et al. (1999) Hyperglycemia and hyperinsulinemia at diagnosis of diabetes and their association with subsequent cardiovascular disease in the United Kingdom prospective diabetes study (UKPDS 47). American Heart Journal 138: S353-S359

Alba M, Ahren B, Inzucchi SE et al. (2013) Sitagliptin and pioglitazone provide complementary effects on postprandial glucose and pancreatic islet cell function. Diabetes, Obesity and Metabolism.15 (12) (pp 1101-1110), 2013.Date of Publication: December 2013. 1101-10

Aljabri K, Kozak, SE (2004) Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. The American journal of medicine 116: 230-235 (Abstract).

Allen BT, DeLong ER, Feussner JR (1990) Impact of glucose self-monitoring on non-insulin-treated patients with type II diabetes mellitus. Randomized controlled trial comparing blood and urine testing. Diabetes Care 13: 1044-50

Arechavaleta R, Seck T, Chen Y et al. (2010) Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: A randomized, double-blind, non-inferiority trial. Diabetes, Obesity and Metabolism.13 (2) (pp 160-168), 2010.Date of Publication: February 2011. 160-8

Arjona Ferreira JC, Marre M, Barzilai N et al. (2013) Efficacy and safety of sitagliptin versus glipizide in patients with type 2 diabetes andmoderate-to-severe chronic renal insufficiency. Diabetes Care.36 (5) (pp 1067-1073), 2013.Date of Publication: May 2013. 1067-73

Aronoff S, Rosenblatt S, Braithwaite S et al. (2000) Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group. Diabetes Care 23: 1605-11

Aschner P, Kipnes MS, Lunceford JK et al. (2006) Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care.29 (12) (pp 2632-2637), 2006.Date of Publication: December 2006. 2632-7

Aschner P, Katzeff HL, Guo H et al. (2010) Efficacy and safety of monotherapy of sitagliptin compared with metformin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism.12 (3) (pp 252-261), 2010.Date of Publication: March 2010. 252-61

Aspinall SL, Smith KJ, Cunningham FE (2011) Incremental cost-effectiveness of various monthly doses of vardenafil. Value in Health 14: 97-101

Bagust A, Beale S (2005) Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. Health Economics 14: 217-30

Barnett AH, Krentz AJ, Strojek K et al. (2008) The efficacy of self-monitoring of blood glucose in the management of patients with type 2 diabetes treated with a gliclazide modified release-based regimen. A multicentre, randomized, parallel-group, 6-month evaluation (DINAMIC 1 study). Diabetes, Obesity & Metabolism 10: 1239-47

Barnett AH, Patel S, Harper R et al. (2012) Linagliptin monotherapy in type 2 diabetes patients for whom metformin is inappropriate: An 18-week randomized, double-blind, placebo-controlled phase iii trial with a 34-week active-controlled extension. Diabetes, Obesity and Metabolism.14 (12) (pp 1145-1154), 2012.Date of Publication: December 2012. 1145-54

Barzilai N, Guo H, Mahoney EM et al. (2011) Efficacy and tolerability of sitagliptin monotherapy in elderly patients with type 2 diabetes: a randomized, double-blind, placebo-controlled trial. Current Medical Research And Opinion 27: 1049-58

Bautista JL, Bugos C, Dirnberger G (2003) Efficacy and safety profile of glimepiride in Mexican American patients with type 2 diabetes mellitus: A randomized, placebo-controlled study. Clinical Therapeutics.25 (1) (pp 194-209), 2003.Date of Publication: 01 Jan 2003. 194-209

Beaudet A, Palmer JL, Timlin L et al. (2011) Cost-utility of exenatide once weekly compared with insulin glargine in patients with type 2 diabetes in the UK. Journal of Medical Economics 14: 357-66

Bergenstal R, Lewin A, Bailey T et al. (2009) Efficacy and safety of biphasic insulin aspart 70/30 versus exenatide in subjects with type 2 diabetes failing to achieve glycemic control with metformin and a sulfonylurea. Current Medical Research & Opinion 25: 65-75

Bergenstal RM, Wysham C, Macconell L et al. (2010) Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. Lancet 376: 431-9

Bhatt DL, Marso SP, Hirsch AT et al. (2002) Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. American Journal of Cardiology 90: 625-8

Bhatt DL, Fox KA, Hacke W et al. (2006) Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. New England Journal of Medicine 354: 1706-17

Birkeland K, Furuseth K, Melander A et al. (1994) Long-Term Randomized Placebo-Controlled Double-Blind Therapeutic Comparison of Glipizide and Glyburide: Glycemic control and insulin secretion during 15 months. Diabetes Care 17: 45-9

Bolli G, Dotta F, Rochotte E (2008) Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. Diabetes, Obesity & Metabolism 10: 82-90

Bolli G, Dotta F, Colin L et al. (2009) Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. Diabetes, Obesity & Metabolism 11: 589-95

Bonomo K, Salve A, Fiora E et al. (2010) Evaluation of a simple policy for pre- and post-prandial blood glucose self-monitoring in people with type 2 diabetes not on insulin. Diabetes research and clinical practice 87: 246-51

Bosi E, Dotta F, Jia Y (2009) Vildagliptin plus metformin combination therapy provides superior glycaemic control to individual monotherapy in treatment-naive patients with type 2 diabetes mellitus. Diabetes, Obesity & Metabolism 11: 506-15

Bosi E, Scavini M, Ceriello A et al. (2013) Intensive structured self-monitoring of blood glucose and glycemic control in noninsulin-treated type 2 diabetes: the PRISMA randomized trial. Diabetes Care 36: 2887-94

Boulton AJM, Selam J-L, Sweeney M et al. (2001) Sildenafil citrate for the treatment of erectile dysfunction in men with Type II diabetes mellitus. Diabetologia.44 (10) (pp 1296-1301), 2001.Date of Publication: 2001. 1296-301

Boyanov MA, Boneva Z, Christov VG (2003) Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male 6: 1-7

Brady EM, Davies MJ, Gray LJ et al. (2014) A randomized controlled trial comparing the GLP-1 receptor agonist liraglutide to a sulphonylurea as add on to metformin in patients with established type 2 diabetes during Ramadan: the Treat 4 Ramadan Trial. Diabetes, Obesity and Metabolism 16: 527-36

Bruce S, Park JS, Fiedorek FT (2006) Beta-cell response to metformin-glibenclamide combination tablets (Glucovance) in patients with type 2 diabetes. International Journal of Clinical Practice 60: 783-90

Bruno G, Merletti F, Boffetta P et al. (1999) Impact of glycaemic control, hypertension and insulin treatment on general and cause-specific mortality: an Italian population-based cohort of type II (non-insulin-dependent) diabetes mellitus. Diabetologia 42: 297-301

Buchanan DR, Collier A, Rodrigues E et al. (1988) Effectiveness of acarbose, an alpha-glucosidase inhibitor, in uncontrolled non-obese non-insulin dependent diabetes. 34: 51-3

Buvat J, Maggi M, Gooren L et al. (2010) Endocrine aspects of male sexual dysfunctions. Journal of Sexual Medicine.7 (4 PART 2) (pp 1627-1656), 2010.Date of Publication: April 2010. 1627-56

Cameron C, Coyle D, Ur E (2010) Cost-effectiveness of self-monitoring of blood glucose in patients with type 2 diabetes mellitus managed without insulin. CMAJ Canadian Medical Association Journal 182: 28-34

Campbell IW, Menzies DG, Chalmers J et al. (1994) One year comparative trial of metformin and glipizide in type 2 diabetes mellitus. Diab+¨te & m+©tabolisme 20: 394

CDC Diabetes Cost-effectiveness Group (2002) Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA 287: 2542-51

Chan JC, Chan KW, HO LL et al. (1998) An Asian Multicenter Clinical Trial to Assess the Efficacy and Tolerability of Acarbose Compared With Placebo in Type 2 Diabetic Patients Previously Treated With Diet. Diabetes Care 21: 1058-61

Chapell R, Gould AL, Alexander CM (2009) Baseline differences in A1C explain apparent differences in efficacy of sitagliptin, rosiglitazone and pioglitazone. Diabetes Obesity and Metabolism 11: 1009-16

Charbonnel B, Roden M, Urquhart R et al. (2005a) Pioglitazone elicits long-term improvements in insulin sensitivity in patients with type 2 diabetes: comparisons with gliclazide-based regimens. 48: 553-60

Charbonnel BH, Matthews DR, Schernthaner G et al. (2005b) A long-term comparison of pioglitazone and gliclazide in patients with Type 2 diabetes mellitus: A randomized, double-blind, parallel-group comparison trial. Diabetic Medicine.22 (4) (pp 399-405), 2005.Date of Publication: April 2005. 399-405

Chawla S, Kaushik N, Singh NP (2013) Effect of addition of either sitagliptin or pioglitazone in patients with uncontrolled type 2 diabetes mellitus on metformin: A randomized controlled trial. Journal of Pharmacology & Pharmacotherapeutics 4: 27-32

Chiasson JL (2001) The Synergistic Effect of Miglitol Plus Metformin Combination Therapy in the Treatment of Type 2 Diabetes. Diabetes Care 24: 989-94

Cho JH, Lee HC, Lim DJ et al. (2009) Mobile communication using a mobile phone with a glucometer for glucose control in Type 2 patients with diabetes: as effective as an Internet-based glucose monitoring system. Journal of Telemedicine & Telecare 15: 77-82

Civera M, Merchante A, Salvador M et al. (2008) Safety and efficacy of repaglinide in combination with metformin and bedtime NPH insulin as an insulin treatment regimen in type 2 diabetes. Diabetes Research & Clinical Practice 79: 42-7

Clar C, Barnard K, Cummins E et al. (2010) Self-monitoring of blood glucose in type 2 diabetes: systematic review. [Review] [142 refs]. Health Technology Assessment (Winchester, England) 14: 1-140

Clarke PM, Gray AM, Holman RR (2002) Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). Medical Decision Making 22: 340-9

Clarke PM, Gray AM, Legood R et al. (2003) The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabetic Medicine 20: 442-50

Clarke PM, Gray AM, Briggs A. et al. (2004) A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 47: 1747-59

Clarke PM, Gray AM, Briggs A et al. (2005) Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72). Diabetologia 48: 868-77

Collier A, Watson HH, Patrick AW et al. (1989) Effect of glycaemic control, metformin and gliclazide on platelet density and aggregability in recently diagnosed type 2 (non-insulin-dependent) diabetic patients. Diabete et Metabolisme 15: 420-5

Coniff RF, Shapiro, JA, Seaton, TB (1995a) Multicenter, placebo-controlled trial comparing acarbose (BAY g 5421) with placebo, tolbutamide, and tolbutamide-plus-acarbose in non-insulin-dependent diabetes mellitus. The American journal of medicine 98: 443-451 (Abstract).

Coniff RF, Shapiro JA, Robbins D et al. (1995b) Reduction of Glycosylated Hemoglobin and Postprandial Hyperglycemia by Acarbose in Patients With NIDDM: A placebo-controlled dose-comparison study. Diabetes Care 18: 817-24

Currie CJ, Morgan CL, Poole CD et al. (2006) Multivariate models of health-related utility and the fear of hypoglycaemia in people -with diabetes. Current Medical Research & Opinion 22: 12523-1534

Curtis L (2014) Unit costs of health and social care 2013.

Damsbo P, Hermann LS, Vaag A et al. (1998) Irreversibility of the Defect in Glycogen Synthase Activity in Skeletal Muscle From Obese Patients With NIDDM Treated With Diet and Metformin. Diabetes Care 21: 1489-94

Davidson MB, Castellanos M, Kain D et al. (2005) The effect of self monitoring of blood glucose concentrations on glycated hemoglobin levels in diabetic patients not taking insulin: A blinded, randomized trial. American Journal of Medicine.118 (4) (pp 422-425), 2005.Date of Publication: April 2005. 422-5

Davies MJ, Chubb BD, Smith IC (2012) Cost-utility analysis of liraglutide compared with sulphonylurea or sitagliptin, all as add-on to metformin monotherapy in Type 2 diabetes mellitus. Diabetic Medicine 29: 313-22

DeFronzo RA (1995) Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus. New England Journal of Medicine 333: 541-9

Dejager S, Razac S, Foley JE (2007) Vildagliptin in drug-naive patients with type 2 diabetes: a 24-week, double-blind, randomized, placebo-controlled, multiple-dose study. Hormone & Metabolic Research 39: 218-23

Del Prato S, Erkelens DW (2003) Six-month efficacy of benfluorex vs. placebo or metformin in diet-failed type 2 diabetic patients. 40: 20-7

Del Prato S, Nicolucci A, Lovagnini-Scher AC et al. (2012) Telecare Provides comparable efficacy to conventional self-monitored blood glucose in patients with type 2 diabetes titrating one injection of insulin glulisine-the ELEONOR study. Diabetes Technology & Therapeutics 14: 175-82

Delgado H, Lehmann T, Bobbioni-Harsch E et al. (2002) Acarbose improves indirectly both insulin resistance and secretion in obese type 2 diabetic patients. Diabetes and Metabolism.28 (3) (pp 195-200), 2002.Date of Publication: 2002. 195-200

Derosa G, Mugellini A, Ciccarelli L et al. (2003) Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: A one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factor. Clinical Therapeutics.25 (2) (pp 472-484), 2003.Date of Publication: 01 Feb 2003. 472-84

Derosa G, D'Angelo A, Fogari E et al. (2007) Effects of nateglinide and glibenclamide on prothrombotic factors in naive type 2 diabetic patients treated with metformin: a 1-year, double-blind, randomized clinical trial. Internal Medicine 46: 1837-46

Derosa G, Maffioli P, Salvadeo SA et al. (2009a) Direct comparison among oral hypoglycemic agents and their association with insulin resistance evaluated by euglycemic hyperinsulinemic clamp: the 60's study. Metabolism: Clinical & Experimental 58: 1059-66

Derosa G, Salvadeo SA, D'Angelo A et al. (2009b) Metabolic effect of repaglinide or acarbose when added to a double oral antidiabetic treatment with sulphonylureas and metformin: a double-blind, cross-over, clinical trial. Current Medical Research & Opinion 25: 607-15

Derosa G, Maffioli P, Salvadeo SA et al. (2010a) Effects of sitagliptin or metformin added to pioglitazone monotherapy in poorly controlled type 2 diabetes mellitus patients. Metabolism: Clinical & Experimental 59: 887-95

Derosa G, Mereu R, D'Angelo A et al. (2010b) Effect of pioglitazone and acarbose on endothelial inflammation biomarkers during oral glucose tolerance test in diabetic patients treated with sulphonylureas and metformin. Journal of Clinical Pharmacy & Therapeutics 35: 565-79

Derosa G, Putignano P, Bossi AC et al. (2011a) Exenatide or glimepiride added to metformin on metabolic control and on insulin resistance in type 2 diabetic patients. European Journal of Pharmacology 666: 251-6

Derosa G, Cicero AF, Fogari E et al. (2011b) Pioglitazone compared to glibenclamide on lipid profile and inflammation markers in type 2 diabetic patients during an oral fat load. Hormone & Metabolic Research 43: 505-12

Derosa G, Maffioli P, Ferrari I et al. (2011c) Acarbose actions on insulin resistance and inflammatory parameters during an oral fat load. European Journal of Pharmacology.651 (1-3) (pp 240-250), 2011.Date of Publication: 25 Jan 2011. 240-50

Derosa G, Cicero AFG, Franzetti IG et al. (2013) A comparison between sitagliptin or glibenclamide in addition to metformin + pioglitazone on glycaemic control and beta-cell function: The triple oral therapy. Diabetic Medicine.30 (7) (pp 846-854), 2013.Date of Publication: July 2013. 846-54

Deyoung L, Chung E, Kovac JR et al. (2012) Daily use of sildenafil improves endothelial function in men with type 2 diabetes. Journal of Andrology 33: 176-80

Diamant M, Van GL, Stranks S et al. (2010) Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Lancet 375: 2234-43

Diamant M, Van GL, Stranks S et al. (2012) Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. Diabetes Care 35: 683-9

Dias S, Welton NJ, Sutton AJ et al. (2011a) NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. http://www.nicedsu.org.uk

Dias S, Sutton AJ, Welton NJ et al. (2011b) NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. http://www.nicedsu.org.uk

Dias S, Welton NJ, Sutton AJ et al. (2011c) NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. http://www.nicedsu.org.uk

Diener HC, Bogousslavsky J, Brass LM et al. (2004) Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 364: 331-7

Donnelly LA, Morris AD, Frier BM et al. (2005) Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. Diabetic Medicine 22: 749-55

Drechsler C, Krane V, Ritz E et al. (2009) Glycemic control and cardiovascular events in diabetic hemodialysis patients. Circulation 120: 2421-8

Duran C, Tuncel E, Ersoy C et al. (2009) The investigation of the efficacy of insulin glargine on glycemic control when combined with either repaglinide or acarbose in obese Type 2 diabetic patients.[Erratum appears in J Endocrinol Invest.2009 Feb;32(2):IV]. Journal of Endocrinological Investigation 32: 69-73

Eastman RC, Javitt JC, Herman WH et al. (1997) Model of complications of NIDDM. II. Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. Diabetes Care 20: 735-44

Ebeling P, Teppo, AM, Koistinen, HA (2001) Concentration of the complement activation product, acylation-stimulating protein, is related to C-reactive protein in patients with type 2 diabetes. Metabolism: clinical and experimental 50: 283-287 (Abstract).

Eeg-Olofsson K, Cederholm J, Nilsson PM et al. (2010) New aspects of HbA1c as a risk factor for cardiovascular diseases in type 2 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Journal of Internal Medicine 268: 471-82

Elbourne DR, Altman DG, Higgins JP et al. (2002) Meta-analyses involving cross-over trials: methodological issues. International Journal of Epidemiology 31: 140-9

Eliaschewitz FG, Calvo C, Valbuena H et al. (2006) Therapy in Type 2 Diabetes: Insulin Glargine vs. NPH Insulin Both in Combination with Glimepiride. Archives of Medical Research.37 (4) (pp 495-501), 2006.Date of Publication: May 2006. 495-501

Erdem G, Dogru T, Tasci I et al. (2008) The effects of pioglitazone and metformin on plasma visfatin levels in patients with treatment naive type 2 diabetes mellitus. Diabetes Research & Clinical Practice 82: 214-8

Erdmann E, Dormandy JA, Charbonnel B et al. (2007) The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients With Type 2 Diabetes and Previous Myocardial Infarction. Results From the PROactive (PROactive 05) Study. Journal of the American College of Cardiology.49 (17) (pp 1772-1780), 2007.Date of Publication: 01 May 2007. 1772-80

Erem C, Ozbas HM, Nuhoglu I et al. (2014) Comparison of effects of gliclazide, metformin and pioglitazone monotherapies on glycemic control and cardiovascular risk factors in patients with newly diagnosed uncontrolled type 2 diabetes mellitus. Experimental and Clinical Endocrinology and Diabetes 122: 295-302

Esposito K, Maiorino MI, Di PC et al. (2011) Effects of pioglitazone versus metformin on circulating endothelial microparticles and progenitor cells in patients with newly diagnosed type 2 diabetes--a randomized controlled trial. Diabetes, Obesity & Metabolism 13: 439-45

Esteghamati A, Ghasemiesfe M, Mousavizadeh M (2014) Pioglitazone and metformin are equally effective in reduction of chemerin in patients with type 2 diabetes. Journal of Diabetes Investigation.5 (pp 327-332), 2014.Date of Publication: May 2014. 327-32

ETDRS Investigators (1992) Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. Journal of the American Medical Association 268: 1292-300

Fang FS, Gong YP, Li CL et al. (2014) Comparison of repaglinide and metformin monotherapy as an initial therapy in Chinese patients with newly diagnosed type 2 diabetes mellitus. European Journal of Endocrinology 170: 901-8

Farmer A, Wade A, Goyder E et al. (2007) Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial. BMJ 335: 132

Farmer AJ, Wade AN, French DP et al. (2009) Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial. Health Technology Assessment (Winchester, England) 13: iii-iiv

Ferrannini E, Fonseca V, Zinman B et al. (2009) Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy.[Erratum appears in Diabetes Obes Metab. 2009 Apr;11(4):405]. Diabetes, Obesity & Metabolism 11: 157-66

Ferrannini E, Seman L, Seewaldt-Becker E et al. (2013) A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism.15 (8) (pp 721-728), 2013.Date of Publication: August 2013. 721-8

Filozof C (2010) A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with Type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study. Diabetic Medicine 27: 318-26

Fischer S, Hanefeld M, Spengler M et al. (1998) European study on dose-response relationship of acarbose as a first-line drug in non-insulin-dependent diabetes mellitus: efficacy and safety of low and high doses. 35: 34-40

Fisman EZ, Tenenbaum A, Boyko V et al. (2001) Oral antidiabetic treatment in patients with coronary disease: time-related increased mortality on combined glyburide/metformin therapy over a 7.7-year follow-up. Clinical Cardiology 24: 151-8

Foley JE (2009) Efficacy and safety comparison between the DPP-4 inhibitor vildagliptin and the sulfonylurea gliclazide after two years of monotherapy in drug-naive patients with type 2 diabetes.[Erratum appears in Horm Metab Res. 2009 Dec;41(12):909]. Hormone & Metabolic Research 41: 905-9

Follmann D, Elliot P, Suh I et al. (1992) Variance imputation for overviews of clinical trials with continuous response. Journal of Clinical Epidemiology 45: 769-73

Fonseca VA, Ferrannini E, Wilding JP et al. (2013) Active- and placebo-controlled dose-finding study to assess the efficacy, safety, and tolerability of multiple doses of ipragliflozin in patients with type 2 diabetes mellitus. Journal of Diabetes and its Complications.27 (3) (pp 268-273), 2013.Date of Publication: May-June 2013. 268-73

Fontbonne A, Billault B, Acosta M et al. (1989) Is glucose self-monitoring beneficial in non-insulin-treated diabetic patients? Results of a randomized comparative trial. Diabète & métabolisme 15: 255-60

Formoso G, De Filippis EA, Michetti N et al. (2008) Decreased in vivo oxidative stress and decreased platelet activation following metformin treatment in newly diagnosed type 2 diabetic subjects. Diabetes/Metabolism Research Reviews 24: 231-7

Forst T, Uhlig-Laske B, Ring A et al. (2010) Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. Diabetic Medicine 27: 1409-19

Franciosi M, Lucisano G, Pellegrini F et al. (2011) ROSES: role of self-monitoring of blood glucose and intensive education in patients with Type 2 diabetes not receiving insulin. A pilot randomized clinical trial. Diabetic Medicine 28: 789-96

Fritsche A, Schweitzer MA, Haring HU et al. (2003) Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. Annals of Internal Medicine 138: 952-9

Fujioka K, Brazg RL, Raz I et al. (2005) Efficacy, doseâ€“response relationship and safety of onceâ€ daily extendedâ€ release metformin (Glucophage-® XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two doubleâ€ blind, placeboâ€ controlled studies. Diabetes, Obesity and Metabolism 7: 28-39

Furlong NJ, Hulme SA, O'Brien SV (2002) Repaglinide versus metformin in combination with bedtime NPH insulin in patients with type 2 diabetes established on insulin/metformin combination therapy. Diabetes Care 25: 1685-90

Furlong NJ, Hulme SA, O'Brien SV (2003) Comparison of repaglinide vs. gliclazide in combination with bedtime NPH insulin in patients with Type 2 diabetes inadequately controlled with oral hypoglycaemic agents. Diabetic Medicine 20: 935-41

Gallwitz B, Rosenstock J, Rauch T et al. (2012) 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet 380: 475-83

Gallwitz B, Rosenstock J, Emser A (2013) Linagliptin is more effective than glimepiride at achieving a composite outcome of target HbA1c < 7% with no hypoglycaemia and no weight gain over 2 years. International Journal of Clinical Practice.67 (4) (pp 317-321), 2013.Date of Publication: April 2013. 317-21

Gao H, Xiao W, Wang C et al. (2008) The metabolic effects of once daily extended-release metformin in patients with type 2 diabetes: a multicentre study. International Journal of Clinical Practice 62: 695-700

Genovese S, De BG, Nicolucci A et al. (2013) Effect of pioglitazone versus metformin on cardiovascular risk markers in type 2 diabetes. Advances in Therapy 30: 190-202

Gerich J, Raskin P, Jean-Louis L et al. (2005) PRESERVE-beta: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. Diabetes Care 28: 2093-9

Gerstein HC, Pogue J (2005) The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis. Diabetologia 48: 1749-55

Goke B, Hershon K, Kerr D et al. (2008) Efficacy and safety of vildagliptin monotherapy during 2-year treatment of drug-naive patients with type 2 diabetes: comparison with metformin. Hormone & Metabolic Research 40: 892-5

Goke B, Gallwitz B, Eriksson J et al. (2010) Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. International Journal of Clinical Practice 64: 1619-31

Goke B, Gallwitz B, Eriksson JG (2013) Saxagliptin vs. glipizide as add-on therapy in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: long-term (52-week) extension of a 52-week randomised controlled trial. International Journal of Clinical Practice 67: 307-16

Goldstein BJ, Feinglos MN, Lunceford JK et al. (2007) Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes.[Erratum appears in Diabetes Care. 2008 Aug;31(8):1713]. Diabetes Care 30: 1979-87

Goldstein I, Young JM, Fischer J et al. (2003) Vardenafil, a New Phosphodiesterase Type 5 Inhibitor, in the Treatment of Erectile Dysfunction in Men With Diabetes A multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 26: 777-83

Goldstein I, Jones LA, Belkoff LH et al. (2012) Avanafil for the treatment of erectile dysfunction: A multicenter, randomized, double-blind study in men with diabetes mellitus. Mayo Clinic Proceedings.87 (9) (pp 843-852), 2012.Date of Publication: September 2012. 843-52

Goudswaard AN, Stolk RP, Zuithoff P et al. (2004) Starting insulin in type 2 diabetes: Continue oral hypoglycemic agents? J Fam Pract 53: 393-9

Gram J, Henriksen JE, Grodum E et al. (2011) Pharmacological treatment of the pathogenetic defects in type 2 diabetes: the randomized multicenter South Danish Diabetes Study. Diabetes Care 34: 27-33

Guerci B, Drouin P, Grangé V et al. (2003) Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: the Auto-Surveillance Intervention Active (ASIA) study. Diabetes & Metabolism 29: 587-94

Haak T, Tiengo A, Draeger E et al. (2005) Lower withinâ€ subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism 7: 56-64

Haak T, Meinicke T, Jones R et al. (2012) Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: A randomized, double-blind, placebo-controlled study. Diabetes, Obesity and Metabolism.14 (6) (pp 565-574), 2012.Date of Publication: June 2012. 565-74

Hackett G, Cole N, Bhartia M et al. (2013) Testosterone Replacement Therapy with Long-Acting Testosterone Undecanoate Improves Sexual Function and Quality-of-Life Parameters vs. Placebo in a Population of Men with Type 2 Diabetes. Journal of Sexual Medicine.10 (6) (pp 1612-1627), 2013.Date of Publication: June 2013. 1612-27

Hammer H, Lammert M, Mejas SM et al. (2009) Costs of managing severe hypoglycaemia in three European countries. Journal of Medical Economics 12: 281-90

Hanefeld M, Herman GA, Wu M et al. (2007) Once-daily sitagliptin, a dipeptidyl peptidase-4 inhibitor, for the treatment of patients with type 2 diabetes. Current Medical Research And Opinion 23: 1329-39

Hanefeld M, Brunetti P, Schernthaner GH et al. (2004) One-Year Glycemic Control With a Sulfonylurea Plus Pioglitazone Versus a Sulfonylurea Plus Metformin in Patients With Type 2 Diabetes. Diabetes Care 27: 141-7

Hartemann-Heurtier A, Halbron M, Golmard JL et al. (2009) Effects of bed-time insulin versus pioglitazone on abdominal fat accumulation, inflammation and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes Research & Clinical Practice 86: 37-43

Hatzichristou D, Gambla M, Rubio-Aurioles E et al. (2008) Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. Diabetic Medicine 25: 138-46

Health and Social Care Information Centre (HSCIC) (2012) Health Survey for England - 2011. Health, social care and lifestyles.

Health and Social Care Information Centre (HSCIC) (2014) Prescribing Cost Analysis, England 2013.

Heine RJ, Van Gaal LF, Johns D et al. (2005) Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial.[Summary for patients in Ann Intern Med. 2005 Oct 18;143(8):I30; PMID: 16230718]. Annals of Internal Medicine 143: 559-69

Heise T, Tack CJ, Cuddihy R et al. (2011) A new-generation ultra-long-acting basal insulin with a bolus boost compared with insulin glargine in insulin-naive people with type 2 diabetes: a randomized, controlled trial. Diabetes Care 34: 669-74

Hemmingsen B, Lund SS, Gluud C et al. (2011) Intensive glycaemic control for patients with type 2 diabetes: Systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ (Online).343 (7834) (pp 1136), 2011.Article Number: d6898.Date of Publication: 03 Dec 2011. 1136

Henricsson M, Nilsson A, Janzon L et al. (1997) The effect of glycaemic control and the introduction of insulin therapy on retinopathy in non-insulin-dependent diabetes mellitus. Diabetic Medicine 14: 123-31

Hermann LS, ©n B, ©n PO et al. (1994) Therapeutic Comparison of Metformin and Sulfonylurea, Alone and in Various Combinations: A double-blind controlled study. Diabetes Care 17: 1100-9

Hermansen K, Kipnes M, Luo E et al. (2007) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes, Obesity & Metabolism 9: 733-45

Herz M, Johns D, Reviriego J et al. (2003) A randomized, double-blind, placebo-controlled, clinical trial of the effects of pioglitazone on glycemic control and dyslipidemia in oral antihyperglycemic medication-naive patients with type 2 diabetes mellitus. Clinical Therapeutics.25 (4) (pp 1074-1095), 2003.Date of Publication: 01 Apr 2003. 1074-95

Hoffmann J (1997) Efficacy of 24-Week Monotherapy With Acarbose, Metformin, or Placebo in Dietary-Treated NIDDM Patients: The Essen-II Study. The American journal of medicine 103: 483-490 (Abstract).

Hoffmann J (1994) Efficacy of 24-Week Monotnerapy With Acarbose, Glibenclamide, or Placebo in NIDDM Patients: The Essen Study. Diabetes Care 17: 561-6

Holman RR, Cull CA, Turner RC (1999) A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44).[Erratum appears in Diabetes Care 1999 Nov;22(11):1922]. Diabetes Care 22: 960-4

Horton ES, Clinkingbeard C, Gatlin M et al. (2000) Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. Diabetes Care 23: 1660-5

Horton ES, Foley JE, Shen SG (2004) Efficacy and tolerability of initial combination therapy with nateglinide and metformin in treatment-naive patients with type 2 diabetes. Current Medical Research & Opinion 20: 883-9

Hotta N, Kakuta H, Sano T et al. (1993) Long-term Effect of Acarbose on Glycaemic Control in Non-insulin-dependent Diabetes Mellitus: A Placebo-controlled Double-blind Study. Diabetic Medicine 10: 134-8

Hsu CC, Chang HY, Huang MC et al. (2012) HbA1c variability is associated with microalbuminuria development in type 2 diabetes: A 7-year prospective cohort study. Diabetologia 55: 3163-72

Hunt KJ, Gebregziabher M, Lynch CP et al. (2013) Impact of diabetes control on mortality by race in a national cohort of veterans. Annals of Epidemiology 23: 74-9

International Diabetes Federation (2011) Definition and diagnosis of diabetes mellitus and immediate hyperglycemia: report of a WHO/IDF consultation.

Iribarren C, Karter AJ, Go AS et al. (2001) Glycemic control and heart failure among adult patients with diabetes. Circulation 103: 2668-73

Ishii N, Nagao K, Fujikawa K et al. (2006) Vardenafil 20mg demonstrated superior efficacy to 10mg in Japanese men with diabetes mellitus suffering from erectile dysfunction. International journal of urology 13: 1066-72

Ismail M, Teng CL, Omar M et al. (2013) Usage of glucometer is associated with improved glycaemic control in type 2 diabetes mellitus patients in Malaysian public primary care clinics: an open-label, randomised controlled trial.[Erratum appears in Singapore Med J. 2013 Aug;54(8):474 Note: Teng, Chong-Lieng [corrected to Teng, Cheong-Lieng]]. Singapore Medical Journal 54: 391-5

Iwamoto Y, Taniguchi T, Nonaka K et al. (2010) Dose-ranging efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. Endocrine Journal 57: 383-94

Jain R, Osei K, Kupfer S et al. (2006) Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy 26: 1388-95

Janka HU, Plewe G, Riddle MC et al. (2005) Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care.28 (2) (pp 254-259), 2005.Date of Publication: February 2005. 254-9

Janka HU, Plewe G (2007) Combination of oral antidiabetic agents with basal insulin versus premixed insulin alone in randomized elderly patients with type 2 diabetes mellitus. Journal of the American Geriatrics Society 55: 182-8

Jendle J, Nauck MA, Matthews DR et al. (2009) Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. Diabetes, Obesity & Metabolism 11: 1163-72

Jeon HJ (2011) Comparison of vildagliptin-metformin and glimepiride-metformin treatments in type 2 diabetic patients. Diabetes & Metabolism Journal 35: 529-35

Johnston PS, Lebovitz HE, Coniff RF et al. (1998) Advantages of +Ý-Glucosidase Inhibition as Monotherapy in Elderly Type 2 Diabetic Patients. Journal of Clinical Endocrinology & Metabolism 83: 1515-22

Joint Formulary Committee (2014) British National Formulary (online).

Josse RG, Chiasson JL, Ryan EA et al. (2003) Acarbose in the treatment of elderly patients with type 2 diabetes. Diabetes research and clinical practice 59: 37-42

Jovanovic L, Dailey G, III, Huang WC et al. (2000) Repaglinide in type 2 diabetes: a 24-week, fixed-dose efficacy and safety study. Journal of Clinical Pharmacology 40: 49-57

Kahn SE, Haffner SM, Heise MA et al. (2006) Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. New England Journal of Medicine 355: 2427-43

Kamenov ZA (2011) Comparison of the first intake of vardenafil and tadalafil in patients with diabetic neuropathy and diabetic erectile dysfunction. Journal of Sexual Medicine 8: 851-64

Karter AJ, Parker MM, Moffet HH et al. (2006) Longitudinal study of new and prevalent use of self-monitoring of blood glucose. Diabetes Care 29: 1757-63

Kato T, Sawai Y, Kanayama H et al. (2009) Comparative study of low-dose pioglitazone or metformin treatment in Japanese diabetic patients with metabolic syndrome. Experimental & Clinical Endocrinology & Diabetes 117: 593-9

Kawamori R, Inagaki N, Araki E et al. (2012) Linagliptin monotherapy provides superior glycaemic control versus placebo or voglibose with comparable safety in Japanese patients with type 2 diabetes: a randomized, placebo and active comparator-controlled, double-blind study. Diabetes, Obesity & Metabolism 14: 348-57

Khajehdrhi P, Roozbeh J, Mostafavi H (2002) A comparative randomized and placebo-controlled short-term trial of aspirin and dipyridamole for overt type-2 diabetic nephropathy. Scandinavian Journal of Urology and Nephrology 36: 145-8

Kikuchi M, Abe N, Kato M et al. (2009) Vildagliptin dose-dependently improves glycemic control in Japanese patients with type 2 diabetes mellitus. Diabetes Research & Clinical Practice 83: 233-40

Kikuchi M, Kaku K, Odawara M (2012) Efficacy and tolerability of rosiglitazone and pioglitazone in drug-naive Japanese patients with type 2 diabetes mellitus: a double-blind, 28 weeks' treatment, comparative study. Current Medical Research & Opinion 28: 1007-16

Kilo C, Mezitis N, Jain R et al. (2003) Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. Journal of diabetes and its complications 17: 307-13

Kirkman MS, Shankar RR, Shankar S et al. (2006) Treating postprandial hyperglycemia does not appear to delay progression of early type 2 diabetes: the Early Diabetes Intervention Program. Diabetes Care 29: 2095-101

Kleefstra N, Hortensius J, Logtenberg SJ et al. (2010) Self-monitoring of blood glucose in tablet-treated type 2 diabetic patients (ZODIAC). Netherlands Journal of Medicine 68: 311-6

Knapp PE, Showers KM, Phipps JC et al. (2009) Self-monitoring of blood glucose with finger tip versus alternative site sampling: effect on glycemic control in insulin-using patients with type 2 diabetes. Diabetes Technology & Therapeutics 11: 219-25

Kokic S, Kokic V, Krnic M et al. (2010) Advantage of prandial insulin as a therapeutic approach in initial secondary pancreatic beta-cell exhaustion in Type 2 diabetic patients. Diabetologia Croatica 39: 37-42

Krobot KJ, Ferrante SA, Davies MJ et al. (2012) Lower risk of hypoglycemia with sitagliptin compared to glipizide when either is added to metformin therapy: a pre-specified analysis adjusting for the most recently measured HbA(1c) value. Current Medical Research & Opinion 28: 1281-7

Kvapil M, Swatko A, Hilberg C (2006) Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes, Obesity and Metabolism 8: 39-48

Kwon HS, Cho JH, Kim HS et al. (2004) Establishment of blood glucose monitoring system using the internet. Diabetes Care 27: 478-83

Lamotte M (2006) A multi-country economic evaluation of low-dose aspirin in the primary prevention of cardiovascular disease. PharmacoEconomics 24(2):155-169

Landman GW, Van Hateren KJJ, Kleefstra N et al. (2010) The relationship between glycaemic control and mortality in patients with type 2 diabetes in general practice (ZODIAC-11). British Journal of General Practice.60 (572) (pp 172-175), 2010.Date of Publication: March 2010. 172-5

Lawrence JM, Reid J, Taylor GJ et al. (2004) Favorable Effects of Pioglitazone and Metformin Compared With Gliclazide on Lipoprotein Subfractions in Overweight Patients With Early Type 2 Diabetes. Diabetes Care 27: 41-6

Lee A (1998) Metformin Decreases Food Consumption and Induces Weight Loss in Subjects with Obesity with Type II Non-Insulin-Dependent Diabetes. Obesity Research 6: 47-53

Li R, Zhang P, Barker LE (2010) Cost-effectiveness of aspirin use among persons with newly diagnosed type 2 diabetes. Diabetes Care 33: 1193-9

Lim S, Kang SM, Shin H et al. (2011) Improved glycemic control without hypoglycemia in elderly diabetic patients using the ubiquitous healthcare service, a new medical information system. Diabetes Care 34: 308-13

Liu SC, Chien KL, Wang CH (2013) Efficacy and safety of adding pioglitazone or sitagliptin to patients with type 2 diabetes insufficiently controlled with metformin and a sulfonylurea. Endocrine Practice 19: 980-8

Lu J, Bu RF, Sun ZL et al. (2011) Comparable efficacy of self-monitoring of quantitative urine glucose with self-monitoring of blood glucose on glycaemic control in non-insulin-treated type 2 diabetes. Diabetes Research & Clinical Practice 93: 179-86

Lund SS, Tarnow L, Frandsen M et al. (2009) Combining insulin with metformin or an insulin secretagogue in non-obese patients with type 2 diabetes: 12 month, randomised, double blind trial. BMJ 339: b4324

Madsbad S, Kilhovd B, Lager I et al. (2001) Comparison between repaglinide and glipizide in Type 2 diabetes mellitus: a 1-year multicentre study. Diabetic Medicine 18: 395-401

Madsbad S, Schmitz O, Ranstam J et al. (2004) Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. Diabetes Care 27: 1335-42

Maffioli P, Fogari E, D'Angelo A (2013) Ultrasonography modifications of visceral and subcutaneous adipose tissue after pioglitazone or glibenclamide therapy combined with rosuvastatin in type 2 diabetic patients not well controlled by metformin. European Journal of Gastroenterology and Hepatology.25 (9) (pp 1113-1122), 2013.Date of Publication: September 2013. 1113-22

Malanda UL, Welschen LM, Riphagen II et al. (2012) Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin. [Review][Update of Cochrane Database Syst Rev. 2005;(2):CD005060; PMID: 15846742]. Cochrane Database of Systematic Reviews 1: CD005060

Malone JK, Kerr LF, Campaigne BN et al. (2004) Combined therapy with insulin lispro mix 75/25 plus metformin or insulin glargine plus metformin: A 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clinical Therapeutics.26 (12) (pp 2034-2044), 2004.Date of Publication: December 2004. 2034-44

Malone JK, Bai S, Campaigne BN et al. (2005) Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. Diabetic Medicine.22 (4) (pp 374-381), 2005.Date of Publication: April 2005. 374-81

Marbury T, Huang WC, Strange P (1999) Repaglinide versus glyburide: a one-year comparison trial. Diabetes Research & Clinical Practice 43: 155-66

Mather KJ, Verma S (2001) Improved endothelial function with metformin in type 2 diabetes mellitus. Journal of the American College of Cardiology 37: 1344-50

Matthews DR, Charbonnel BH, Hanefeld M et al. (2005) Long-term therapy with addition of pioglitazone to metformin compared with the addition of gliclazide to metformin in patients with type 2 diabetes: A randomized, comparative study. Diabetes/Metabolism Research and Reviews.21 (2) (pp 167-174), 2005.Date of Publication: March/April 2005. 167-74

Matthews DR, Dejager S, Ahren B et al. (2010) Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. Diabetes, Obesity & Metabolism 12: 780-9

Matyjaszek-Matuszek B, Lenart-Lipinska M (2013) Exenatide twice daily versus insulin glargine for the treatment of type 2 diabetes in Poland - Subgroup data from a randomised multinational trial GWAA. Endokrynologia Polska.64 (5) (pp 375-382), 2013.Date of Publication: 2013. 375-82

Matza LS, Boye KS, Yurgin N et al. (2007) Utilities and disutilities for type 2 diabetes treatment-related attributes. Quality of Life Research 16: 1251-65

McEwan P., Poole C.D., Tetlow T et al. (2007) Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 2 diabetes in the UK. Current Medical Research & Opinion 23: S21-S31

Mehta SR, Yusuf S, Peters RJ et al. (2001) Effects of pretreatment with clopidogrel and aspirin followed by long- term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 358: 527-33

Meneghini L, Kesavadev J, Demissie M (2013) Once-daily initiation of basal insulin as add-on to metformin: a 26-week, randomized, treat-to-target trial comparing insulin detemir with insulin glargine in patients with type 2 diabetes. Diabetes, Obesity and Metabolism 15: 729-36

Milicevic Z, Hancu N, Car N et al. (2009) Effect of two starting insulin regimens in patients with type II diabetes not controlled on a combination of oral antihyperglycemic medications. Experimental & Clinical Endocrinology & Diabetes 117: 223-9

Mohan V, Yang W, Son HY et al. (2009) Efficacy and safety of sitagliptin in the treatment of patients with type 2 diabetes in China, India, and Korea. Diabetes Research & Clinical Practice 83: 106-16

Molyneaux LM, Constantino MI, McGill M et al. (1998) Better glycaemic control and risk reduction of diabetic complications in Type 2 diabetes: comparison with the DCCT. Diabetes Research & Clinical Practice 42: 77-83

Moreland EC, Volkening LK, Lawlor MT et al. (2006) Use of a blood glucose monitoring manual to enhance monitoring adherence in adults with diabetes: a randomized controlled trial. Archives of Internal Medicine 166: 689-95

Morisaki N, Watanabe S, Kobayashi J et al. (1994) Diabetic control and progression of retinopathy in elderly patients: five-year follow-up study. Journal of the American Geriatrics Society 42: 142-5

Moses RG, Gomis R, Frandsen KB et al. (2001) Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. Diabetes Care 24: 11-5

Mount Hood 4 Modeling Group (2007) Computer modeling of diabetes and its complications: a report on the Fourth Mount Hood Challenge Meeting. Diabetes Care 30: 1638-46

Muchmore DB, Springer J, Miller M (1994) Self-monitoring of blood glucose in overweight type 2 diabetic patients. Acta diabetologica 31: 215-9

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Nakagami T, Kawahara R, Hori S et al. (1997) Glycemic control and prevention of retinopathy in Japanese NIDDM patients. A 10-year follow-up study. Diabetes Care 20: 621-2

Nakamura T, Matsuda, T, Kawagoe, Y et al. (2004) Effect of pioglitazone on carotid intima-media thickness and arterial stiffness in type 2 diabetic nephropathy patients. Metabolism: clinical and experimental 53: 1382-1386 (Abstract).

Nathan DM, Turgeon H, Regan S (2007) Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia 50: 2239-44

Nauck M, Frid A, Hermansen K et al. (2009) Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in type 2 diabetes. Diabetes Care.32 (1) (pp 84-90), 2009.Date of Publication: January 2009. 84-90

Nauck MA, Meininger G, Sheng D et al. (2007a) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes, Obesity & Metabolism 9: 194-205

Nauck MA, Duran S, Kim D et al. (2007b) A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. Diabetologia 50: 259-67

Nauck MA, Haastert B, Trautner C et al. (2014) A randomised, controlled trial of self-monitoring of blood glucose in patients with type 2 diabetes receiving conventional insulin treatment. Diabetologia.57 (5) (pp 868-877), 2014.Date of Publication: May 2014. 868-77

Nonaka K, Kakikawa T, Sato A et al. (2008) Efficacy and safety of sitagliptin monotherapy in Japanese patients with type 2 diabetes. Diabetes research and clinical practice 79: 291-8

O'Kane MJ, Bunting B, Copeland M et al. (2008) Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial. BMJ 336: 1174-7

Ogawa H, Nakayama M, Morimoto T et al. (2008) Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial.[Erratum appears in JAMA. 2009 May 13;301(18):1882]. JAMA 300: 2134-41

Olsson PO (2002) Combination-therapy with bedtime NPH insulin and sulphonylureas gives similar glycaemic control but lower weight gain than insulin twice daily in patients with type 2 diabetes. Diabetes and Metabolism.28 (4 I) (pp 272-277), 2002.Date of Publication: September 2002. 272-7

Palmer AJ, Roze S, Valentine WJ et al. (2004a) Impact of changes in HbA1c, lipids and blood pressure on long-term outcomes in type 2 diabetes patients: an analysis using the CORE Diabetes Model. Current Medical Research & Opinion 20: Suppl-8

Palmer AJ, Roze S, Valentine WJ et al. (2004b) The CORE Diabetes Model: Projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Current Medical Research & Opinion 20: S5-S26

Palmer AJ, Dinneen S, Gavin JR, III et al. (2006) Cost-utility analysis in a UK setting of self-monitoring of blood glucose in patients with type 2 diabetes. Current Medical Research & Opinion 22: 861-72

Pan C, Yang W, Barona JP et al. (2008) Comparison of vildagliptin and acarbose monotherapy in patients with Type 2 diabetes: a 24-week, double-blind, randomized trial. Diabetic Medicine 25: 435-41

Pan CY, Sinnassamy P, Chung KD et al. (2007) Insulin glargine versus NPH insulin therapy in Asian Type 2 diabetes patients. Diabetes Research & Clinical Practice 76: 111-8

Pan CY, Yang W, Tou C et al. (2012) Efficacy and safety of saxagliptin in drug-naive Asian patients with type 2 diabetes mellitus: A randomized controlled trial. Diabetes/Metabolism Research and Reviews.28 (3) (pp 268-275), 2012.Date of Publication: March 2012. 268-75

Papathanassiou K, Naka KK, Kazakos N et al. (2009) Pioglitazone vs glimepiride: Differential effects on vascular endothelial function in patients with type 2 diabetes. Atherosclerosis 205: 221-6

Park CY, Kang JG, Chon S et al. (2014) Comparison between the Therapeutic Effect of Metformin, Glimepiride and Their Combination as an Add-On Treatment to Insulin Glargine in Uncontrolled Patients with Type 2 Diabetes. PLoS ONE [Electronic Resource] 9: e87799

Pavo I, Jermendy G, Varkonyi TT et al. (2003) Effect of Pioglitazone Compared with Metformin on Glycemic Control and Indicators of Insulin Sensitivity in Recently Diagnosed Patients with Type 2 Diabetes. Journal of Clinical Endocrinology & Metabolism 88: 1637-45

Pfutzner A, Schondorf T, Tschope D et al. (2011) PIOfix-study: effects of pioglitazone/metformin fixed combination in comparison with a combination of metformin with glimepiride on diabetic dyslipidemia. Diabetes Technology & Therapeutics 13: 637-43

Pi-Sunyer FX, Schweizer A, Mills D (2007) Efficacy and tolerability of vildagliptin monotherapy in drug-naive patients with type 2 diabetes. Diabetes Research & Clinical Practice 76: 132-8

Pimazoni-Netto A, Rodbard D, Zanella MT (2011) Rapid improvement of glycemic control in type 2 diabetes using weekly intensive multifactorial interventions: Structured glucose monitoring, patient education, and adjustment of therapy - A randomized controlled trial. Diabetes Technology and Therapeutics.13 (10) (pp 997-1004), 2011.Date of Publication: 01 Oct 2011. 997-1004

Pollock RF, Valentine WJ, Goodall G (2010) Evaluating the cost-effectiveness of self-monitoring of blood glucose in type 2 diabetes patients on oral anti-diabetic agents. Swiss Medical Weekly 140: w13103

Pollock RF, Curtis RH, Smith-Palmer J et al. (2012) A UK Analysis of the Cost-Effectiveness of Humalog Mix 75/25 and Mix 50/50 Versus Long-Acting Basal Insulin. Advances in Therapy 29: 1051-66

Polonsky WH, Fisher L, Schikman CH et al. (2011) A structured self-monitoring of blood glucose approach in type 2 diabetes encourages more frequent, intensive, and effective physician interventions: results from the STeP study. Diabetes Technology & Therapeutics 13: 797-802

Pratley R, Nauck M, Bailey T et al. (2011) One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. International Journal of Clinical Practice 65: 397-407

Pratley RE, Jauffret-Kamel S, Galbreath E (2006) Twelve-week monotherapy with the DPP-4 inhibitor vildagliptin improves glycemic control in subjects with type 2 diabetes. Hormone & Metabolic Research 38: 423-8

Pratley RE, Nauck M, Bailey T et al. (2010) Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 375: 1447-56

Quinn CC, Shardell MD, Terrin ML et al. (2011) Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. Diabetes Care.34 (9) (pp 1934-1942), 2011.Date of Publication: September 2011. 1934-42

Ray JA, Boye K.S., Yurgin N et al. (2007) Exenatide versus insulin glargine in patients with type 2 diabetes in the UK: a model of long-term clinical and cost outcomes. Current Medical Research & Opinion 23: 609-22

Raz I, Stranks S, Filipczak R et al. (2005) Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: An 18-week, randomized, open-label study. Clinical Therapeutics.27 (9) (pp 1432-1443), 2005.Date of Publication: September 2005. 1432-43

Raz I, Hanefeld M, Xu L et al. (2006) Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. 49: 2564-71

Rendell MS, Rajfer J, Wicker PA et al. (1999) Sildenafil for treatment of erectile dysfunction in men with diabetes. JAMA: the journal of the American Medical Association 281: 421-6

Riddle M, Hart J, Bingham P et al. (1992) Combined therapy for obese type 2 diabetes: suppertime mixed insulin with daytime sulfonylurea. The American journal of the medical sciences 303: 151-6

Riddle MC (1998) Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone. Diabetes Care 21: 1052-7

Ristic S, Byiers S, Foley J (2005) Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response. Diabetes, Obesity & Metabolism 7: 692-8

Ristic S, Collober-Maugeais C, Pecher E (2006) Comparison of nateglinide and gliclazide in combination with metformin, for treatment of patients with Type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone. Diabetic Medicine 23: 757-62

Ristic S, Collober-Maugeais C, Cressier F et al. (2007) Nateglinide or gliclazide in combination with metformin for treatment of patients with type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone: 1-year trial results. Diabetes, Obesity & Metabolism 9: 506-11

Robbins DC, Beisswenger PJ, Ceriello A et al. (2007) Mealtime 50/50 basal + prandial insulin analogue mixture with a basal insulin analogue, both plus metformin, in the achievement of target HbA1c and pre- and postprandial blood glucose levels in patients with type 2 diabetes: a multinational, 24-week, randomized, open-label, parallel-group comparison. Clinical Therapeutics 29: 2349-64

Roden M, Weng J, Eilbracht J et al. (2013) Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Diabetes and Endocrinology.1 (3) (pp 208-219), 2013.Date of Publication: November 2013. 208-19

Rosenstock J, Kim SW, Baron MA et al. (2007) Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. Diabetes, Obesity & Metabolism 9: 175-85

Rosenstock J, Raccah D, Koranyi L et al. (2013) Efficacy and safety of lixisenatide once daily versus exenatide twice daily in type 2 diabetes inadequately controlled on metformin: a 24-week, randomized, open-label, active-controlled study (GetGoal-X). Diabetes Care 36: 2945-51

Rosenthal J (2002) Effects on Blood Pressure of the +Ý-Glucosidase Inhibitor Acarbose Compared with the Insulin Enhancer Glibenclamide in Patients with Hypertension and Type 2 Diabetes Mellitus. 22: 695-701

Russell-Jones D, Vaag A, Schmitz O et al. (2009) Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. Diabetologia 52: 2046-55

Sacco M, Pellegrino F, Roncaglioni MC et al. (2003) Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. Diabetes Care 26: 3264-72

Saenz de Tejada I, Anglin G, Knight JR et al. (2002) Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 25: 2159-64

Safarinejad MR (2004) Oral sildenafil in the treatment of erectile dysfunction in diabetic men- A randomized double-blind and placebo-controlled study. Journal of diabetes and its complications 18: 205-10

Saleem K, Yasin MA (2011) Comparison of repaglinide with glibenclamide in the reduction of HbA1C of type 2 diabetic patients. Pakistan Journal of Medical and Health Sciences.5 (1) (pp 23-26), 2011.Date of Publication: January-March 2011. 23-6[j]

Salinero-Fort MA, San Andres-Rebollo FJ, de Burgos-Lunar C et al. (2013) Four-Year Incidence of Diabetic Retinopathy in a Spanish Cohort: The MADIABETES Study. PLoS ONE.8 (10) , 2013.Article Number: e76417.Date of Publication: 17 Oct 2013.

Santilli F, Formoso G, Sbraccia P et al. (2010) Postprandial hyperglycemia is a determinant of platelet activation in early type 2 diabetes mellitus. Journal of Thrombosis & Haemostasis 8: 828-37

Scherbaum WA, Goke B (2002) Metabolic Efficacy and Safety of Once-Daily Pioglitazone Monotherapy in Patients with Type 2 Diabetes: A Double-Blind, Placebo-Controlled Study. Horm Metab Res 34: 589-95

Scherbaum WA, Schweizer A, Mari A et al. (2008a) Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycaemia. Diabetes, Obesity & Metabolism 10: 1114-24

Scherbaum WA, Schweizer A, Mari A et al. (2008b) Efficacy and tolerability of vildagliptin in drug-naive patients with type 2 diabetes and mild hyperglycaemia. Diabetes, Obesity and Metabolism.10 (8) (pp 675-682), 2008.Date of Publication: August 2008. 675-82

Scherbaum WA, Ohmann C, Abholz HH et al. (2008) Effect of the frequency of self-monitoring blood glucose in patients with type 2 diabetes treated with oral antidiabetic drugs- a multi-centre, randomized controlled trial. PLoS ONE [Electronic Resource] 3: e3087

Schernthaner G, Matthews DR, Charbonnel B et al. (2004a) Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. Journal of Clinical Endocrinology & Metabolism 89: 6068-76

Schernthaner G, Grimaldi A, Di Mario U et al. (2004b) GUIDE study: doubleâ€ blind comparison of onceâ€ daily gliclazide MR and glimepiride in type 2 diabetic patients. European journal of clinical investigation 34: 535-42

j In November 2015, close to publication, NICE became aware that the following 3 papers on repaglinide (Jibran 2006, Saleem 2011 and Shah 2011) were referred for suspected scientific misconduct. The Pakistan Journal of Medical and Health Sciences has subsequently retracted Saleem 2011 and Shah 2011 because of ethical misconduct.

Schulze MB, Shai I, Manson JE et al. (2004) Joint role of non-HDL cholesterol and glycated haemoglobin in predicting future coronary heart disease events among women with type 2 diabetes. Diabetologia 47: 2129-36

Schwartz S, Fonseca V, Berner B et al. (2006) Efficacy, tolerability, and safety of a novel once-daily extended-release metformin in patients with type 2 diabetes. Diabetes Care.29 (4) (pp 759-764), 2006.Date of Publication: 2006. 759-64

Schwarz B, Gouveia M, Chen J et al. (2008a) Cost-effectiveness of sitagliptin-based treatment regimens in European patients with type 2 diabetes and haemoglobin A1c above target on metformin monotherapy. Diabetes, Obesity & Metabolism 10: 43-55

Schwarz SL, Gerich JE, Marcellari A et al. (2008b) Nateglinide, alone or in combination with metformin, is effective and well tolerated in treatment-naive elderly patients with type 2 diabetes. Diabetes, Obesity & Metabolism 10: 652-60

Schwedes U, Siebolds M, Mertes G (2002) Meal-related structured self-monitoring of blood glucose: effect on diabetes control in non-insulin-treated type 2 diabetic patients. Diabetes Care 25: 1928-32

Schweizer A, Couturier A, Foley JE (2007) Comparison between vildagliptin and metformin to sustain reductions in HbA(1c) over 1 year in drug-naive patients with Type 2 diabetes. Diabetic Medicine 24: 955-61

Schweizer A, Dejager S (2009) Comparison of vildagliptin and metformin monotherapy in elderly patients with type 2 diabetes: a 24-week, double-blind, randomized trial. Diabetes, Obesity & Metabolism 11: 804-12

Scott R, Lintott, CJ, Zimmet, P et al. (1999) Will acarbose improve the metabolic abnormalities of insulin-resistant type 2 diabetes mellitus? Diabetes research and clinical practice 43: 179-185 (Abstract).

Scott R, Wu M, Sanchez M (2007) Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. International Journal of Clinical Practice 61: 171-80

Seck T, Nauck M, Sheng D et al. (2010) Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: a 2-year study. International Journal of Clinical Practice 64: 562-76

Segal P, Feig PU, Schernthaner G et al. (1997) The Efficacy and Safety of Miglitol Therapy Compared With Glibenclamide in Patients With NIDDM Inadequately Controlled by Diet Alone. Diabetes Care 20: 687-91

Selvin E, Marinopoulos S, Berkenblit G et al. (2004) Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Annals of Internal Medicine 141: 421-31

Seufert J (2008) 2-year effects of pioglitazone add-on to sulfonylurea or metformin on oral glucose tolerance in patients with type 2 diabetes. Diabetes Research & Clinical Practice 79: 453-60

Shah ZH, Saleem K (2011) A comparative study of repaglinide and glibenclamide in type 2 diabetic patients. Pakistan Journal of Medical and Health Sciences.5 (3) (pp 476-479), 2011.Date of Publication: July-September 2011. 476-9[j]

Shanmugasundar G, Bhansali A, Walia R et al. (2012) Comparison of thrice daily biphasic human insulin (30/70) versus basal detemir & bolus aspart in patients with poorly controlled type 2 diabetes mellitus - A pilot study. Indian Journal of Medical Research.135 (1) (pp 78-83), 2012.Date of Publication: January 2012. 78-83

Shihara N, Kitaoka M, Inagaki N et al. (2011) Randomized controlled trial of single-agent glimepiride and pioglitazone in Japanese patients with type 2 diabetes: A comparative study. Journal of Diabetes Investigation.2 (5) (pp 391-398), 2011.Date of Publication: October 2011. 391-8

Simon J, Gray A, Clarke P et al. (2008) Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. BMJ 336: 1177-80

Smith KJ, Roberts, MS (2000) The cost-effectiveness of sildenafil. Annals of Internal Medicine 132(12):933-7

Srivastava S, Saxena GN, Keshwani P (2012) Comparing the efficacy and safety profile of sitagliptin versus glimepiride in patients of type 2 diabetes mellitus inadequately controlled with metformin alone. Journal of the Association of Physicians of India 60: 27-30

Stehouwer MHA, DeVries JH, Lumeij JAE et al. (2003) Combined bedtime insulinâ€“daytime sulphonylurea regimen compared with two different daily insulin regimens in type 2 diabetes: effects on HbA1c and hypoglycaemia rateâ€”a randomised trial. Diabetes/metabolism research and reviews 19: 148-52

Steinhubl SR, Berger PB, Mann JTI et al. (2002) Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. Journal of the American Medical Association 288: 2411-20

Stolk EA, Busschbacn, JJV, Caffa, M et al. (2000) Cost utility analysis of sildenafil compared with papaverine-phentolamine injections. British Medical Journal 320:1165-1168

Stuckey BGA, Jadzinsky MN, Murphy LJ et al. (2003) Sildenafil Citrate for Treatment of Erectile Dysfunction in Men With Type 1 Diabetes Results of a randomized controlled trial. Diabetes Care 26: 279-84

Tan MH, Baksi A, Krahulec B et al. (2005) Comparison of pioglitazone and gliclazide in sustaining glycemic control over 2 years in patients with type 2 diabetes. Diabetes Care.28 (3) (pp 544-550), 2005.Date of Publication: March 2005. 544-50

Taslimi S, Esteghamati A, Rashidi A et al. (2013) Treatment with pioglitazone is associated with decreased preprandial ghrelin levels: a randomized clinical trial. Peptides 40: 89-92

Teramoto T, Yamada N, Shirai K (2007) Effects of pioglitazone hydrochloride on Japanese patients with type 2 diabetes mellitus. Journal of Atherosclerosis & Thrombosis 14: 86-93

Tessier D, Maheux P, Khalil A (1999) Effects of gliclazide versus metformin on the clinical profile and lipid peroxidation markers in type 2 diabetes. Metabolism: clinical and experimental 48: 897-903

The Health Improvement Network (THIN) (2014) The Health Improvement Network (THIN).

Tildesley HD, Mazanderani AB, Ross SA (2010) Effect of Internet therapeutic intervention on A1C levels in patients with type 2 diabetes treated with insulin. Diabetes Care 33: 1738-40

Torffvit O, Agardh C-D (2001) The impact of metabolic and blood pressure control on incidence and progression of nephropathy: A 10-year study of 385 type 2 diabetic patients. Journal of diabetes and its complications 15: 307-13

Tosi F, Muggeo, M, Brun, E et al. (2003) Combination treatment with metformin and glibenclamide versus single-drug therapies in type 2 diabetes mellitus: a randomized, double-blind, comparative study. Metabolism: clinical and experimental 52: 862-867 (Abstract).

Tunis SL (2008) Self-monitoring of blood glucose in type 2 diabetes: cost-effectiveness in the united states. American Journal of Managed Care 14: 131-40

Tunis SL, Willis WD (2010) Self-monitoring of blood glucose (SMBG) in patients with type 2 diabetes on oral anti-diabetes drugs: cost-effectiveness in France, Germany, Italy, and Spain. Current Medical Research & Opinion 26: 163-75

Tunis SL (2010) Self-monitoring of blood glucose (SMBG) for type 2 diabetes patients treated with oral anti-diabetes drugs and with a recent history of monitoring: cost-effectiveness in the US. Current Medical Research & Opinion 26: 151-62

Uehara MH, Kohlmann NEB, Zanella MT (2001) Metabolic and haemodynamic effects of metformin in patients with type 2 diabetes mellitus and hypertension. Diabetes, Obesity and Metabolism.3 (5) (pp 319-325), 2001.Date of Publication: 2001. 319-25

Umpierrez G, Issa M (2006) Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. Current Medical Research and Opinion-® 22: 751-9

Ushakova O, Sokolovskaya V, Morozova A et al. (2007) Comparison of biphasic insulin aspart 30 given three times daily or twice daily in combination with metformin versus oral antidiabetic drugs alone in patients with poorly controlled type 2 diabetes: a 16-week, randomized, open-label, parallel-group trial conducted in russia. Clinical Therapeutics 29: 2374-84

Valentine WJ, Palmer AJ, Lammert M. et al. (2005) Long-term clinical and cost outcomes of treatment with biphasic insulin aspart 30/70 versus insulin glargine in insulin naive type 2 diabetes patients: cost-effectiveness analysis in the UK setting. Current Medical Research & Opinion 21: 2063-71

Valentine WJ, Palmer AJ, Nicklasson L et al. (2006) Improving life expectancy and decreasing the incidence of complications associated with type 2 diabetes: a modelling study of HbA1c targets. [Review] [38 refs]. International Journal of Clinical Practice 60: 1138-45

van der Meer R, Rijzewijk LJ, de Jong HWAM et al. (2009) Pioglitazone improves cardiac function and alters myocardial substrate metabolism without affecting cardiac triglyceride accumulation and high-energy phosphate metabolism in patients with well controlled type 2 diabetes mellitus. Circulation 119: 2069-77

Vardi M, Nini A (2007) Phosphodiesterase inhibitors for erectile dysfunction in patients with diabetes mellitus. Cochrane Database of Systematic Reviews

Viberti G, Kahn SE, Greene DA et al. (2002) A Diabetes Outcome Progression Trial (ADOPT): An international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. Diabetes Care 25: 1737-43

Vigersky RA, Fonda SJ, Chellappa M et al. (2012) Short- and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. Diabetes Care 35: 32-8

Wang H, Ni Y, Yang S et al. (2013) The Effects of Gliclazide, Metformin, and Acarbose on Body Composition in Patients with Newly Diagnosed Type 2 Diabetes Mellitus. Current Therapeutic Research - Clinical and Experimental.75 (pp 88-92), 2013.Date of Publication: December 2013. -92

Wang JS, Lin SD, Lee WJ et al. (2011) Effects of acarbose versus glibenclamide on glycemic excursion and oxidative stress in type 2 diabetic patients inadequately controlled by metformin: a 24-week, randomized, open-label, parallel-group comparison. Clinical Therapeutics 33: 1932-42

Watanabe I, Tani, S, Anazawa, T et al. (2005) Effect of pioglitazone on arteriosclerosis in comparison with that of glibenclamide. Diabetes research and clinical practice 68: 104-110 (Abstract).

Waugh N, Cummins E, Royle P et al. (2010) Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. [Review]. Health Technology Assessment (Winchester, England) 14: 1-248

Welschen LM, Bloemendal E, Nijpels G et al. (2005) Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin. Cochrane Database of Systematic Reviews : CD005060

Williams-Herman D, Johnson J, Teng R et al. (2009) Efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: a 54-week study. Current Medical Research & Opinion 25: 569-83

Williams-Herman D, Johnson J, Teng R et al. (2010) Efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes. Diabetes, Obesity & Metabolism 12: 442-51

Wing RR, Epstein LH, Nowalk MP et al. (1986) Does self-monitoring of blood glucose levels improve dietary compliance for obese patients with type II diabetes? The American journal of medicine 81: 830-6

Woehl A, Evans M, Tetlow AP (2008) Evaluation of the cost effectiveness of exenatide versus insulin glargine in patients with sub-optimally controlled type 2 diabetes in the United Kingdom. Cardiovascular Diabetology 7: 24

Yamanouchi T, Sakai T, Igarashi K et al. (2005) Comparison of metabolic effects of pioglitazone, metformin, and glimepiride over 1- year in Japanese patients with newly diagnosed Type 2 diabetes. Diabetic Medicine 22: 980-5

Yang W, Chen L, Ji Q et al. (2011) Liraglutide provides similar glycaemic control as glimepiride (both in combination with metformin) and reduces body weight and systolic blood pressure in Asian population with type 2 diabetes from China, South Korea and India: a 16-week, randomized, double-blind, active control trial(*). Diabetes, Obesity & Metabolism 13: 81-8

Yang W, Liu J, Shan Z et al. (2014) Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomised trial. Lancet Diabetes and Endocrinology 2: 46-55

Yi Y, Philips Z, Bergman G et al. (2010) Economic models in type 2 diabetes. Current Medical Research And Opinion 26: 2105-18

Yki-Jarvinen H, Kauppinen-Makelin R, Tiikkainen M et al. (2006) Insulin glargine or NPH combined with metformin in type 2 diabetes: The LANMET study. Diabetologia.49 (3) (pp 442-451), 2006.Date of Publication: March 2006. 442-51

Yki-JaÝˆrvinen H, Ryysy L, NikkilaÝˆ K et al. (1999) Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitusa randomized, controlled trial. Annals of Internal Medicine 130: 389-96

Yoo HJ, An HG, Park SY et al. (2008) Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes Research & Clinical Practice 82: 73-9

Yoon KH, Shin JA, Kwon HS et al. (2011) Comparison of the efficacy of glimepiride, metformin, and rosiglitazone monotherapy in korean drug-naive type 2 diabetic patients: the practical evidence of antidiabetic monotherapy study. Diabetes & Metabolism Journal 35: 26-33

Yusuf S, Zhao F, Mehta SR et al. (2001) Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. New England Journal of Medicine 2001: 7-494

Zhao W, Katzmarzyk PT, Horswell R et al. (2013) HbA1c and lower-extremity amputation risk in low-income patients with diabetes. Diabetes Care.36 (11) (pp 3591-3598), 2013.Date of Publication: November 2013. 3591-8

Ziegler D, Merfort F, van AH et al. (2006) Efficacy and safety of flexible-dose vardenafil in men with type 1 diabetes and erectile dysfunction. Journal of Sexual Medicine.3 (5) (pp 883-891), 2006.Date of Publication: September 2006. 883-91

Zinman B, Fulcher G, Rao PV et al. (2011) Insulin degludec, an ultra-long-acting basal insulin, once a day or three times a week versus insulin glargine once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial. Lancet 377: 924-31

Zoungas S, Chalmers J, Ninomiya T et al. (2012) Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. Diabetologia 55: 636-43

10.2 Reference for sections in CG66 not updated in 2015 (4, 5, 6, 9.1, 9.2 and 9.4)

1. National Institute for Health and Clinical Excellence. Guidelines manual. London: NICE, 2006.
2. International Diabetes Federation. Definition and diagnosis of diabetes mellitus and immediate hyperglycemia: report of a WHO/IDF consultation. Geneva: World Health Organisation, 2006.
3. Department of Health. Health survey for England 2004. London: DH, 2005.
4. International Diabetes Federation. Diabetes atlas. Brussels: IDF, 2006.
5. Morgan CL, Currie CJ, Peters JR. Relationship between diabetes and mortality: a population study using record linkage. Diabetes Care 2000;23(8):1103–1107.
6. Anon. British National Formulary for Children (3). UK: BMJ Publishing Group Ltd and RPS Publishing, 2007. http://bnfc.org/bnfc
7. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: methodology pack. London: NCC-CC, 2006.
8. Healthcare Commission. Managing diabetes: improving services for people with diabetes. London: Commission for Healthcare Audit and Inspection, 2007.
9. Christensen NK, Williams P, Pfister R. Cost savings and clinical effectiveness of an extension service diabetes program. Diabetes Spectrum 2004;17(3):171–175.
10. Mortimer D, Kelly J. Economic evaluation of the good life club intervention for diabetes self-management. Australian Journal of Primary Health 2006;12(1):91–100.
11. Connor H, Annan F, Bunn E et al. The implementation of nutritional advice for people with diabetes. Diabetic Medicine 2003;20(10):786–807.
12. National Institute for Health and Clinical Excellence. Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children (CG43). London: NICE, 2006.
13. Li Z, Hong K, Saltsman P et al. Long-term efficacy of soy-based meal replacements vs an individualized diet plan in obese type II DM patients: Relative effects on weight loss, metabolic parameters, and C-reactive protein. European Journal of Clinical Nutrition 2005;59(3):411–418.
14. Barnard ND, Cohen J, Jenkins DJA et al. A low-fat vegan diet improves glycemic control and cardio- vascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care 2006; 29(8):1777–1783.
15. Brinkworth GD, Noakes M. Long-term effects of advice to consume a high-protein, low-fat diet, rather than a conventional weight-loss diet, in obese adults with type 2 diabetes: one-year follow-up of a randomised trial. Diabetologia 2004;47(10):1677–1686.
16. Daly ME, Paisey R. Short-term effects of severe dietary carbohydrate-restriction advice in Type 2 diabetes – a randomized controlled trial. Diabetic Medicine 2006;23(1):15–20.
17. Redmon JB, Susan KR, Kristell PR et al. One-year outcome of a combination of weight loss therapies for subjects with type 2 diabetes: A randomized trial. Diabetes Care 2003;26(9):2505.
18. Stern L, Iqbal N, Seshadri P et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Annals of Internal Medicine 2004; 140(10):778–785.
19. The Diabetes and Nutrition Study Group of the Spanish Diabetes Association (GSEDNu). Diabetes nutrition and complications trial: adherence to the ADA nutritional recommendations, targets of metabolic control, and onset of diabetes complications. A 7-year, prospective, population-based, observational multicenter study. Journal of Diabetes & its Complications 2006;20(6):361–366.

20. Van ST, Van de Laar FA, Van Leeuwe JF et al. The dieting dilemma in patients with newly diagnosed type 2 diabetes: does dietary restraint predict weight gain 4 years after diagnosis? Health Psychology 2007; 26(1):105–112.

21. Anderson RJ, Freedland KE, Clouse RE et al. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24(6):1069–1078.

22. Rubin RR, Ciechanowski P, Egede LE et al. Recognizing and treating depression in patients with diabetes. Current Diabetes Reports 2004;4(2):119–125.

23. de Groot M, Anderson R, Freedland KE et al. Association of depression and diabetes complications: a meta-analysis. Psychosomatic Medicine 2001;63(4):619–630.

24. Lin EH, Katon W, Von KM et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care 2004;27(9):2154–2160.

25. Egede LE, Zheng D, Simpson K. Comorbid depression is associated with increased health care use and expenditures in individuals with diabetes. Diabetes Care 2002;25(3):464–470.

26. National Institute for Health and Clinical Excellence. Diagnosis and management of type 1 diabetes in children, young people and adults (CG15). London: NICE, 2004.

27. National Institute for Clinical Excellence. Depression: management of depression in primary and secondary care (CG23). London: NICE, 2004.

28. Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. British Medical Journal 2000;321(7258):405–412.

29. Selvin E, Marinopoulos S, Berkenblit G et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Annals of Internal Medicine 2004;141(6):421–431.

30. Gerstein HC, Pogue J. The relationship between dysglycaemia and cardiovascular and renal risk in diabetic and non-diabetic participants in the HOPE study: a prospective epidemiological analysis. Diabetologia 2005;48(9):1749–1755.

31. Iribarren C, Karter AJ, Go AS et al. Glycemic control and heart failure among adult patients with diabetes. Circulation 2001;103(22):2668–2673.

32. Oglesby AK, Secnik K, Barron J, Al-Zakwani I, Lage MJ. The association between diabetes related medical costs and glycemic control: A retrospective analysis. Cost Effectiveness & Resource Allocation 2006;4:1.

33. Clarke PM, Gray AM, Briggs A et al. Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72). Diabetologia 2005;48(5):868–877.

34. Clarke P, Gray A, Adler A et al. Cost-effectiveness analysis of intensive blood-glucose control with metformin in overweight patients with type II diabetes (UKPDS no. 51). Diabetologia 2001;44(3):298–304.

35. ACCORD. ACCORD Study Announcement www.accordtrial.org. Date of message: 6 February 2008.

36. Sarol JN, Nicodemus NA, Tan KM et al. Self-monitoring of blood glucose as part of a multi-component therapy among non-insulin requiring type 2 diabetes patients: a meta-analysis (1966–2004). Current Medical Research & Opinion 2005;21(2):173–184.

37. Welschen LM, Bloemendal E, Nijpels G et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: a systematic review. Diabetes Care 2005;28(6):1510–1517.

38. Welschen LM, Bloemendal E, Nijpels G et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin. Cochrane Database of Systematic Reviews 2005;(2):CD005060.

39. Jansen JP. Self-monitoring of glucose in type 2 diabetes mellitus: a Bayesian meta-analysis of direct and indirect comparisons. Current Medical Research & Opinion 2006;22(4):671–681.
40. Farmer A, Wade A, French DP et al. The DiGEM trial protocol: a randomised controlled trial to determine the effect on glycaemic control of different strategies of blood glucose self-monitoring in people with type 2 diabetes. BMC Family Practice 2005;6(25)
41. Moreland EC, Volkening LK, Lawlor MT et al. Use of a blood glucose monitoring manual to enhance monitoring adherence in adults with diabetes: a randomized controlled trial. Archives of Internal Medicine 2006;166(6):689–695.
42. Siebolds M, Gaedeke O, Schwedes U et al. Self-monitoring of blood glucose – psychological aspects relevant to changes in HbA1c in type 2 diabetic patients treated with diet or diet plus oral antidiabetic medication. Patient Education & Counseling 2006;62(1):104–110.
43. Karter AJ, Chan J, Parker MM et al. Longitudinal study of new and prevalent use of self-monitoring of blood glucose. Diabetes Care 2006;29(8).
44. Martin S, Schneider B, Heinemann L et al. Self-monitoring of blood glucose in type 2 diabetes and long- term outcome: an epidemiological cohort study. Diabetologia 2006;49(2):271–278.
45. Wen L, Parchman ML, Linn WD et al. Association between self-monitoring of blood glucose and glycemic control in patients with type 2 diabetes mellitus. American Journal of Health-System Pharmacy 2004; 61(22):2401–2405.
46. Davis WA, Bruce DG, Davis TM. Is self-monitoring of blood glucose appropriate for all type 2 diabetic patients? The Fremantle Diabetes Study. Diabetes Care 2006;29(8):1764–1770.
47. Schutt M, Kern W, Krause U et al. Is the frequency of self-monitoring of blood glucose related to long- term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. Experimental & Clinical Endocrinology & Diabetes 2006;114(7):384–388.
48. Kalergis M, Nadeau J, Pacaud D et al. Accuracy and reliability of reporting self-monitoring of blood glucose results in adults with type 1 and type 2 diabetes. Canadian Journal of Diabetes 2006;30(3):241–247.
49. Lawton J, Peel E, Douglas M et al. 'Urine testing is a waste of time': newly diagnosed type 2 diabetes patients' perceptions of self-monitoring. Diabetic Medicine 2004;21(9):1045–1048.
50. Peel E, Parry O, Douglas M et al. Blood glucose self-monitoring in non-insulin-treated type 2 diabetes: a qualitative study of patients' perspectives. British Journal of General Practice 2004;54(500):183–188.
51. Palmer AJ, Dinneen S, Gavin JR, III et al. Cost-utility analysis in a UK setting of self-monitoring of blood glucose in patients with type 2 diabetes. Current Medical Research & Opinion 2006;22(5):861–872.
52. Gray A, Clarke P, Farmer A et al. Implementing intensive control of blood glucose concentration and blood pressure in type 2 diabetes in England: Cost analysis (UKPDS 63). British Medical Journal 2002; 325(7369):860–863.
53. UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UKPDS Group. Lancet 1998;352(9131):837–853.
54. Kahn SE, Haffner SM, Heise MA et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. New England Journal of Medicine 2006;355(23):2427–2443.
55. UK Prospective Diabetes Study Group. UK prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 1995;44(11):1249–1258.

56. Saenz A, Fernandez-Esteban I, Mataix A et al. Metformin monotherapy for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2005;(3):CD002966.
57. Salpeter S, Greyber E, Pasternak G et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2003;(2):CD002967.
58. Cryer DR, Nicholas SP, Henry DH et al. Comparative outcomes study of metformin intervention versus conventional approach the COSMIC Approach Study. Diabetes Care 2005;28(3):539–543.
59. Schernthaner G, Matthews DR, Charbonnel B et al. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. Journal of Clinical Endocrinology & Metabolism 2004;89(12):6068–6076.
60. Derosa G, Franzetti I, Gadaleta G et al. Metabolic variations with oral antidiabetic drugs in patients with type 2 diabetes: comparison between glimepiride and metformin. Diabetes, Nutrition & Metabolism – Clinical & Experimental 2004;17(3):143–150.
61. Weissman P, Goldstein BJ, Rosenstock J et al. Effects of rosiglitazone added to submaximal doses of metformin compared with dose escalation of metformin in type 2 diabetes: the EMPIRE Study. Current Medical Research & Opinion 2005;21(12):2029–2035.
62. Bailey CJ, Bagdonas A, Rubes J et al. Rosiglitazone/metformin fixed-dose combination compared with uptitrated metformin alone in type 2 diabetes mellitus: a 24-week, multicenter, randomized, double-blind, parallel-group study. Clinical Therapeutics 2005;27(10):1548–1561.
63. Marre M, Van GL, Usadel KH et al. Nateglinide improves glycaemic control when added to metformin monotherapy: results of a randomized trial with type 2 diabetes patients. Diabetes, Obesity & Metabolism 2002;4(3):177–186.
64. Kvapil M, Swatko A, Hilberg C et al. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes, Obesity & Metabolism 2006;8(1):39–48.
65. Fujioka K, Pans M, Joyal S. Glycemic control in patients with type 2 diabetes mellitus switched from twice- daily immediate-release metformin to a once-daily extended-release formulation. Clinical Therapeutics 2003;25(2):515–529.
66. Fujioka K, Brazg RL, Raz I et al. Efficacy, dose-response relationship and safety of once-daily extended- release metformin (Glucophage XR) in type 2 diabetic patients with inadequate glycaemic control despite prior treatment with diet and exercise: results from two double-blind, placebo-controlled studies. Diabetes, Obesity & Metabolism 2005;7(1):28–39.
67. Blonde L, Dailey G, Jabbour SA et al. Gastrointerstinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. Current Medical Research & Opinion 2006;20(4):565–572.
68. Mohammad F, Fenna I, Leong K et al. Audit of metformin sustained release (SR) in patients intolerant of immediate release metformin. Diabetic Medicine 2006;23(Suppl 2):111.
69. Nagle A, Brake J, Hopkins M et al. Glucophage SR. Can it really make a difference? Diabetic Medicine 2006;23(Suppl 2):110.
70. Thomas Z, Phillips SM, Hogan D et al. The tolerability of prolonged-release metformin (Glucophage SR) in previously metformin intolerant patients – review of local experience. Diabetic Medicine 2006; 23(Suppl 2):111.
71. Yousseif A, Roberts S, Malik S et al. Patient reported side effects and compliance with Glucophage SR. Diabetic Medicine 2006;23(Suppl 2):111.
72. Palmer AJ, Roze S, Lammert M et al. Comparing the long-term cost-effectiveness of repaglinide plus metformin versus nateglinide plus metformin in type 2 diabetes patients

with inadequate glycaemic control: an application of the CORE Diabetes Model in type 2 diabetes. Current Medical Research & Opinion 2004;20(Suppl 1):S41–S51.

73. Salas M, Ward A, Caro J. Health and economic effects of adding nateglinide to metformin to achieve dual control of glycosylated hemoglobin and postprandial glucose levels in a model of type 2 diabetes mellitus. Clinical Therapeutics 2002;24(10):1690–1705.

74. Ward AJ, Salas M, Caro JJ, Owens D. Health and economic impact of combining metformin with nateglinide to achieve glycemic control: comparison of the lifetime costs of complications in the UK. Cost Effectiveness & Resource Allocation 2004;2:2.

75. Caro JJ, Salas M, Ward AJ et al. Combination therapy for type 2 diabetes: what are the potential health and cost implications in Canada? Canadian Journal of Diabetes 2003;27(1):33–41.

76. Alvarsson M, Sundkvist G, Lager I et al. Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. Diabetes Care 2003; 26(8):2231–2237.

77. Tong PC, Chow CC, Jorgensen LN et al. The contribution of metformin to glycaemic control in patients with type 2 diabetes mellitus receiving combination therapy with insulin. Diabetes Research & Clinical Practice 2002;57(2):93–98.

78. Inukai K, Watanabe M, Nakashima Y et al. Efficacy of glimepiride in Japanese type 2 diabetic subjects. Diabetes Research & Clinical Practice 2005;68(3):250–257.

79. Jibran R, Suliman MI, Qureshi F et al. Safety and efficay of repaglinide compared with glibenclamide in the management of type 2 diabetic Pakistani patients. Pakistan Journal of Medical Sciences 2006;22(4): 385–390.

80. Saloranta C, Hershon K, Ball M et al. Efficacy and safety of nateglinide in type 2 diabetic patients with modest fasting hyperglycemia. Journal of Clinical Endocrinology & Metabolism 2002;87(9):4171–4176.

81. Bengel FM, Abletshauser C, Neverve J et al. Effects of nateglinide on myocardial microvascular reactivity in type 2 diabetes mellitus: a randomized study using positron emission tomography. Diabetic Medicine 2005;22(2):158–163.

82. Moses RG, Gomis R, Frandsen KB et al. Flexible meal-related dosing with repaglinide facilitates glycemic control in therapy-naive type 2 diabetes. Diabetes Care 2001;24(1):11–15.

83. Rosenstock J, Hassman DR, Madder RD et al. Repaglinide versus nateglinide monotherapy: a randomized, multicenter study. Diabetes Care 2004;27(6):1265–1270.

84. Derosa G, Mugellini A, Ciccarelli L et al. Comparison between repaglinide and glimepiride in patients with type 2 diabetes mellitus: a one-year, randomized, double-blind assessment of metabolic parameters and cardiovascular risk factors. Clinical Therapeutics 2003;25(2):472–484.

85. Madsbad S, Kilhovd B, Lager I et al. Comparison between repaglinide and glipizide in type 2 diabetes mellitus: a 1-year multicentre study. Diabetic Medicine 2001;18(5):395–401.

86. Esposito K, Giugliano D, Nappo F et al. Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. Circulation 2004;110(2):214–219.

87. Furlong NJ, Hulme SA, O'Brien SV et al. Comparison of repaglinide vs. gliclazide in combination with bedtime NPH insulin in patients with type 2 diabetes inadequately controlled with oral hypoglycaemic agents. Diabetic Medicine 2003;20(11):935–941.

88. Raskin P, Klaff L, McGill J et al. Efficacy and safety of combination therapy: repaglinide plus metformin versus nateglinide plus metformin. Diabetes Care 2003;26(7):2063–2068.

89. Gerich J, Raskin P, Jean LL et al. PRESERVE-beta: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. Diabetes Care 2005;28(9):2093–2099.

90. Ristic S, ColloberMaugeais C, Pecher E et al. Comparison of nateglinide and gliclazide in combination with metformin, for treatment of patients with type 2 diabetes mellitus inadequately controlled on maximum doses of metformin alone. Diabetic Medicine 2006;23(7):757–762.

91. Horton ES, Foley JE, Shen SG et al. Efficacy and tolerability of initial combination therapy with nateglinide and metformin in treatment-naive patients with type 2 diabetes. Current Medical Research & Opinion 2004;20(6):883–889.

92. Dashora UK, Sibal L, Ashwell SG et al. Insulin glargine in combination with nateglinide in people with type 2 diabetes: a randomized placebo-controlled trial. Diabetic Medicine 2007;24(4):344–349.

93. Schernthaner G, Grimaldi A, Di MU et al. GUIDE study: double-blind comparison of once-daily gliclazide MR and glimepiride in type 2 diabetic patients. European Journal of Clinical Investigation 2004;34(8): 535–542.

94. Lu CH, Chang CC, Chuang LM et al. Double-blind, randomized, multicentre study of the efficacy and safety of gliclazide-modified release in the treatment of Chinese type 2 diabetic patients. Diabetes, Obesity & Metabolism 2006;8(2):184–191.

95. Charpentier G, Fleury F, Kabir M et al. Improved glycaemic control by addition of glimepiride to metformin monotherapy in type 2 diabetic patients. Diabetic Medicine 2001;18(10):828–834.

96. Forst T, Eriksson JW, Strotmann HJ et al. Metabolic effects of mealtime insulin lispro in comparison to glibenclamide in early type 2 diabetes. Experimental & Clinical Endocrinology & Diabetes 2003;111(2): 97–103.

97. Wright AD, Cull CA, Macleod KM et al. Hypoglycemia in type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis (UKPDS 73). Journal of Diabetes & its Complications 2006;20(6):395–401.

98. Gray A, Raikou M, McGuire A et al. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: Economic analysis alongside randomised controlled trial (UKPDS 41). British Medical Journal 2000;320(7246):1373–1378.

99. Van de Laar FA, Lucassen PL, Akkermans RP et al. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2005;(2):CD003639.

100. Ko GTC, Tsang CC, Ng CW et al. Effects on blood pressure of the a-glucosidase inhibitor acarbose compared with the insulin enhancer glibenclamide in patients with hypertension and type 2 diabetes mellitus. Clinical Drug Investigation 2001;21(6):401–408.

101. Goke B, German Pioglitazone Study Group. Effects on blood pressure of the a-glucosidase inhibitor acarbose compared with the insulin enhancer glibenclamide in patients with hypertension and type 2 diabetes mellitus. Treatments in Endocrinology 2002;1(5):329–336.

102. Feinbock C, Luger A, Klingler A et al. Effects on blood pressure of the a-glucosidase inhibitor acarbose compared with the insulin enhancer glibenclamide in patients with hypertension and type 2 diabetes mellitus. Diabetes, Nutrition & Metabolism - Clinical & Experimental 2003;16(4):214–221.

103. Hwu CM, Ho LT, Fuh MM et al. Effects on blood pressure of the a-glucosidase inhibitor acarbose compared with the insulin enhancer glibenclamide in patients with hypertension and type 2 diabetes mellitus. Diabetes Research & Clinical Practice 2003;60(2):111–118.

104. Phillips P, Karrasch J, Scott R et al. Effects on blood pressure of the a-glucosidase inhibitor acarbose compared with the insulin enhancer glibenclamide in patients with hypertension and type 2 diabetes mellitus. Diabetes Care 2003;26(2):269–273.

105. Bachmann W, Petzinna D, Raptis SA et al. Effects on blood pressure of the a-glucosidase inhibitor acarbose compared with the insulin enhancer glibenclamide in

patients with hypertension and type 2 diabetes mellitus. Clinical Drug Investigation 2003;23(10):679–686.

106. Lin BJ, Wu HP, Huang HS et al. Effects on blood pressure of the a-glucosidase inhibitor acarbose compared with the insulin enhancer glibenclamide in patients with hypertension and type 2 diabetes mellitus. Journal of Diabetes & its Complications 2003;17(4):179–185.

107. Segal P, Eliahou HE, Petzinna D et al. Effects on blood pressure of the a-glucosidase inhibitor acarbose compared with the insulin enhancer glibenclamide in patients with hypertension and type 2 diabetes mellitus. Clinical Drug Investigation 2005;25(9):589–595.

108. White TJ, Vanderplas A, Chang E et al. The costs of non-adherence to oral antihyperglycemic medication in individuals with diabetes mellitus and concomitant diabetes mellitus and cardiovascular disease in a managed care environment. Disease Management and Health Outcomes 2004;12(3):181–188.

109. Quilici S, Chancellor J, Maclaine G et al. Cost-effectiveness of acarbose for the management of impaired glucose tolerance in Sweden. International Journal of Clinical Practice 2005;59(10):1143–1152.

110. Huang ES, Shook M, Jin L et al. The impact of patient preferences on the cost-effectiveness of intensive glucose control in older patients with new-onset diabetes. Diabetes Care 2006;29(2):259–264.

111. Johnson JA, Simpson SH, Toth EL et al. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. Diabetic Medicine 2005;22(4):497–502.

112. Evans JMM, Ogston SA, EmslieSmith A et al. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: A comparison of patients treated with sulfonylureas and metformin. Diabetologia 2006;49(5):930–936.

113. National Institute for Health and Clinical Excellence. Glitazones in the treatment of type 2 diabetes (Review of TA9 and TA21). (TA63). London: NICE, 2003.

114. European Medicines Agency. 2007. www.emea.europa.eu

115. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. New England Journal of Medicine 2007;356(24):2457–2471.

116. Home PD, Pocock SJ, Beck-Nielsen H et al. Rosiglitazone evaluated for cardiovascular outcomes – an interim analysis. New England Journal of Medicine 2007;357(1):28–38.

117. Lincoff AM, Wolski K, Nicholls SJ et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. The Journal of the American Medical Association 2007;298(10):1180–1188.

118. Diamond GA, Bax L, Kaul S. Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death. Annals of Internal Medicine 2007;147(8):578–581.

119. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis [see comment]. The Journal of the American Medical Association 2007;298(10):1189–1195.

120. Lago RM, Singh PP, Nesto RW. Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet 2007;370(9593):1129–1136.

121. GlaxoSmithKline. Coronary heart disease outcomes in patients receiving antidiabetic agents. Uxbridge, Middlesex: GlaxoSmithKline, 2008.

122. Richter B, Bandeira-Echtler E, Bergerhoff K et al. Rosiglitazone for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2007;(3):CD006063.

123. Derosa G, Gaddi AV, Piccinni MN et al. Differential effect of glimepiride and rosiglitazone on metabolic control of type 2 diabetic patients treated with metformin: a randomized, double-blind, clinical trial. Diabetes, Obesity & Metabolism 2006;8(2):197–205.
124. Rosenstock J, Goldstein BJ, Vinik AI et al. Effect of early addition of rosiglitazone to sulphonylurea therapy in older type 2 diabetes patients (>60 years): the Rosiglitazone Early vs. SULphonylurea Titration (RESULT) study. Diabetes, Obesity & Metabolism 2006;8(1):49–57.
125. Raskin P, McGill J, Saad MF et al. Combination therapy for type 2 diabetes: repaglinide plus rosiglitazone. Diabetic Medicine 2004;21(4):329–335.
126. Bakris GL, Ruilope LM, McMorn SO et al. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria. Journal of Hypertension 2006;24(10):2047–2055.
127. Vongthavaravat V, Wajchenberg BL, Waitman JN et al. An international study of the effects of rosiglitazone plus sulphonylurea in patients with type 2 diabetes. Current Medical Research & Opinion 2002;18(8):456–461.
128. St John SM, Rendell M, Dandona P et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care 2002;25(11): 2058–2064.
129. Hanefeld M, Patwardhan R, Jones NP et al. A one-year study comparing the efficacy and safety of rosiglitazone and glibenclamide in the treatment of type 2 diabetes. Nutrition Metabolism & Cardiovascular Diseases 2007;17(1):13–23.
130. Kerenyi Z, Samer H, James R et al. Combination therapy with rosiglitazone and glibenclamide compared with upward titration of glibenclamide alone in patients with type 2 diabetes mellitus. Diabetes Research & Clinical Practice 2004;63(3):213–223.
131. Derosa G, Gaddi AV, Piccinni MN et al. Antithrombotic effects of rosiglitazone-metformin versus glimepiride-metformin combination therapy in patients with type 2 diabetes mellitus and metabolic syndrome. Pharmacotherapy 2005;25(5):637–645.
132. Baksi A, James RE, Zhou B et al. Comparison of uptitration of gliclazide with the addition of rosiglitazone to gliclazide in patients with type 2 diabetes inadequately controlled on half-maximal doses of a sulphonylurea. Acta Diabetologica 2004;41(2):63–69.
133. Derosa G, D'Angelo A, Ragonesi PD et al. Metabolic effects of pioglitazone and rosiglitazone in patients with diabetes and metabolic syndrome treated with metformin. Internal Medicine Journal 2007;37(2): 79–86.
134. Rosenstock J, Rood J, Cobitz A et al. Initial treatment with rosiglitazone/metformin fixed-dose combination therapy compared with monotherapy with either rosiglitazone or metformin in patients with uncontrolled type 2 diabetes. Diabetes, Obesity & Metabolism 2006;8(6):650–660.
135. Stewart MW, Cirkel DT, Furuseth K et al. Effect of metformin plus roziglitazone compared with metformin alone on glycaemic control in well-controlled type 2 diabetes. Diabetic Medicine 2006;23(10): 1069–1078.
136. Home PD, Jones NP, Pocock SJ et al. Rosiglitazone RECORD study: glucose control outcomes at 18 months. Diabetic Medicine 2007;24(6):626–634.
137. Raskin P, Rendell M, Riddle MC et al. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated type 2 diabetes. Diabetes Care 2001;24(7):1226–1232.
138. Home PD, Bailey CJ, Donaldson J et al. A double-blind randomized study comparing the effects of continuing or not continuing rosiglitazone + metformin therapy when starting insulin therapy in people with type 2 diabetes. Diabetic Medicine 2007;24(6):618–625.

139. Rosenstock J, Sugimoto D, Strange P et al. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients. Diabetes Care 2006;29(3):554–559.

140. Vinik AI, Zhang Q. Adding insulin glargine versus rosiglitazone: health-related quality-of-life impact in type 2 diabetes. Diabetes Care 2007;30(4):795–800.

141. Richter B, Bandeira-Echtler E, Bergerhoff K et al. Pioglitazone for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2006;(4):CD006060.

142. Dormandy JA. PROactive study. Lancet 2006;367(9405):26–27.

143. Yudkin J.S., Freemantle N. PROactive study. Lancet 2006;367(3504):24–25.

144. PROactive Study Executive Committee and Data and Safety Monitoring Committee. PROactive study. Lancet 2006;367(9515):982.

145. Mattoo V, Eckland D, Widel M et al. Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: results of a six-month, randomized, double-blind, prospective, multicenter, parallel-group study. Clinical Therapeutics 2005;27(5):554–567.

146. Davidson JA, Perez A, Zhang J. Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: results of a double-blind, multicentre, randomized study. Diabetes, Obesity & Metabolism 2006;8(2):164–174.

147. Raz I, Stranks S, Filipczak R et al. Efficacy and safety of biphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: an 18-week, randomized, open-label study. Clinical Therapeutics 2005;27(9):1432–1443.

148. Charbonnel B, Schernthaner G, Brunetti P et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia 2005;48(6):1093–1104.

149. Jain R, Osei K, Kupfer S et al. Long-term safety of pioglitazone versus glyburide in patients with recently diagnosed type 2 diabetes mellitus. Pharmacotherapy 2006;26(10):1388–1395.

150. Erdmann E, Dormandy JA, Charbonnel B et al. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. Journal of the American College of Cardiology 2007;49(17):1772–1780.

151. Mazzone T, Meyer PM, Feinstein SB et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. The Journal of the American Medical Association 2006;296(21):2572–2581.

152. Wilcox R, Bousser MG, Betteridge DJ et al. effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke 2007;38(3):865–873.

153. Berlie HD, Kalus JS, Jaber LA. Thiazolidinediones and the risk of edema: a meta-analysis. Diabetes Research & Clinical Practice 2007;76(2):279–289.

154. Czoski-Murray C, Warren E, Chilcott J et al. Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation (structured abstract). Health Technology Assessment 2004;8(13)

155. National Institute for Health and Clinical Excellence. Diabetes (type 2) – pioglitazone (replaced by TA63) (TA21). London: NICE, 2001.

156. Beale S, Bagust A, Shearer AT et al. Cost-effectiveness of rosiglitazone combination therapy for the treatment of type 2 diabetes mellitus in the UK. Pharmacoeconomics 2006;24(Suppl 1):21–34.

157. Tilden DP, Mariz S, O'BryanTear G et al. A lifetime modelled economic evaluation comparing pioglitazone and rosiglitazone for the treatment of type 2 diabetes mellitus in the UK. Pharmacoeconomics 2007;25(1):39–54.

158. Dormandy JA, Charbonnel B, Eckland DJ et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366(9493):1279–1289.
159. Buse JB, Henry RR, Han J et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004;27(11):2628–2635.
160. DeFronzo RA, Ratner RE, Han J et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28(5):1092–1100.
161. Kendall DM, Riddle MC, Rosenstock J et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. Diabetes Care 2005;28(5):1083–1091.
162. Blonde L, Klein EJ, Han J et al. Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes. Diabetes, Obesity & Metabolism 2006;8(4):436–447.
163. Poon T, Nelson P, Shen L et al. Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study. Diabetes Technology & Therapeutics 2005;7(3):467–477.
164. Heine RJ, Van Gaal LF, Johns D et al. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Annals of Internal Medicine 2005;143(8):559–569.
165. Secnik BK, Matza LS, Oglesby A et al. Patient-reported outcomes in a trial of exenatide and insulin glargine for the treatment of type 2 diabetes. Health & Quality of Life Outcomes 2006;4(80).
166. Nauck MA, Duran S, Kim D et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non- inferiority study. Diabetologia 2007;50(2):259–267.
167. Zinman B, Hoogwerf BJ, Duran GS et al. The effect of adding exenatide to a thiazolidinedione in suboptimally controlled type 2 diabetes: a randomized trial. Annals of Internal Medicine 2007;146(7): 477–485.
168. European Medicines Agency. EPARs for authorised medicinal products for human use. Available from: www.emea.europa.eu. Last accessed on: 19 January 2008.
169. Ray JA, Boye KS, Yurgin N et al. Exenatide versus insulin glargine in patients with type 2 diabetes in the UK: a model of long-term clinical and cost outcomes. Current Medical Research & Opinion 2007;23(3): 609–622.
170. Goudswaard AN, Furlong NJ, Rutten GE et al. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2004;(4):CD003418.
171. Kokic SB. Lispro insulin and metformin versus other combination in the diabetes mellitus type 2 management after secondary oral antidiabetic drug failure. Collegium Antropologicum 2003;27(1):181–187.
172. Olsson PO, Lindstrom T. Combination-therapy with bedtime nph insulin and sulphonylureas gives similar glycaemic control but lower weight gain than insulin twice daily in patients with type 2 diabetes. Diabetes & Metabolism 2002;28(4:Pt 1):272–277.
173. Altuntas Y, Ozen B, Ozturk B et al. Comparison of additional metformin or NPH insulin to mealtime insulin lispro therapy with mealtime human insulin therapy in secondary OAD failure. Diabetes, Obesity & Metabolism 2003;5(6):371–378.
174. Kabadi MU, Kabadi UM. Efficacy of sulfonylureas with insulin in type 2 diabetes mellitus. Annals of Pharmacotherapy 2003;37(11):1572–1576.

175. Zargar AH, Masoodi SR, Laway BA et al. Response of regimens of insulin therapy in type 2 diabetes mellitus subjects with secondary failure. Journal of the Association of Physicians of India 2002;50(5):641–646.
176. Douek IF, Allen SE, Ewings P et al. Continuing metformin when starting insulin in patients with type 2 diabetes: a double-blind randomized placebo-controlled trial. Diabetic Medicine 2005;22(5):634–640.
177. Goudswaard AN, Stolk RP, Zuithoff P et al. Starting insulin in type 2 diabetes: continue oral hypoglycemic agents? A randomized trial in primary care. Journal of Family Practice 2004;53(5):393–399.
178. Janka HU, Plewe G, Riddle MC et al. Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. Diabetes Care 2005; 28(2):254–259.
179. Stehouwer MH, DeVries JH, Lumeij JA et al. Combined bedtime insulin – daytime sulphonylurea regimen compared with two different daily insulin regimens in type 2 diabetes: effects on HbA1c and hypo- glycaemia rate – a randomised trial. Diabetes/Metabolism Research and Reviews 2003;19(2):148–152.
180. Lechleitner M, Roden M, Haehling E et al. Insulin glargine in combination with oral antidiabetic drugs as a cost-equivalent alternative to conventional insulin therapy in type 2 diabetes mellitus. Wiener Klinische Wochenschrift 2005;117(17):593–598.
181. Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for economic evaluation of health care programmes, 2nd edn. Oxford: Oxford University Press, 2003.
182. Christiansen JS, Vaz JA, Metelko Z. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. Diabetes, Obesity & Metabolism 2003;5(6):446–454.
183. Kilo C, Mezitis N, Jain R et al. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. Journal of Diabetes & its Complications 2003;17(6):307–313.
184. Ceriello A, Del PS, Bue VJ et al. Premeal insulin lispro plus bedtime NPH or twice-daily NPH in patients with type 2 diabetes: acute postprandial and chronic effects on glycemic control and cardiovascular risk factors. Journal of Diabetes & its Complications 2007;21(1):20–27.
185. Siebenhofer A, Plank J, Berghold A et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database of Systematic Reviews 2006;(2):CD003287.
186. Boehm BO, Home PD, Behrend C et al. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients [erratum appears in Diabetic Medicine. 2002 Sep;19(9):797]. Diabetic Medicine 2002;19(5):393–399.
187. Boehm BO, Vaz JA, Brondsted L et al. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. European Journal of Internal Medicine 2004;15(8):496–502.
188. Abrahamian H, Ludvik B, Schernthaner G et al. Improvement of glucose tolerance in type 2 diabetic patients: traditional vs. modern insulin regimens (results from the Austrian Biaspart Study). Hormone & Metabolic Research 2005;37(11):684–689.
189. Schernthaner G, Kopp HP, Ristic S et al. Metabolic control in patients with type 2 diabetes using Humalog Mix50 injected three times daily: crossover comparison with human insulin 30/70. Hormone & Metabolic Research 2004;36(3):188–193.
190. Ligthelm RJ, Mouritzen U, Lynggaard H et al. Biphasic insulin aspart given thrice daily is as efficacious as a basal-bolus insulin regimen with four daily injections: a randomised

open-label parallel group four months comparison in patients with type 2 diabetes. Experimental & Clinical Endocrinology & Diabetes 2006;114(9):511–519.

191. Joshi SR, Kalra S, Badgandi M et al. Designer insulins regimens in clinical practice – pilot multicenter Indian study. Journal of the Association of Physicians of India 2005;53(Sept):775–779.

192. Davies M, Storms F, Shutler S. Initiation of Insulin Glargine in type 2 patients with suboptimal glycaemic control on twice-daily premix insulin: results from the AT.LANTUS trial. Diabetologia 2004;47(Suppl 1): 319.

193. National Institute for Clinical Excellence. The clinical effectiveness and cost effectiveness of long acting insulin analogues for diabetes (TA53). London: NICE, 2002.

194. Rosenstock J, Dailey G, Massi-Benedetti M et al. Reduced hypoglycemia risk with insulin glargine: a meta- analysis comparing insulin glargine with human NPH insulin in type 2 diabetes. Diabetes Care 2005; 28(4):950–955.

195. Horvath K, Jeitler K, Berghold A et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2007;(2):CD005613.

196. Yki JH, Kauppinen MR, Tiikkainen M et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. Diabetologia 2006;49(3):442–451.

197. Herman WH, Ilag LL, Johnson SL et al. A clinical trial of continuous subcutaneous insulin infusion versus multiple daily injections in older adults with type 2 diabetes. Diabetes Care 2005;28(7):1568–1573.

198. Raskin P, Allen E, Hollander P et al. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care 2005;28(2):260–265.

199. Eliaschewitz FG, Calvo C, Valbuena H et al. Therapy in type 2 diabetes: insulin glargine vs. NPH insulin both in combination with glimepiride. Archives of Medical Research 2006;37(4):495–501.

200. Rosskamp R. Safety and efficacy of insulin glargine (HOE 901) versus NPH insulin in combination with oral treatment in type 2 diabetic patients. Diabetic Medicine 2003;20(7):545–551.

201. Malone JK, Kerr LF, Campaigne BN et al. Combined therapy with insulin lispro mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clinical Therapeutics 2004;26(12):2034–2044.

202. Malone JK, Bai S, Campaigne BN et al. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with type 2 diabetes. Diabetic Medicine 2005;22(4): 374–381.

203. Jacober SJ, Scism BJ, Zagar AJ. A comparison of intensive mixture therapy with basal insulin therapy in insulin-naive patients with type 2 diabetes receiving oral antidiabetes agents. Diabetes, Obesity & Metabolism 2006;8(4):448–455.

204. Kann PH, Wascher T, Zackova V et al. Starting insulin therapy in type 2 diabetes: twice-daily biphasic insulin aspart 30 plus metformin versus once-daily insulin glargine plus glimepiride. Experimental & Clinical Endocrinology & Diabetes 2006;114(9):527–532.

205. Kazda C, Hulstrunk H, Helsberg K et al. Prandial insulin substitution with insulin lispro or insulin lispro mid mixture vs. basal therapy with insulin glargine: a randomized controlled trial in patients with type 2 diabetes beginning insulin therapy. Journal of Diabetes & its Complications 2006;20(3):145–152.

206. Pan CY, Sinnassamy P, Chung KD et al. Insulin glargine versus NPH insulin therapy in Asian type 2 diabetes patients. Diabetes Research & Clinical Practice 2007;76(1):111–118.

207. Raskin PR, Hollander PA, Lewin A et al. Basal insulin or premix analogue therapy in type 2 diabetes patients. European Journal of Internal Medicine 2007;18(1):56–62.

208. Yokoyama H, Tada J, Kamikawa F et al. Efficacy of conversion from bedtime NPH insulin to morning insulin glargine in type 2 diabetic patients on basal-prandial insulin therapy. Diabetes Research & Clinical Practice 2006;73(1):35–40.

209. Standl E, Maxeiner S, Raptis S et al. Once-daily insulin glargine administration in the morning compared to bedtime in combination with morning glimepiride in patients with type 2 diabetes: an assessment of treatment flexibility. Hormone & Metabolic Research 2006;38(3):172–177.

210. Gerstein HC, Yale JF, Harris SB et al. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. Diabetic Medicine 2006;23(7):736–742.

211. Fritsche A, Schweitzer MA, Haring HU et al. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. Annals of Internal Medicine 2003;138(12):952–959.

212. Massi BM, Humburg E, Dressler A et al. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with type 2 diabetes. Hormone & Metabolic Research 2003;35(3):189–196.

213. Riddle MC, Rosenstock J, Gerich J et al. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003;26(11):3080–3086.

214. Rosenstock J, Schwartz SL, Clark CM Jr et al. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. Diabetes Care 2001;24(4):631–636.

215. Warren E, Weatherley-Jones E, Chilcott J et al. Systematic review and economic evaluation of a long- acting insulin analogue, insulin glargine. Health Technology Assessment 2004;8(45):iii, 1–57.

216. McEwan P, Poole CD, Telow T et al. Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK. Current Medical Research & Opinion 2007;23(1): S7–S19.

217. National Institute for Health and Clinical Excellence. The clinical effectiveness and cost effectiveness of insulin pump therapy (TA57). London: NICE, 2003.

218. Little RR, Rohilfing CL, Wiedmeyer HM et al. The National Glycohaemoglobin Standardization Program (NGSP): a five-year progress report. Clinical Chemistry 2001;47:1985–1992.

219. Coscelli C. Safety, efficacy, acceptability of a pre-filled insulin pen in diabetic patients over 60 years old. Diabetes Research & Clinical Practice 1995;28(3):173–177.

220. Fox C, McKinnon C, Wall A et al. Ability to handle, and patient preference for, insulin delivery devices in visually impaired patients with type 2 diabetes. Practical Diabetes International 2002;19(4):104–107.

221. Kadiri A, Chraibi A, Marouan F et al. Comparison of NovoPen 3 and syringes/vials in the acceptance of insulin therapy in NIDDM patients with secondary failure to oral hypoglycaemic agents. Diabetes Research & Clinical Practice 1998;41(1):15–23.

222. Korytkowski M, Bell D, Jacobsen C et al. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. Clinical Therapeutics 2003;25(11):2836–2848.

223. Shelmet J. Preference and resource utilization in elderly patients: InnoLet versus vial/syringe. Diabetes Research & Clinical Practice 2004;63(1):27–35.

224. Stockl K, Ory C, Vanderplas A et al. An evaluation of patient preference for an alternative insulin delivery system compared to standard vial and syringe. Current Medical Research & Opinion 2007;23(1):133–146.

225. Asakura T, Seino H. Assessment of dose selection attributes with audible notification in insulin pen devices. Diabetes Technology & Therapeutics 2005;7(4):620–626.

226. Turner R, Holman R, Stratton I et al. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). British Medical Journal 1998;317:703–713.

227. Sibal L, Law HN, Gebbie J et al. Cardiovascular risk factors predicting the development of distal symmetrical polyneuropathy in people with type 1 diabetes: A 9-year follow-up study. Annals of the New York Academy of Sciences 2006;1084:304–318.

228. Pohl MA, Blumenthal S, Cordonnier DJ et al. Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. Journal of the American Society of Nephrology 2005;16(10):3027–3037.

229. Berl T, Hunsicker LG, Lewis JB et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. Journal of the American Society of Nephrology 2005;16(7):2170–2179.

230. Matthews DR, Stratton IM, Aldington SJ et al. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus (UKPDS 69). Archives of Opthalmology 2004;122(11):1631–1640.

231. Bakris GL, Weir MR, Shanifar S et al. Effects of blood pressure level on progression of diabetic nephropathy: results from the RENAAL study. Archives of Internal Medicine 2003;163(13):1555–1565.

232. Estacio RO, Coll JR, Tran ZV et al. Effect of intensive blood pressure control with valsartan on urinary albumin excretion in normotensive patients with type 2 diabetes. American Journal of Hypertension 2006;19(12):1241–1248.

233. Schrier RW, Estacio RO, Esler A et al. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney International 2002;61(3):1086–1097.

234. Turnbull F, Neal B, Algert C et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Archives of Internal Medicine 2005;165(12):1410–1419.

235. Torffvit O, Agardh CD. A blood pressure cut-off level identified for renal failure, but not for macro- vascular complications in type 2 diabetes: a 10-year observation study. Hormone & Metabolic Research 2002;34(1):32–35.

236. Strippoli GF, Craig M, Craig JC. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database of Systematic Reviews 2005;(4):CD004136.

237. Strippoli GF, Bonifati C, Craig M et al. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database of Systematic Reviews 2006;(4):CD006257.

238. Casas JP, Chua W, Loukogeorgakis S et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. Lancet 2005;366(9502): 2026–2033.

239. Mann JF, Gerstein HC, Yi QL et al. Progression of renal insufficiency in type 2 diabetes with and without microalbuminuria: results of the Heart Outcomes and Prevention Evaluation (HOPE) randomized study. American Journal of Kidney Diseases 2003;42(5):936–942.

240. Mann JF, Gerstein HC, Yi QL et al. Development of renal disease in people at high cardiovascular risk: results of the HOPE randomized study. Journal of the American Society of Nephrology 2003;14(3):641–647.

241. Bosch J. Long-term effects of ramipril on cardiovascular events and on diabetes: results of the HOPE study extension. Circulation 2005;112(9):1339–1346.

242. Barnett AH, Bain SC, Bouter P et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. New England Journal of Medicine 2004;351(19):1952–1961.

243. Sengul AM, Altuntas Y, Kurklu A et al. Beneficial effect of lisinopril plus telmisartan in patients with type 2 diabetes, microalbuminuria and hypertension. Diabetes Research & Clinical Practice 2006;71(2):210–219.

244. Dalla VM, Pozza G, Mosca A et al. Effect of lercanidipine compared with ramipril on albumin excretion rate in hypertensive type 2 diabetic patients with microalbuminuria: DIAL study (diabete, ipertensione, albuminuria, lercanidipina). Diabetes, Nutrition & Metabolism – Clinical & Experimental 2004;17(5):259–266.

245. Fogari R, Preti P, Zoppi A et al. Effects of amlodipine fosinopril combination on microalbuminuria in hypertensive type 2 diabetic patients. American Journal of Hypertension 2002;15(12):1042–1049.

246. Ruggenenti P, Perna A, Ganeva M et al. Impact of blood pressure control and angiotensin-converting enzyme inhibitor therapy on new-onset microalbuminuria in type 2 diabetes: a post hoc analysis of the BENEDICT trial. Journal of the American Society of Nephrology 2006;17(12):3472–3481.

247. Whelton PK, Barzilay J, Cushman WC et al. Clinical outcomes in antihypertensive treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Archives of Internal Medicine 2005;165(12): 1401–1409.

248. Fernandez R, Puig JG, Rodriguez PJ et al. Effect of two antihypertensive combinations on metabolic control in type-2 diabetic hypertensive patients with albuminuria: a randomised, double-blind study. Journal of Human Hypertension 2001;15(12):849–856.

249. Holzgreve H, Nakov R, Beck K et al. Antihypertensive therapy with verapamil SR plus trandolapril versus atenolol plus chlorthalidone on glycemic control. American Journal of Hypertension 2003;16(5:Pt 1):381–386.

250. Derosa G, Cicero AF, Gaddi A et al. Effects of doxazosin and irbesartan on blood pressure and metabolic control in patients with type 2 diabetes and hypertension. Journal of Cardiovascular Pharmacology 2005;45(6):599–604.

251. Derosa G, Cicero AF, Bertone G et al. Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study. Clinical Therapeutics 2004;26(8):1228–1236.

252. Viberti G, Wheeldon NM, MicroAlbuminuria Reduction With VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation 2002;106(6):672–678.

253. Appel GB, Radhakrishnan J, Avram MM et al. Analysis of metabolic parameters as predictors of risk in the RENAAL study. Diabetes Care 2003;26(5):1402–1407.

254. Remuzzi G, Ruggenenti P, Perna A et al. Continuum of renoprotection with losartan at all stages of type 2 diabetic nephropathy: a post hoc analysis of the RENAAL trial results. Journal of the American Society of Nephrology 2004;15(12):3117–3125.

255. Andersen S, Bröchner-Mortensen J, Parving HH et al. Kidney function during and after withdrawal of long-term irbesartan treatment in patients with type 2 diabetes and microalbuminuria. Diabetes Care 2003;26(12):3296–3302.

256. Lindholm LH, Ibsen H. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For End point reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359(9311):1004–1010.

257. Lewis EJ, Hunsicker LG, Clarke WR et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. New England Journal of Medicine 2001; 345(12):851–860.
258. Zanchetti A, Julius S, Kjeldsen S et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. Journal of Hypertension 2006;24(11):2163–2168.
259. Pepine CJ, Handberg EM, Cooper-DeHoff RM et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil- Trandolapril Study (INVEST): a randomized controlled trial. The Journal of the American Medical Association 2003;290(21):2805–2816.
260. Bakris GL, Fonseca V. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. The Journal of the American Medical Association 2004;292(18):2227–2236.
261. Black HR, Elliott WJ, Grandits G et al. Principal results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial. The Journal of the American Medical Association 2003; 289(16):2073–2082.
262. Dahlöf B. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366(9489):895–906.
263. Beard SM, Gaffney L, Backhouse ME. An economic evaluation of ramipril in the treatment of patients at high risk for cardiovascular events due to diabetes mellitus (structured abstract). Journal of Medical Economics 2001;4:199–205.
264. Schadlich PK, Brecht JG, Rangoonwala B et al. Cost effectiveness of ramipril in patients at high risk for cardiovascular events: economic evaluation of the HOPE (Heart Outcomes Prevention Evaluation) study for Germany from the Statutory Health Insurance perspective. Pharmacoeconomics 2004;22(15):955–973.
265. Gray A, Clarke P, Raikou M et al. An economic evaluation of atenolol vs. captopril in patients with type 2 diabetes (UKPDS 54). Diabetic Medicine 2001;18(6):438–444.
266. Palmer AJ, Annemans L, Roze S et al. An economic evaluation of the Irbesartan in Diabetic Nephropathy Trial (IDNT) in a UK setting. Journal of Human Hypertension 2004;18:733–738.
267. Rodby RA, Chiou CF, Borenstein J et al. The cost-effectiveness of irbesartan in the treatment of hypertensive patients with type 2 diabetic nephropathy. Clinical Therapeutics 2003;25(7):2102–2119.
268. Coyle D, Rodby RA. Economic evaluation of the use of irbesartan and amlodipine in the treatment of diabetic nephropathy in patients with hypertension in Canada. Canadian Journal of Cardiology 2004;20(1):71–79.
269. Vora J, Carides G, Robinson P. Effects of losartan-based therapy on the incidence of end-stage renal disease and associated costs in type 2 diabetes mellitus: A retrospective cost-effectiveness analysis in the United Kingdom. Current Therapeutic Research, Clinical & Experimental 2005;66(6):475–485.
270. Smith DG, Nguyen AB, Peak CN et al. Markov modeling analysis of health and economic outcomes of therapy with valsartan versus amlodipine in patients with type 2 diabetes and microalbuminuria. Journal of Managed Care Pharmacy 2004;10(1):26–32.
271. International currency rates. Available from: Financial Times. Last accessed on: 13 March 2007.
272. National Institute for Health and Clinical Excellence. Hypertension: management of hypertension in adults in primary care (CG34). London: NICE, 2006.

273. Haffner SM, Lehto S, Ronnemaa T et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. New England Journal of Medicine 1998;339(4):229–234.

274. Eddy DM, Schlessinger L. Validation of the archimedes diabetes model. Diabetes Care 2003;26(11): 3102–3110.

275. Song SH, Brown PM. Coronary heart disease risk assessment in diabetes mellitus: comparison of UKPDS risk engine with Framingham risk assessment function and its clinical implications. Diabetic Medicine 2004;21(3):238–245.

276. Stephens JW, Ambler G, Vallance P et al. Cardiovascular risk and diabetes. Are the methods of risk prediction satisfactory? European Journal of Cardiovascular Prevention and Rehabilitation 2004;11(6): 521–528.

277. Guzder RN, Gatling W, Mullee MA et al. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed type 2 diabetes: results from a United Kingdom study. Diabetic Medicine 2005;22(5):554–562.

278. Coleman RL, Stevens RJ, Renakaran R et al. Framington, SCORE and DECODE do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes Care 2007;30(5):1292–1293.

279. Stevens RJ, Kothari V, Adler AI et al. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clinical Science 2001;101(6):671–679.

280. Tuomilehto J, Rastenyte D. Epidemiology of macrovascular disease and hypertension in diabetes mellitus. International textbook of diabetes mellitus, 2nd edn. Chichester: John Wiley, 1997: 1559–1583.

281. Baigent C, Keech A, Kearney PM et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366(9493): 1267–1278.

282. Vijan S, Hayward RA, American College of Physicians. Pharmacologic lipid-lowering therapy in type 2 diabetes mellitus: background paper for the American College of Physicians. Annals of Internal Medicine 2004;140(8):650–658.

283. National Institute for Health and Clinical Excellence. Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease (TA94). London: NICE, 2006.

284. National Institute for Health and Clinical Excellence. Ezetimibe for the treatment of primary (heterozygous familial and non-familial) hypercholesterolaemia (TA132). London: NICE, 2007.

285. Insull W, Kafonek S, Goldner D et al. Comparison of efficacy and safety of atorvastatin (10mg) with simvastatin (10mg) at six weeks. ASSET Investigators. American Journal of Cardiology 2001;87(5):554–559.

286. van Venrooij FV, van de Ree MA, Bots ML et al. Aggressive lipid lowering does not improve endothelial function in type 2 diabetes: the Diabetes Atorvastatin Lipid Intervention (DALI) Study: a randomized, double-blind, placebo-controlled trial. Diabetes Care 2002;25(7):1211–1216.

287. Miller M, Dobs A, Yuan Z et al. Effectiveness of simvastatin therapy in raising HDL-C in patients with type 2 diabetes and low HDL-C. Current Medical Research & Opinion 2004;20(7):1087–1094.

288. Berne C, Siewert DA, URANUS study investigators. Comparison of rosuvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus: results from the URANUS study. Cardiovascular Diabetology 2005;4:7.

289. Colhoun HM, Betteridge DJ, Durrington PN et al. Rapid emergence of effect of atorvastatin on cardiovascular outcomes in the Collaborative Atorvastatin Diabetes Study (CARDS). Diabetologia 2005;48(12):2482–2485.

290. Sever PS, Poulter NR, Dahlof B et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial – lipid-lowering arm (ASCOT-LLA). Diabetes Care 2005;28(5):1151–1157.

291. Shepherd J, Barter P, Carmena R et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care 2006;29(6):1220–1226.

292. Steiner G, Hamsten A, Hosking J et al. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet 2001; 357(9260):905–910.

293. Vakkilainen J, Steiner G, Ansquer JC et al. Relationships between low-density lipoprotein particle size, plasma lipoproteins, and progression of coronary artery disease: the Diabetes Atherosclerosis Intervention Study (DAIS). Circulation 2003;107(13):1733–1737.

294. Keech A, Simes R, Barter P et al. Effects of long–term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. Lancet 2005; 366(9500):1849–1861.

295. Derosa G, Cicero AE, Bertone G et al. Comparison of fluvastatin + fenofibrate combination therapy and fluvastatin monotherapy in the treatment of combined hyperlipidemia, type 2 diabetes mellitus, and coronary heart disease: a 12-month, randomized, double-blind, controlled trial. Clinical Therapeutics 2004;26(10):1599–1607.

296. Athyros VG, Papageorgiou VV, Athyrou DS et al. Atorvastatin and micronized fenofibrate alone and in combination, in type-2 diabetes mellitus with combined hyperlipidemia. Atherosclerosis 2002;3(2):70.

297. Durrington PN, Tuomilehto J, Hamann A et al. Rosuvastatin and fenofibrate alone and in combination in type 2 diabetes patients with combined hyperlipidaemia. Diabetes Research & Clinical Practice 2004;64(2):137–151.

298. Muhlestein JB, May HT, Jensen JR et al. The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. Journal of the American College of Cardiology 2006;48(2):396–401.

299. Rubins HB, Robins SJ, Collins D et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT). Archives of Internal Medicine 2002;162(22):2597–2604.

300. Ashraf R, Amir K, Shaikh AR. Comparison between duration dependent effects of simvastatin and gemfibrozil on dyslipidemia in patients with type 2 diabetes. Journal of the Pakistan Medical Association 2005;55(8):324–327.

301. Schweitzer M, Tessier D, Vlahos WD et al. A comparison of pravastatin and gemfibrozil in the treatment of dyslipoproteinemia in patients with non-insulin-dependent diabetes mellitus. Atherosclerosis 2002;162(1):201–210.

302. Wagner AM, Jorba O, Bonet R et al. Efficacy of atorvastatin and gemfibrozil, alone and in low dose combination, in the treatment of diabetic dyslipidemia. Journal of Clinical Endocrinology & Metabolism 2003;88(7):3212–3217.

303. Feher MD, Langley-Hawthorne CE, Byrne CD. Cost-outcome benefits of fibrate therapy in type 2 diabetes. British Journal of Diabetes & Vascular Disease 2003;3(2):124–130.

304. Elam MB, Hunninghake DB, Davis KB et al. Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. Arterial Disease Multiple Intervention Trial. The Journal of the American Medical Association 2000;284(10):1263–1270.

305. Grundy SM, Vega GL, McGovern ME et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the

assessment of diabetes control and evaluation of the efficacy of niaspan trial. Archives of Internal Medicine 2002;162(14):1568–1576.

306. Garg A, Grundy SM. Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. The Journal of the American Medical Association 1990;264(6):723–726.

307. Tsalamandris C, Panagiotopoulos S, Sinha A et al. Complementary effects of pravastatin and nicotinic acid in the treatment of combined hyperlipidaemia in diabetic and non-diabetic patients. Journal of Cardiovascular Risk 1994;1(3):231–239.

308. Armstrong EP, Zachry WM III, Malone DC. Cost-effectiveness analysis of simvastatin and lovastatin/extended-release niacin to achieve LDL and HDL goal using NHANES data. Journal of Managed Care Pharmacy 2004;10(3):251–258.

309. Olson BM, Malone DC, Armstrong EP. Modeling the cost-effectiveness of doubling atorvastatin's dose versus adding niacin ER. Formulary 2001;36(10):730–746.

310. Roze S, Wierzbicki AS, Liens D et al. Cost-effectiveness of adding prolonged-release nicotinic acid in statin-treated patients who achieve LDL cholesterol goals but remain at risk due to low HDL cholesterol: a UK-based economic evaluation. British Journal of Cardiology 2006;13(6):411–418.

311. Farmer A, Montori V, Dinneen S et al. Fish oil in people with type 2 diabetes mellitus. Cochrane Database of Systematic Reviews 2001;(3):CD003205.

312. Hartweg J, Farmer AJ, Holman RR et al. Meta-analysis of the effects of n-3 polyunsaturated fatty acids on haematological and thrombogenic factors in type 2 diabetes. Diabetologia 2007;50(2):250–258.

313. Jain S, Gaiha M, Bhattacharjee J et al. Effects of low-dose omega-3 fatty acid substitution in type-2 diabetes mellitus with special reference to oxidative stress – a prospective preliminary study. Journal of the Association of Physicians of India 2002;50(Aug):1028–1033.

314. Woodman RJ, Mori TA, Burke V et al. Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. American Journal of Clinical Nutrition 2002;76(5):1007–1015.

315. Pedersen H, Petersen M, Major-Pedersen A et al. Influence of fish oil supplementation on in vivo and in vitro oxidation resistance of low-density lipoprotein in type 2 diabetes. European Journal of Clinical Nutrition 2003;57(5):713–720.

316. Petersen M, Pedersen H, Major-Pedersen A et al. Effect of fish oil versus corn oil supplementation on LDL and HDL subclasses in type 2 diabetic patients. Diabetes Care 2002;25(10):1704–1708.

317. Dunstan DW, Mori TA, Puddey IB et al. Exercise and fish intake: effects on serum lipids and glycemic control for type 2 diabetics. Cardiology Review 1998;15(8):34–37.

318. Hooper L, Thompson RL, Harrison RA et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. British Medical Journal 2006;332(7544):752–760.

319. Wood D, Durrington P, McInnes G et al. Joint British recommendations on prevention of coronary heart disease in clinical practice. Heart 1998;80(Suppl 2):1S–29S.

320. McIntosh A, Hutchinson A, Home PD, Brown F, Bruce A. Clinical guidelines and evidence review for type 2 diabetes: management of blood glucose. Sheffield: School of Health and Related Research, 2001.

321. National Institute for Health and Clinical Excellence. Clopidogrel and modified release dipyridamole in the prevention of occlusive vascular events. (TA90). London: NICE, 2005.

322. Khajehdehi P, Roozbeh J, Mostafavi H. A comparative randomized and placebo-controlled short-term trial of aspirin and dipyridamole for overt type-2 diabetic nephropathy. Scandinavian Journal of Urology & Nephrology 2002;36(2):145–148.

323. Sacco M, Pellegrini F, Roncaglioni MC et al. Primary prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients: results of the Primary Prevention Project (PPP) trial. Diabetes Care 2003;26(12):3264–3272.

324. Neri Serneri GG, Coccheri S, Marubini E et al. Picotamide, a combined inhibitor of thromboxane A2 synthase and receptor, reduces 2-year mortality in diabetics with peripheral arterial disease: The DAVID study. European Heart Journal 2004;25(20):1845–1852.

325. Diener HC, Bogousslavsky J, Brass LM et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364(9431):331–337.

326. Bhatt DL, Marso SP, Hirsch AT et al. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. American Journal of Cardiology 2002;90(6):625–628.

327. Yusuf S, Zhao F, Mehta SR et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. New England Journal of Medicine 2001;345(7): 494–502.

328. Bhatt DL, Fox KA, Hacke W et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. New England Journal of Medicine 2006;354(16):1706–1717.

329. Steinhubl SR, Berger PB, Mann JT III et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. The Journal of the American Medical Association 2002;288(19):2411–2420.

330. Mehta SR, Yusuf S, Peters RJ et al. Effects of pretreatment with clopidogrel and aspirin followed by long- term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358(9281):527–533.

331. Jonsson B, Hansson L, Stalhammar NO. Health economics in the Hypertension Optimal Treatment (HOT) study: costs and cost-effectiveness of intensive blood pressure lowering and low-dose aspirin in patients with hypertension. Journal of Internal Medicine 2003;253(4):472–480.

332. National Institute for Health and Clinical Excellence. Clopidogrel in the treatment of non-ST-segment- elevation acute coronary syndrome. (TA80). London: NICE, 2004.

333. Weintraub WS, Mahoney EM, Lamy A et al. Long-term cost-effectiveness of clopidogrel given for up to one year in patients with acute coronary syndromes without ST-segment elevation. Journal of the American College of Cardiology 2005;45(6):838–845.

334. Ringborg A, Lindgren P, Jonsson B. The cost-effectiveness of dual oral antiplatelet therapy following percutaneous coronary intervention: a Swedish analysis of the CREDO trial. European Journal of Health Economics 2005;6(4):354–362.

335. Cowper PA, Udayakumar K, Sketch MH Jr et al. Economic effects of prolonged clopidogrel therapy after percutaneous coronary intervention. Journal of the American College of Cardiology 2005;45(3):369–376.

336. Harvey JN. Trends in the prevalence of diabetic nephropathy in type 1 and type 2 diabetes. Current Opinion in Nephrology & Hypertension 2003;12(3):317–322.

337. Banerjee S, Ghosh US, Saha SJ. Role of GFR estimation in assessment of the status of nephropathy in type 2 diabetes mellitus. Journal of the Association of Physicians of India 2005;53:181–4.

338. Baskar V, Venugopal H, Holland MR et al. Clinical utility of estimated glomerular filtration rates in predicting renal risk in a district diabetes population. Diabetic Medicine 2006;23(10):1057–1060.

339. Cortes SL, Martinez RH, Hernandez JL et al. Utility of the Dipstick Micraltest II in the screening of microalbuminuria of diabetes mellitus type 2 and essential hypertension. Revista de Investigacion Clinica 2006;58(3):190–197.

340. Incerti J, Zelmanovitz T, Camargo JL et al. Evaluation of tests for microalbuminuria screening in patients with diabetes. Nephrology Dialysis Transplantation 2005;20(11):2402–2407.

341. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S et al. Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes Care 2004;27(1):195–200.

342. Middleton RJ, Foley RN, Hegarty J et al. The unrecognized prevalence of chronic kidney disease in diabetes. Nephrology Dialysis Transplantation 2006;21(1):88–92.

343. Parikh CR, Fischer MJ, Estacio R et al. Rapid microalbuminuria screening in type 2 diabetes mellitus: simplified approach with Micral test strips and specific gravity [erratum appears in Nephrol Dial Transplant 2004;19(9):2425]. Nephrology Dialysis Transplantation 2004;19(7):1881–1885.

344. Poggio ED, Wang X, Greene T et al. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. Journal of the American Society of Nephrology 2005;16(2):459–466.

345. Rigalleau V, Lasseur C, Perlemoine C et al. A simplified Cockcroft-Gault formula to improve the prediction of the glomerular filtration rate in diabetic patients. Diabetes & Metabolism 2006;32(1):56–62.

346. Younis N, Broadbent DM, Vora JP et al. Incidence of sight-threatening retinopathy in patients with type 2 diabetes in the Liverpool Diabetic Eye Study: a cohort study. Lancet 2003;361(9353):195–200.

347. UK National Screening Committee. Essential elements in developing a diabetic retinopathy screening programme. Workbook 4:(1–79). Available from: UK National Screening Committee.

348. Max MB, Lynch SA, Muir J et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. New England Journal of Medicine 1992;326(19):1250–1256.

349. Sindrup SH, Gram LF, Skjold T et al. Clomipramine vs desipramine vs placebo in the treatment of diabetic neuropathy symptoms. A double-blind cross-over study. British Journal of Clinical Pharmacology 1990;30(5):683–691.

350. Sindrup SH, Tuxen C. Lack of effect of mianserin on the symptoms of diabetic neuropathy. European Journal of Clinical Pharmacology 1992;43(3):251–255.

351. Morello CM, Leckband SG, Stoner CP et al. Randomized double-blind study comparing the efficacy of gabapentin with amitriptyline on diabetic peripheral neuropathy pain. Archives of Internal Medicine 1999;159(16):1931–1937.

352. Jose VM, Bhansali A, Hota D et al. Randomized double-blind study comparing the efficacy and safety of lamotrigine and amitriptyline in painful diabetic neuropathy. Diabetic Medicine 2007;24(4):377–383.

353. Kvinesdal B, Molin J, Froland A et al. Imipramine treatment of painful diabetic neuropathy. The Journal of the American Medical Association 1984;251(13):1727–1730.

354. Max MB, Kishore KR, Schafer SC et al. Efficacy of desipramine in painful diabetic neuropathy: a placebo- controlled trial. Pain 1991;45(1):3–9.

355. Max MB, Culnane M, Schafer SC et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. Neurology 1987;37(4):589–596.

356. Sindrup SH, Ejlertsen B. Imipramine treatment in diabetic neuropathy: relief of subjective symptoms without changes in peripheral and autonomic nerve function. European Journal of Clinical Pharmacology 1989;37(2):151–153.

357. Raskin J, Smith TR, Wong K et al. Duloxetine versus routine care in the long-term management of diabetic peripheral neuropathic pain. Journal of Palliative Medicine 2006;9(1):29–40.

358. Raskin J, Pritchett YL, Wang F et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. Pain Medicine 2005;6(5): 346–356.

359. Goldstein DJ, Lu Y, Detke MJ et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain 2005;116(1–2):109–118.

360. Hardy T, Sachson R, Shen S et al. Does treatment with duloxetine for neuropathic pain impact glycemic control? Diabetes Care 2007;30(1):21–26.

361. Raskin J, Wang F, Pritchett YL et al. Duloxetine for patients with diabetic peripheral neuropathic pain: a 6-month open-label safety study. Pain Medicine 2006;7(5):373–385.

362. Wernicke JF, Pritchett YL, D'Souza DN et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006;67(8):1411–1420.

363. Wernicke JF, Raskin J, Rosen A et al. Duloxetine in the long-term management of diabetic peripheral neuropathic pain: An open-label, 52-week extension of a randomized controlled clinical trial. Current Therapeutic Research, Clinical & Experimental 2006;67(5):283–304.

364. Gomez-Perez FJ, PerezMonteverde A, Nascimento O et al. Gabapentin for the treatment of painful diabetic neuropathy: dosing to achieve optimal clinical response. British Journal of Diabetes & Vascular Disease 2004;4(3):173–178.

365. Gorson KC, Schott C, Herman R et al. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. Journal of Neurology, Neurosurgery, and Psychiatry 1999;66(2):251–252.

366. Backonja M, Beydoun A, Edwards KR et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. The Journal of the American Medical Association 1998;280(21):1831–1836.

367. Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. Journal of Clinical Neuromuscular Disease 2001;3(2):53–62.

368. Lesser H, Sharma U, Lamoreaux L et al. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. Neurology 2004;63(11):2104–2110.

369. Richter RW, Portenoy R, Sharma U et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. Journal of Pain 2005;6(4):253–260.

370. Rosenstock J, Tuchman M, Lamoreaux L et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110(3):628–638.

371. Rull JA, Quibrera R, Gonzalez MH et al. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial. Diabetologia 1969;5(4):215–218.

372. Wilton TD. Tegretol in the treatment of diabetic neuropathy. South African Medical Journal 1974;48(20):869–872.

373. Gomez-Perez FJ, Choza R, Rios JM et al. Nortriptyline-fluphenazine vs. carbamazepine in the symptomatic treatment of diabetic neuropathy. Archives of Medical Research 1996;27(4):525–529.

374. Beydoun A, Kobetz SA, Carrazana EJ. Efficacy of oxcarbazepine in the treatment of painful diabetic neuropathy. Clinical Journal of Pain 2004;20(3):174–178.

375. Dogra S, Beydoun S, Mazzola J et al. Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study. European Journal of Pain 2005;9(5):543–554.

376. Grosskopf J, Mazzola J, Wan Y et al. A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy. Acta Neurologica Scandinavica 2006;114(3):177–180.

377. Cepeda MS, Farrar JT. Economic evaluation of oral treatments for neuropathic pain. Journal of Pain 2006;7(2):119–128.

378. Maizels M, McCarberg B. Antidepressants and antiepileptic drugs for chronic non-cancer pain. American Family Physician 2005;71(3):483–490.

379. Wu EQ, Birnbaum HG, Mareva MN et al. Cost-effectiveness of duloxetine versus routine treatment for U.S. patients with diabetic peripheral neuropathic pain. Journal of Pain 2006;7(6):399–407.

380. National Institute for Health and Clinical Excellence. Type 2 diabetes: prevention and management of foot problems (CG10). London: NICE, 2004.

381. Braun AP. Domperidone in the treatment of symptoms of delayed gastric emptying in diabetic patients. Advances in Therapy 1989;6(2):51–62.

382. Samsom M. Effects of oral erythromycin on fasting and postprandial antroduodenal motility in patients with type I diabetes, measured with an ambulatory manometric technique. Diabetes Care 1997; 20(2):129–134.

383. Janssens J, Peeters TL, Vantrappen G et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. New England Journal of Medicine 1990;322(15):1028–1031.

384. McCallum RW, Ricci DA, Rakatansky H et al. A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. Diabetes Care 1983;6(5):463–467.

385. Ricci DA, Saltzman MB, Meyer C et al. Effect of metoclopramide in diabetic gastroparesis. Journal of Clinical Gastroenterology 1985;7(1):25–32.

386. Farup CE, Leidy NK, Murray M et al. Effect of domperidone on the health-related quality of life of patients with symptoms of diabetic gastroparesis. Diabetes Care 1998;21(10):1699–1706.

387. Erbas T, Varoglu E, Erbas B et al. Comparison of metoclopramide and erythromycin in the treatment of diabetic gastroparesis. Diabetes Care 1993;16(11):1511–1514.

388. Patterson D, Abell T, Rothstein R et al. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. American Journal of Gastroenterology 1999;94(5):1230–1234.

389. McCulloch DK, Campbell IW, Wu FC et al. The prevalence of diabetic impotence. Diabetologia 1980;18(4):279–283.

390. Price DE, Gingell JC, Gepi AS et al. Sildenafil: study of a novel oral treatment for erectile dysfunction in diabetic men. Diabetic Medicine 1998;15(10):821–825.

391. Rendell MS, Rajfer J. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. The Journal of the American Medical Association. 1999;281(5):421–426.

392. Boulton AJM, Selam JL, Sweeney M et al. Sildenafil citrate for the treatment of erectile dysfunction in men with type II diabetes mellitus. Diabetologia 2001;44(10):1296–1301.

393. Saenz de Tejada I, Anglin G, Knight JR et al. Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care 2002;25(12):2159–2164.

394. Goldstein I, Young JM, Fischer J et al. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care 2003;26(3):777–783.

395. Stuckey BGA, Jadzinsky MN, Murphy LJ et al. Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: results of a randomized controlled trial. Diabetes Care 2003;26(2):279–284.

396. Safarinejad MR. Oral sildenafil in the treatment of erectile dysfunction in diabetic men: a randomized double-blind and placebo-controlled study. Journal of Diabetes & its Complications 2004;18(4):205–210.

397. Ishii N, Nagao K, Fujikawa K et al. Vardenafil 20-mg demonstrated superior efficacy to 10-mg in Japanese men with diabetes mellitus suffering from erectile dysfunction. International Journal of Urology 2006;13(8):1066–1072.

398. Ziegler D, Merfort F, van Ahlen et al. Efficacy and safety of flexible-dose vardenafil in men with type 1 diabetes and erectile dysfunction. Journal of Sexual Medicine 2006;3(5):883–891.

399. Buvat J, van Ahlen, Schmitt H et al. Efficacy and safety of two dosing regimens of tadalafil and patterns of sexual activity in men with diabetes mellitus and erectile dysfunction: scheduled use vs. on-demand regimen evaluation (SURE) study in 14 European countries. Journal of Sexual Medicine 2006;3(3):512–520.

400. Weinstein MC, O'Brien B, Hornberger J et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices – Modeling Studies. Value in Health 2003;6:9–17.

401. Clarke PM, Gray AM, Briggs A et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). Diabetologia 2004;47(10):1747–1759.

402. Clarke P, Gray A, Legood R et al. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). Diabetic Medicine 2003; 20(6):442–450.

403. Curtis L, Netten A. Unit costs of health and social care 2006. Canterbury: Personal Social Services Research Unit, 2006.

404. Calvert MJ, McManus RJ, Freemantle N. Management of type 2 diabetes with multiple oral hypoglycaemic agents or insulin in primary care: retrospective cohort study. British Journal of General Practice 2007; 57(539):455–460.

405. Scottish Medicines Consortium. Glasgow. New product assessment form – exenatide 2006. Personal communication.

406. Melanie Davies, 31 May 2007. Personal communication.

407. Warren E. The cost-effectiveness of long-acting insulin analogue, insulin glargine. Sheffield: ScHARR, 16 August 2002.

408. Currie CJ, Morgan CL, Poole CD et al. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Current Medical Research & Opinion 2006;22(8):1523–1534.

409. Anon. Contributed poster presentations. Value in Health 2006;9(3):A24–A173. 410 Rowlett R. How many? A dictionary of units of measurement 2001.

410. Glenny AM, Altman DG, Song F et al. Indirect comparisons of competing interventions. Health Technology Assessment 2005;9(26):1–iv.

411. GlaxoSmithKline. Rosiglitazone maleate ZM2006/00207/00(meta-analysis)1–8. GlaxoSmithKline. 27 June 2006.

412. Food and Drug Administration. Avandia (rosiglitazone maleate) NDA21-071 supplement 022 FDA. 2007. 414 National Institute for Health and Clinical Excellence. Management of type 2 diabetes – management of blood pressure and blood lipids (Guideline H). London: NICE, 2002.

11 Glossary and Abbreviations

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11.1 Glossary

Cohort study

(also known as follow-up, incidence, longitudinal, or prospective study): an observational study in which a defined group of people (the cohort) is followed over time. Outcomes are compared in subsets of the cohort who were exposed or not exposed (or exposed at different levels) to an intervention or other factor of interest.

Comorbidity

Two or more diseases or conditions occurring at the same time, such as depression and anxiety.

Confidence interval (CI)

The range within which the 'true' values (for example, size of effect of an intervention) are expected to lie with a given degree of certainty (for example, 95% or 99%). (Note: confidence intervals represent the probability of random errors, but not systematic errors or bias.)

Cost-effectiveness analysis (CEA)

An economic evaluation that compares alternative options for a specific patient group looking at a single effectiveness dimension measured in a non-monetary (natural) unit. It expresses the result in the form of an incremental (or average or marginal) cost-effectiveness ratio (ICER).

Economic evaluation

Technique developed to assess both costs and consequences of alternative health strategies and to provide a decision-making framework.

Guideline Development Group (GDG)

A group of healthcare professionals, patients, carers and members of the Short Clinical Guidelines Technical Team who develop the recommendations for a clinical guideline. The group writes draft guidance, and then revises it after a consultation with organisations registered as stakeholders.

Generalisability

The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.

Heterogeneity

A term used to illustrate the variability or differences between studies in the estimates of effects.

Odds ratio (OR)

A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

Quality-adjusted life year (QALY)

A statistical measure, representing 1 year of life with full quality of life.

Randomised controlled trial

A form of clinical trial to assess the effectiveness of medicines or procedures. Considered reliable because it tends not to be biased.

Relative risk (RR)

Also known as risk ratio; the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. An RR of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR that is less than 1 indicates that the intervention was effective in reducing the risk of that outcome.

Systematic review

Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

11.2 Abbreviations

Table 102: Abbreviations

Abbreviation	Term
BMI	body mass index
CI	confidence interval
CrI	credible intervals
CUA	cost-utility analysis
DIC	deviance information criterion
DPP-4	dipeptidyl peptidase-4
GDG	guideline development group
GEQ	global efficacy question
GLP-1	glucagon-like peptide-1
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein
ICER	incremental cost-effectiveness ratio
IFCC	International Federation of Clinical Chemistry
IIEF	International index of erectile dysfunction
IIEF-EF	erectile function domain of the IIEF
ITT	intention-to-treat
LOCF	last observation carried forward
MHRA	Medicines and Healthcare products Regulatory Authority
MID	minimal important difference
NICE DSU TSD	NICE Decision Support Unit's Technical Support Documents
NIT	non-insulin based therapy
NMA	network meta-analysis
NPH insulin	neutral protamine Hagedorn insulin
OAD	oral antidiabetic drug
OR	odds ratio
QALY	quality-adjusted life year
RR	relative risk
SD	standard deviation
SE	standard error
SEP	Sexual encounter profile
SPC	summary of product characteristics
UKPDS	UK Prospective Diabetes Study

12 Appendices A–K are in a separate file

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