Appendix G: NICE Clinical Guideline 66 Deleted Text

There are 3 deleted text appendices for the type 2 diabetes in adults guideline. This appendix has a summary table of all the recommendations from NICE clinical guideline 87 which have been stood down, including the text and appendices information for NICE clinical guideline 66 (CG66), which was the first iteration of the type 2 diabetes in adults guideline.

The other 2 appendices, appendix H and I contain the write up of NICE clinical guideline 87 (CG87) [appendix H contains the full guideline and appendix I contains the appendices] which reviewed the evidence on newer agents in the pharmacological management of type 2 diabetes.

Table 1: Deleted recommendations from CG66 & CG87

Recommendation in 2009 guideline	Comment
Follow the recommendations in Depression: management of depression in primary and secondary care clinical guideline (NICE clinical guideline 23). [1.2.2.1]	This statement has been deleted because this is now mentioned in the 'Related guidance' section. Depression: Depression: management of depression in primary and secondary care clinical guideline (NICE clinical guideline 23) has also been updated and is now NICE clinical guideline 90.
When setting a target glycated haemoglobin (HbA1c): • involve the person in decisions about their individual HbA1c target level, which may be above that of 6.5% set for people with type 2 diabetes in general • encourage the person to maintain their individual target unless the resulting side • effects (including hypoglycaemia) or their efforts to achieve this impair their quality • of life offer therapy (lifestyle and medication) to help achieve and maintain the HbA1c target level • inform a person with a higher HbA1c that any reduction in HbA1c towards the agreed target is advantageous to future health • avoid pursuing highly intensive management to levels of less than 6.5%. [1.3.1]	This recommendation has been deleted because this entire section has been updated in 2015.
Offer self-monitoring of plasma glucose to a person newly diagnosed with type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon. [1.4.1]	This recommendation has been deleted because this entire section has been updated in 2015.
Self-monitoring of plasma glucose should be available: • to those on insulin treatment • to those on oral glucose-lowering medications to provide information on hypoglycaemia • to assess changes in glucose control resulting from medications and lifestyle changes	This recommendation has been deleted because this entire section has been updated in 2015.

• to monitor changes during intercurrent illness • to ensure safety during activities, including driving. [1.4.2]	
If self-monitoring is appropriate but blood glucose monitoring is unacceptable to the individual, discuss the use of urine glucose monitoring.	The recommendation has been deleted because the guideline development group working on the update believed it was not supported by the evidence.
Start metformin treatment in a person who is overweight or obese (tailoring the assessment of body-weight-associated risk according to ethnic group[4]) and whose blood glucose is inadequately controlled (see 1.3.1) by lifestyle interventions (nutrition and exercise) alone. [1.5.1.1]	This recommendation has been deleted because this entire section has been updated in 2015.
Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight. [1.5.1.2]	This recommendation has been deleted because this entire section has been updated in 2015.
Continue with metformin if blood glucose control remains or becomes inadequate (see 1.3.1) and another oral glucose-lowering medication (usually a sulfonylurea) is added. [1.5.1.3]	This recommendation has been deleted because this entire section has been updated in 2015.
Step up metformin therapy gradually over weeks to minimise risk of gastrointestinal (GI) side effects. Consider a trial of extended-absorption metformin tablets where GI tolerability prevents continuation of metformin therapy. [1.5.1.4]	This recommendation has been deleted because this entire section has been updated in 2015.
The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that: • due consideration can be given to the cardiovascular-protective effects of the drug • an informed decision can be made on whether to continue or stop the metformin. [1.5.1.6]	This recommendation has been deleted because this entire section has been updated in 2015.
Consider a sulfonylurea as an option for first-line glucose-lowering therapy if: • the person is not overweight • the person does not tolerate metformin (or it is contraindicated) or • a rapid response to therapy is required because of hyperglycaemic symptoms. [1.5.2.1]	This recommendation has been deleted because this entire section has been updated in 2015.
Add a sulfonylurea as second-line therapy when blood glucose control	This recommendation has been deleted because this entire section has been

remains or becomes inadequate (see 1.3.1) with metformin. [1.5.2.2]	updated in 2015.
Continue with a sulfonylurea if blood glucose control remains or becomes inadequate (see 1.3.1) and another oral glucose-lowering medication is added. [1.5.2.3]	This recommendation has been deleted because this entire section has been updated in 2015.
Prescribe a sulfonylurea with a low acquisition cost (but not glibenclamide) when an insulin secretagogue is indicated (see 1.5.2.1 and 1.5.2.2). [1.5.2.4]	This recommendation has been deleted because this entire section has been updated in 2015.
When drug concordance is a problem, offer a once-daily, long-acting sulfonylurea. [1.5.2.5]	This recommendation has been deleted because this entire section has been updated in 2015.
Educate a person being treated with an insulin secretagogue, particularly if renally impaired, about the risk of hypoglycaemia. [1.5.2.6]	This recommendation has been deleted because this entire section has been updated in 2015.
Consider offering a rapid-acting insulin secretagogue to a person with an erratic lifestyle. [1.5.3.1]	This recommendation has been deleted because this entire section has been updated in 2015.
Consider acarbose for a person unable to use other oral glucose-lowering medications. [1.5.4.1]	This recommendation has been deleted because this entire section has been updated in 2015.
Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if: • the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or • the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated. [1.6.1.1]	This recommendation has been deleted because this entire section has been updated in 2015.
Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if: • the person does not tolerate metformin, or metformin is	This recommendation has been deleted because this entire section has been updated in 2015.

contraindicated. [1.6.1.2]	
Consider adding sitagliptin[5] as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[6]. [1.6.1.3]	This recommendation has been deleted because this entire section has been updated in 2015.
Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months). [1.6.1.4]	This recommendation has been deleted because this entire section has been updated in 2015.
Discuss the potential benefits and risks of treatment with a DPP-4 inhibitor (sitagliptin, vildagliptin) with the person to enable them to make an informed decision. A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to a thiazolidinedione (pioglitazone) if: • further weight gain would cause or exacerbate significant problems associated with a high body weight, or • a thiazolidinedione (pioglitazone) is contraindicated, or • the person has previously had a poor response to, or did not tolerate, a thiazolidinedione (pioglitazone). There may be some people for whom either a DPP-4 inhibitor (sitagliptin, vildagliptin) or a thiazolidinedione (pioglitazone) may be suitable and, in this case, the choice of treatment should be based on patient preference. [1.6.1.5]	This recommendation has been deleted because this entire section has been updated in 2015.
Consider adding a thiazolidinedione (pioglitazone) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if: • the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or • a person does not tolerate a	This recommendation has been deleted because this entire section has been updated in 2015.

sulfonylurea or a sulfonylurea is contraindicated. [1.6.2.1]	
Consider adding a thiazolidinedione (pioglitazone) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if: • the person does not tolerate metformin or metformin is contraindicated. [1.6.2.2]	This recommendation has been deleted because this entire section has been updated in 2015.
Consider adding a thiazolidinedione (pioglitazone) as third-line therapy to firstline metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[7]. [1.6.2.3]	This recommendation has been deleted because this entire section has been updated in 2015.
Do not commence or continue a thiazolidinedione (pioglitazone) in people who have heart failure, or who are at higher risk of fracture. [1.6.2.4]	This recommendation has been deleted because this entire section has been updated in 2015.
When selecting a thiazolidinedione (pioglitazone), take into account up-to-date advice from the relevant regulatory bodies (the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency), cost, safety and prescribing issues (see 1.6.2.8). [1.6.2.5]	This recommendation has been deleted because this entire section has been updated in 2015.
Only continue thiazolidinedione therapy (pioglitazone) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months). [1.6.2.6]	This recommendation has been deleted because this entire section has been updated in 2015.
Consider combining pioglitazone with insulin therapy[6] for a person: • who has previously had a marked glucose-lowering response to thiazolidinedione therapy (pioglitazone), or • who is on high-dose insulin therapy and whose blood glucose is inadequately controlled. [1.6.2.7]	This recommendation has been deleted because this entire section has been updated in 2015.
Discuss the potential benefits and risks of treatment with a thiazolidinedione (pioglitazone) with the person to enable them to make an informed decision. A	This recommendation has been deleted because this entire section has been updated in 2015.

thiazolidinedione (pioglitazone) may be preferable to a DPP-4 inhibitor (sitagliptin, vildagliptin) if: • the person has marked insulin insensitivity, or • a DPP-4 inhibitor (sitagliptin, vildagliptin) is contraindicated, or • the person has previously had a poor response to, or did not tolerate, a DPP-4 inhibitor (sitagliptin, vildagliptin). There may be some people for whom either a thiazolidinedione (pioglitazone) or a DPP-4 inhibitor (sitagliptin, vildagliptin) may be suitable and, in this case, the choice of treatment should be based on patient preference. [1.6.2.8]	
Consider adding a GLP-1 mimetic (exenatide) as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5%, or other higher level agreed with the individual), and the person has: • a body mass index (BMI) ≥ 35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or • medical problems associated with high body weight, or • a BMI < 35.0 kg/m^2, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. [1.6.3.1]	This recommendation has been deleted because this entire section has been updated in 2015.
Discuss the potential benefits and risks of treatment with a GLP-1 mimetic (exenatide) with the person to enable them to make an informed decision. [1.6.3.3]	This recommendation has been deleted because this entire section has been updated in 2015.
When starting basal insulin therapy: • continue with metformin and the sulfonylurea (and acarbose, if used) • review the use of the sulfonylurea if hypoglycaemia occurs. [1.7.1.1]	This recommendation has been deleted because this entire section has been updated in 2015.
When starting pre-mixed insulin therapy (or mealtime plus basal insulin	This recommendation has been deleted because this entire section has been updated in 2015.

regimens): • continue with metformin • continue the sulfonylurea initially, but review and discontinue if hypoglycaemia occurs. [1.7.1.2]	
Discuss the benefits and risks of insulin therapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) with other measures. Start insulin therapy if the person agrees. [1.7.2.1]	This recommendation has been deleted because this entire section has been updated in 2015.
For a person on dual therapy who is markedly hyperglycaemic, consider starting insulin therapy in preference to adding other drugs to control blood glucose unless there is strong justification[7] not to. [1.7.2.2]	This recommendation has been deleted because this entire section has been updated in 2015.
Offer education to a person who requires insulin about using an injection device (usually a pen injector and cartridge or a disposable pen) that they and/or their carer find easy to use. [1.7.3.1]	NICE took the decision to stand down this recommendation because the Type1 diabetes guideline undertook an updated evidence review in this area. The guideline development group for type 2 diabetes agreed that the management of insulin delivery within the type 2 diabetes population would be similar and therefore it would be appropriate to cross refer to the Type 1 diabetes guideline for insulin delivery.
Appropriate local arrangements should be in place for the disposal of sharps.	NICE took the decision to stand down this recommendation because the Type1 diabetes guideline undertook an updated evidence review in this area. The guideline development group for type 2 diabetes agreed that the management of insulin delivery within the type 2 diabetes population would be similar and therefore it would be appropriate to cross refer to the Type 1 diabetes guideline for insulin delivery.
If a person has a manual or visual disability and requires insulin, offer a device or adaptation that: • takes into account his or her individual needs • he or she can use successfully	NICE took the decision to stand down this recommendation because the Type1 diabetes guideline undertook an updated evidence review in this area. The guideline development group for type 2 diabetes agreed that the management of insulin delivery within the type 2 diabetes population would be similar and therefore it would be appropriate to cross refer to the Type 1 diabetes guideline for insulin delivery.
Review cardiovascular risk status annually by assessment of cardiovascular risk factors, including	The type 2 diabetes Guideline Development Group (GDG) wanted to stand down the outstanding lipids recs

features of the metabolic syndrome and waist circumference, and change in personal or family cardiovascular history. [1.10.1.1]	1.10.1.1, 1.10.1.4, 1.10.2.1 and 1.10.2.2 but these are not directly updated by the lipids guideline. This is because the GDG felt these recommendations were covered by NICE's lipids guideline (CG181) and it is advisable to have all recommendations on lipid management in 1 place. The type 2 diabetes GDG felt it would be very important to cross refer to management of lipid levels within CG181 because management of cardiovascular risk is an essential part of managing type 2 diabetes.
Once a person has been started on cholesterol-lowering therapy, assess his or her lipid profile (together with other modifiable risk factors and any new diagnosis of cardiovascular disease) 1–3 months after starting treatment, and annually thereafter. In those not on cholesterol-lowering therapy, reassess cardiovascular risk annually and consider initiating a statin (see 1.10.1.2 and 1.10.1.3). [1.10.1.4]	The type 2 diabetes GDG wanted to stand down the outstanding lipids recs 1.10.1.1, 1.10.1.4, 1.10.2.1 and 1.10.2.2 but these are not directly updated by the lipids guideline. This is because the GDG felt these recommendations were covered by NICE's lipids guideline (CG181) and it is advisable to have all recommendations on lipid management in 1 place. The type 2 diabetes GDG felt it would be very important to cross refer to management of lipid levels within CG181 because management of cardiovascular risk is an essential part of managing type 2 diabetes.
If there is a history of elevated serum triglycerides, perform a full fasting lipid profile (including HDL cholesterol and triglyceride estimations) when assessing cardiovascular risk annually. [1.10.2.1]	The type 2 diabetes GDG wanted to stand down the outstanding lipids recs 1.10.1.1, 1.10.1.4, 1.10.2.1 and 1.10.2.2 but these are not directly updated by the lipids guideline. This is because the GDG felt these recommendations were covered by NICE's lipids guideline (CG181) and it is advisable to have all recommendations on lipid management in 1 place. The type 2 diabetes GDG felt it would be very important to cross refer to management of lipid levels within CG181 because management of cardiovascular risk is an essential part of managing type 2 diabetes.
Assess possible secondary causes of high serum triglyceride levels, including poor blood glucose control (others include hypothyroidism, renal impairment and liver inflammation, particularly from alcohol). If a secondary cause is identified, manage according to need. [1.10.2.2]	The type 2 diabetes GDG wanted to stand down the outstanding lipids recs 1.10.1.1, 1.10.1.4, 1.10.2.1 and 1.10.2.2 but these are not directly updated by the lipids guideline. This is because the GDG felt these recommendations were covered by NICE's lipids guideline (CG181) and it is advisable to have all recommendations on lipid management in 1 place. The type 2 diabetes GDG felt it would be very important to cross refer to management of lipid levels within

	CG181 because management of cardiovascular risk is an essential part of managing type 2 diabetes.
Offer low-dose aspirin, 75 mg daily, to a person who is 50 years old or over, if blood pressure is below 145/90 mmHg[8]. [1.11.1]	This recommendation has been deleted because this entire section has been updated in 2015.
Offer low-dose aspirin, 75 mg daily, to a person who is under 50 years old and has significant other cardiovascular risk factors (features of the metabolic syndrome, strong early family history of cardiovascular disease, smoking, hypertension, extant cardiovascular disease, microalbuminuria)[8]. [1.11.2]	This recommendation has been deleted because this entire section has been updated in 2015.
Clopidogrel should be used instead of aspirin only in those with clear aspirin intolerance (except in the context of acute cardiovascular events and procedures). Follow the recommendations in 'Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events' (NICE technology appraisal guidance 90). [1.11.3]	This recommendation has been deleted because this entire section has been updated in 2015.
Ask all people with or without detected nephropathy to bring in a first-pass morning urine specimen once a year. In the absence of proteinuria/urinary tract infection (UTI), send this for laboratory estimation of albumin:creatinine ratio. Request a specimen on a subsequent visit if UTI prevents analysis. [1.12.1]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
Make the measurement on a spot sample if a first-pass sample is not provided (and repeat on a first-pass specimen if abnormal) or make a formal arrangement for a first-pass specimen to be provided. [1.12.2]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
Measure serum creatinine and estimate the glomerular filtration rate (using the method-abbreviated modification of diet in renal disease [MDRD] four-variable equation) annually at the time of albumin:creatinine ratio estimation. [1.12.3]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
Repeat the test if an abnormal albumin:creatinine ratio is obtained (in the absence of proteinuria/UTI) at each of the next two clinic visits but within a maximum of 3–4 months. Take the result to be confirming microalbuminuria if a further specimen (out of two more) is also abnormal (> 2.5 mg/mmol for men, > 3.5	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.

mg/mmol for women). [1.12.4]	
Suspect renal disease other than diabetic nephropathy and consider further investigation or referral when the albumin:creatinine ratio (ACR) is raised and any of the following apply: • there is no significant or progressive retinopathy • blood pressure is particularly high or resistant to treatment • the person previously had a documented normal ACR and develops heavy proteinuria (ACR > 100 mg/mmol) • significant haematuria is present • the glomerular filtration rate has worsened rapidly • the person is systemically ill. [1.12.5]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
Discuss the significance of a finding of abnormal albumin excretion rate, and its trend over time, with the individual concerned. [1.12.6]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
Start ACE inhibitors with the usual precautions and titrate to full dose in all individuals with confirmed raised albumin excretion rate (> 2.5 mg/mmol for men, > 3.5 mg/mmol for women). [1.12.7]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
Have an informed discussion before starting an ACE inhibitor in a woman for whom there is a possibility of pregnancy, assessing the relative risks and benefits of the use of the ACE inhibitor. [1.12.8]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
Substitute an angiotensin II-receptor antagonist for an ACE inhibitor for a person with an abnormal albumin:creatinine ratio if an ACE inhibitor is poorly tolerated. [1.12.9]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
For a person with an abnormal albumin:creatinine ratio, maintain blood pressure below 130/80 mmHg. [1.12.10]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
Agree referral criteria for specialist renal care between local diabetes specialists and nephrologists.[1.12.11]	Recommendations on chronic kidney disease in NICE clinical guideline 87 have been updated by NICE clinical guideline 182.
For the management of foot problems relating to type 2 diabetes, follow recommendations in Type 2 diabetes: prevention and management of foot problems (NICE clinical guideline 10). [1.14.1]	NICE clinical guideline 10 is currently being updated and replaced. We will cross refer to the updated guideline on diabetic foot problems.
Make a formal enquiry annually about the	Will be deleted and will cross refer to

development of neuropathic symptoms causing distress. • Discuss the cause and prognosis (including possible medium-term remission) of troublesome neuropathic symptoms, if present (bearing in mind alternative diagnoses). • Agree appropriate therapeutic options and review understanding at each clinical contact. [1.14.2.1]	neuropathic pain (NICE clinical guideline 173).
Be alert to the psychological consequences of chronic, painful diabetic neuropathy and offer psychological support according to the needs of the individual. [1.14.2.2]	Will be deleted and will cross refer to neuropathic pain (NICE clinical guideline 173).
If neuropathic symptoms cannot be controlled adequately, it may be helpful to further discuss: • the reasons for the problem • the likelihood of remission in the medium term • the role of improved blood glucose control. [1.14.2.7]	Will be deleted and will cross refer to neuropathic pain (NICE clinical guideline 173).

Preface

In 2007, the Centers for Disease Control and Prevention in the USA took the step, unusual for a non-infectious disease, of classifying the increase in the incidence of diabetes as an epidemic, their projections suggesting that the prevalence of this already common disease will have doubled by 2050. In the UK, diabetes already affects approximately 1.9 million adults overall, and some estimates suggest that there are an additional 0.5 million with undiagnosed diabetes.[a] This makes diabetes one of the commonest of all chronic medical conditions, and represents a huge potential problem for our health services.

Over 90% of people with diabetes have Type 2 diabetes. This is still perceived as the milder form, and while this may be true in some respects, such as the risk of ketoacidosis, the causation of Type 2 diabetes is more complex and the management is not necessarily easier. Type 2 diabetes can cause severe complications, affecting the eye, the nervous system and the kidney. The overall risk of cardiovascular disease is more than doubled, and life expectancy is reduced by an average 7 years. In 2002, NICE published a suite of five guidelines dealing with different aspects of the care of Type 2 diabetes. The rising prevalence of the disease, and the range of complications which can arise, reinforce the importance of up-to-date guidance and accordingly NICE have asked the National Collaborating Centre for Chronic Conditions (NCC-CC) to produce this guideline, amalgamating and updating the previously published work.

The guideline is informed by extensive literature and covers many aspects of diabetes management, although it is not intended to be a comprehensive textbook. It covers those topics of particular relevance to life expectancy such as control of cholesterol and lipid levels, and management of hypertension. It deals with major complications such as renal disease. There are also key recommendations in areas of great importance to patients such as structured education and the monitoring of glucose levels. Naturally, there are also sections dealing with control of blood glucose levels and the use of the various drugs available for this purpose.

The guideline development group(GDG) have had a particularly difficult task during development. The remit they were given was unusually large, and I have already mentioned the vast amount of evidence which they were required to consider. They were required to incorporate several existing NICE technology appraisals (TAs) within the guideline. In addition, they had to contend with a major safety scare over one of the glucose lowering agents which evolved over the course of guideline development. It is a measure of their commitment and appetite for hard work that, despite the size of the existing task, they were frustrated rather than relieved at not being able to include information about newer agents such as the DPP-4 inhibitors, the first of which was licensed towards the end of the development process (these agents will be covered at a later date in a separate, short guideline). All at the NCC-CC are extremely grateful to the GDG for the tremendous effort they have put into producing this guideline on schedule. The challenge now is to implement its recommendations and to make a genuine difference to the well-being and health of those with Type 2 diabetes.

Dr Bernard Higgins MD FRCP

Director, National Collaborating Centre for Chronic Conditions

a Department of Health. Health survey for England 2003. London: Stationary Office, 2004.

1 Introduction

1.1 Background

The underlying disorder is usually that of a background of insulin insensitivity plus a failure of pancreatic insulin secretion to compensate for this.The insulin deficiency is progressive over time, such that the high glucose levels usually worsen relentlessly over a timescale of years, requiring continued escalation of blood glucose lowering therapy. The worsening insulin deficiency with age also means that diabetes can appear in elderly people who are quite thin. In some people in middle age the condition can be difficult to distinguish from slow onset Type 1 diabetes.

In people whose hyperglycaemia has yet to be treated, glucose metabolism may be sufficiently disturbed to cause symptoms, typically of polyuria, thirst, weight loss and fatigue. Diabetic coma (ketoacidosis) is uncommon in Type 2 diabetes unless exacerbating factors (infection, drugs) are present, but insulin deficiency and high sugar intake can lead to a related state (hyperosmolar coma).

Type 2 diabetes is notable for the increased cardiovascular risk that it carries. This can be manifest as coronary artery disease (heart attacks, angina), peripheral artery disease (leg claudication, gangrene), and carotid artery disease (strokes, dementia). Many people with Type 2 diabetes have the same risk of a cardiovascular event as someone without diabetes who has already had their first heart attack; people with diabetes and a previous cardiovascular event are at very high risk – around 10 times the background population. Accordingly management of cardiovascular risk factors plays a large part in care of people with Type 2 diabetes, and is particularly cost effective.

Because of the problems of maintaining good blood glucose control associated with the increasing insulin deficiency, the degree of hyperglycaemia occurring in some individuals is sufficient to give rise to a risk of the specific ('microvascular') complications of diabetes. Due to early death caused by cardiovascular disease these are less common than in people with Type 1 diabetes, but include eye damage (sometimes blindness), kidney damage (sometimes requiring dialysis or transplantation), and nerve damage (resulting in amputation, painful symptoms, erectile dysfunction, and other problems).

This situation of multiple vascular risk factors and multiple complications leads to multiple targets for reduction of risk and improvement of health in people with Type 2 diabetes. Such targets for management include obesity, activity levels, plasma glucose control, blood pressure control, blood lipid control, reduction of thrombogenicity, laser therapy for eye damage, drug therapy to delay kidney damage, local foot care, and symptomatic treatments for various types of nerve damage. As a result diabetes care is typically complex and time consuming.

The necessary lifestyle changes, the complexities of management, and the side effects of therapy, together make self-monitoring and education for people with diabetes central parts of management.

1.2 Definition

The GDG worked to the World Health Organization (WHO) definition of diabetes, which requires a degree of high plasma glucose levels sufficient to put the individual at risk of the specific (microvascular) complications of diabetes. Diagnosis is not addressed in this guideline. This definition was reconfirmed by the WHO in 2006, but, like earlier versions, does not contain a specific definition for Type 2 diabetes.[2]

People are normally thought to have Type 2 diabetes if they do not have Type 1 diabetes (rapid onset, often in childhood, insulin-dependent, ketoacidosis if neglected) or other medical conditions or treatment suggestive of secondary diabetes. However, there can be uncertainty in the diagnosis particularly in overweight people of younger age. A further area of confusion is the group of disorders classified as monogenetic diabetes – formally Maturity Onset Diabetes of the Young (MODY) – which are usually not insulin requiring but which present in the first decades of life.

It is noted that Type 1 diabetes with onset after childhood can be confused with Type 2 diabetes. However, lower body weight, more rapid progression to insulin therapy, and absence of features of the metabolic syndrome often give useful distinguishing clues.

1.3 Prevalence

The prevalence of diabetes in the UK is increasing as is the prevalence of obesity, decreased physical activity, but also increased longevity after diagnosis thanks to better cardiovascular risk protection. The current prevalence of Type 2 diabetes is unknown, and will vary with factors such as mix of ethnic groups and degree of social deprivation.

Table 1.1 The prevalence of doctor-diagnosed diabetes (2003)[3]

	Men (≥55 years)	Women (≥55 years)
General population (%)	4.3	3.4
Black Caribbean	10.0	8.4
Black African	5.0	2.1
Indian	10.1	5.9
Pakistani	7.3	8.6
Bangladeshi	8.2	5.2
Chinese	3.8	3.3
Irish	3.6	2.3

Prevalence estimates vary from around 3.5 to 5.0%, the third edition of the International Diabetes Federation (IDF) Atlas suggesting 4.0%, being 1.71 million in the 20- to 79-year-old age group, of whom it is conventional to assume 85% have Type 2 diabetes.[4] Current prevalence estimates are a poor pointer to future burden of diabetes due to their continuing increase. The healthcare burden is also affected by the improved longevity of people with diabetes with better management, which means that overall they carry a larger burden of complications and insulin deficiency needing more complex care.

1.4 Health and resource burden

Mortality attributed to people with diabetes is suggested as 4.2% of deaths in men and 7.7% of deaths in women in the UK. These are likely to be underestimates as deaths from vascular events such as stroke and myocardial infarction (MI) are notorious for under-recording of the underlying causative disease. In a population-based study in Cardiff, at a time when population prevalence was only 2.5%, deaths in people with diabetes accounted for over 10% of the total, with around 60% attributable to diabetes.[5] Life years lost vary considerably with factors such as blood glucose, blood pressure and blood lipid control, and smoking, as well as age, and can be estimated by comparing United Kingdom Prospective Diabetes

Study (UKPDS) risk engine estimates to UK government statistical tables. Typically a 60-year-old man, newly diagnosed and without existing arterial disease can expect to lose 8–10 years of life without proper management.

The direct cost of Type 2 diabetes to the NHS is unknown, as much is classified as cardiovascular or renal disease. However, with prevalence estimates of 3.5–5.0%, and healthcare costs double those of the background population or more, estimates of 7–12% of total NHS expenditure seem not unreasonable. The IDF Atlas notes that in industrialised countries healthcare costs in people with diabetes tend to be double those of the background population. This suggests a £2.8 billion attributable cost for the UK for 2007.[4]

2 Methodology

2.1 Aim

The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide a user-friendly, clinical, evidence-based guideline for the NHS in England and Wales that:

- offers best clinical advice for the management of Type 2 diabetes
- is based on best published clinical and economic evidence, alongside expert consensus
- takes into account patient choice and informed decision making
- defines the major components of NHS care provision for Type 2 diabetes
- details areas of uncertainty or controversy requiring further research
- provides a choice of guideline versions for differing audiences.

2.2 Scope

The guideline was developed in accordance with a scope, which detailed the remit of the guideline originating from the Department of Health (DH) and specified those aspects of Type 2 diabetes care to be included and excluded. The application of the guideline to children has not been excluded but we were not able to specifically search for paediatric literature due to volume of work. When health carers are applying these guidelines to children they need to use their clinical judgement in doing so. For further assistance with applying this guideline to children please refer to the British National Formulary (BNF) for children.[6]

Prior to the commencement of the guideline development, the scope was subjected to stake-holder consultation in accordance with processes established by the National Institute for Health and Clinical Excellence (NICE).1 The full scope is shown in appendix B. Available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

2.3 Audience

The guideline is intended for use by the following people or organisations:

- all healthcare professionals
- people with Type 2 diabetes and their parents and carers
- patient support groups
- commissioning organisations
- service providers.

2.4 Involvement of people with type 2 diabetes

The NCC-CC was keen to ensure the views and preferences of people with Type 2 diabetes and their carers informed all stages of the guideline. This was achieved by:

- having two people with Type 2 diabetes as patient representatives on the GDG
- consulting the Patient and Public Involvement Programme (PPIP) housed within NICE during the pre-development (scoping) and final validation stages of the guideline project
- the inclusion of patient groups as registered stakeholders for the guideline.

2.5 Guideline limitations

The guideline has the following limitations.

- NICE clinical guidelines usually do not cover issues of service delivery, organisation or provision (unless specified in the remit from the DH).
- NICE is primarily concerned with health services and so recommendations are not provided for social services and the voluntary sector. However, the guideline may address important issues in how NHS clinicians interface with these other sectors.
- Generally, the guideline does not cover rare, complex, complicated or unusual conditions.
- Where a meta-analysis was available, generally the individual papers contained within were not appraised.
- It is not possible in the development of a clinical guideline to complete an extensive systematic literature review of all pharmacological toxicity, although NICE expect their guidelines to be read alongside the summaries of product characteristics (SPCs).

2.6 Other work relevant to the guideline

The guideline will update the following NICE technology appraisals (TAs) but only in relation to Type 2 diabetes:

- 'Guidance on the use of glitazones for the treatment of Type 2 diabetes', NICE technology appraisal guidance no. 63 (2003)
- 'Guidance on the use of patient-education models for diabetes', NICE technology appraisal guidance no. 60 (2003)
- 'Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine', NICE technology appraisal guidance no. 53 (2002).

Related NICE public health guidance:

- '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', Public health programme guidance no. PH010 (February 2008)
- 'Physical activity guidance for the Highways Agency, local authorities, primary care, pharmacists, health visitors and community nurses, schools, workplaces, the leisure and fitness industry and sports clubs', Public health programme guidance no. PH008 (January 2007).

Related NICE clinical guidelines:

- 'Cardiovascular risk assessment: the modification of blood lipids for the primary and secondary prevention of cardiovascular disease' (expected date of publication May 2008)
- 'Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period', NICE clinical guideline no. 63 (2008)
- 'Hypertension: management of hypertension in adults in primary care' (partial update of NICE CG18), NICE clinical guideline no. 34 (2006)
- 'Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children', NICE clinical guideline no. 43 (2006)
- 'Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults', NICE clinical guideline no. 15 (2004, to be reviewed 2008)
- 'Type 2 diabetes: prevention and management of foot problems', NICE clinical guideline no. 10 (2004).

Related TA guidance:

- 'Guidance on the use of ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia', NICE technology appraisal guidance no. 132 (2007)
- 'Guidance on the use of statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease', NICE technology appraisal guidance no. 94 (2006)
- 'Guidance on the use of inhaled insulin for the treatment of Type 1 and Type 2 diabetes',

NICE technology appraisal guidance no. 113 (2006)

- 'Guidance on the use of clopidogrel and dipyridamole for the prevention of artherosclerotic events', NICE technology appraisal guidance no. 90 (2005)
- 'Guidance on the use of the clinical effectiveness and cost effectiveness of insulin pump therapy', NICE technology appraisal guidance no. 57 (2003).

2.7 Background

The development of this evidence-based clinical guideline draws upon the methods described by the NICE's 'Guideline development methods manual'[1] and the methodology pack[7] specifically developed by the NCC-CC for each chronic condition guideline (see www.rcplondon.ac.uk/clinical-standards/ncc-cc/Pages/NCC-CC.aspx). The developers' role and remit is summarised in table 2.1.

Table 2.1 Role and remit of the developers	
NCC-CC	The NCC-CC was set up in 2001 and is housed within the Royal College of Physicians (RCP). The NCC-CC undertakes commissions received from NICE. A multiprofessional partners' board inclusive of patient groups and NHS management governs the NCC-CC.
NCC-CC Technical Team	The technical team met approximately two weeks before each GDG meeting and comprised the following members: GDG Chair GDG Clinical Adviser Information Scientist Two Research Fellows Health Economist Project Manager.
GDG	The GDG met monthly (June 2006 to July 2007) and comprised a multidisciplinary team of professionals and people with Type 2 diabetes who were supported by the technical team. The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline.
Guideline Project Executive	The Project Executive was involved in overseeing all phases of the guideline. It also reviewed the quality of the guideline and compliance with the DH remit and NICE scope. The Project Executive comprises: NCC- CC Director NCC-CC Assistant Director NCC- CC Manager NICE Commissioning Manager Technical Team.
Formal consensus	At the end of the guideline development process the GDG met to review and agree the guideline recommendations.
Members of the GDG declared any interests in accordance with the NICE technical manual.[1] A register is given in appendix D, available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247	

2.8 The process of guideline development

The basic steps in the process of producing a guideline are:

- developing clinical evidence-based questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- grading the evidence statements
- agreeing the recommendations

- structuring and writing the guideline
- updating the guideline.

Developing evidence-based questions

The technical team drafted a series of clinical questions that covered the guideline scope. The GDG and Project Executive refine and approve these questions, which are shown in appendix A. Available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

Searching for the evidence

The information scientist developed a search strategy for each question. Key words for the search were identified by the GDG. In addition, the health economist searched for additional papers providing economic evidence or to inform detailed health economic work (for example, modelling). Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence by the GDG. Conference paper abstracts and non-English language papers were excluded from the searches.

Each clinical question dictated the appropriate study design that was prioritised in the search strategy but the strategy was not limited solely to these study types. The research fellow or health economist identified titles and abstracts from the search results that appeared to be relevant to the question. Exclusion lists were generated for each question together with the rationale for the exclusion. The exclusion lists were presented to the GDG. Full papers were obtained where relevant. See appendix A for literature search details. Available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

Appraising the evidence

The research fellow or health economist, as appropriate, critically appraised the full papers. In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details. Critical appraisal checklists were compiled for each full paper. One research fellow undertook the critical appraisal and data extraction. The evidence was considered carefully by the GDG for accuracy and completeness.

All procedures are fully compliant with the:

- NICE methodology as detailed in the 'Guideline Development Methods – Information for National Collaborating Centres and Guideline Developers' Manual[1]
- NCC-CC quality assurance document and systematic review chart available at www.rcplondon.ac.uk/clinical-standards/ncc-cc/Pages/NCC-CC.aspx.

Health economic evidence

Areas for health economic modelling were agreed by the GDG after the formation of the clinical questions. The health economist reviewed the clinical questions to consider the potential application of health economic modelling, and these priorities were agreed with the GDG.

The health economist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

Distilling and synthesising the evidence and developing recommendations

The evidence from each full paper was distilled into an evidence table and synthesised into evidence statements before being presented to the GDG. This evidence was then reviewed

by the GDG and used as a basis upon which to formulate recommendations. The criteria for grading evidence are shown in table 2.2.

Evidence tables are available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

Grading the evidence statements

Table 2.2 Grading the evidence statements[1]

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.*
2++	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.*
3	Non-analytic studies (for example case reports, case series).
4	Expert opinion, formal consensus.

*Studies with a level of evidence '–' are not used as a basis for making a recommendation.
RCT, randomised controlled trial

Agreeing the recommendations

The GDG employed formal consensus techniques to:

- ensure that the recommendations reflected the evidence base
- approve recommendations based on lesser evidence or extrapolations from other situations
- reach consensus recommendations where the evidence was inadequate
- debate areas of disagreement and finalise recommendations.

The GDG also reached agreement on the following:

- five recommendations as key priorities for implementation
- five key research recommendations
- algorithms.

In prioritising key recommendations for implementation, the GDG took into account the following criteria:

- high clinical impact
- high impact on reducing variation
- more efficient use of NHS resources

- allowing the patient to reach critical points in the care pathway more quickly.

Audit criteria for this guideline will be produced for NICE by Clinical Accountability Service Planning and Evaluation (CASPE) Research following publication in order to provide suggestions of areas for audit in line with the key recommendations for implementation.

Structuring and writing the guideline

The guideline is divided into sections for ease of reading. For each section the layout is similar and contains the following parts.

- *Clinical introduction* sets a succinct background and describes the current clinical context.
- *Methodological introduction* describes any issues or limitations that were apparent when reading the evidence base.
- *Evidence statements* provide a synthesis of the evidence base and usually describes what the evidence showed in relation to the outcomes of interest.
- *Health economics* presents, where appropriate, an overview of the cost effectiveness evidence base, or any economic modelling.
- *From evidence to recommendations* sets out the GDG decision-making rationale providing a clear and explicit audit trail from the evidence to the evolution of the recommendations.
- *Recommendations* provide stand alone, action-orientated recommendations.
- *Evidence tables* are not published as part of the full guideline but are available online at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247. These describe comprehensive details of the primary evidence that was considered during the writing of each section.

Writing the guideline

The first draft version of the guideline was drawn up by the technical team in accord with the decisions of the GDG, incorporating contributions from individual GDG members in their expert areas and edited for consistency of style and terminology. The guideline was then submitted for a formal public and stakeholder consultation prior to publication. The registered stakeholders for this guideline are detailed on the NICE website, www.nice.org.uk. Editorial responsibility for the full guideline rests with the GDG.

Table 2.3 Versions of this guideline

Full version	Details the recommendations, the supporting evidence base and the expert considerations of the GDG. Published by the NCC-CC. Available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247
NICE version	Documents the recommendations without any supporting evidence. Available at www.nice.org.uk
'Quick reference guide'	An abridged version. Available at www.nice.org.uk
'Understanding NICE guidance'	A lay version of the guideline recommendations. Available at www.nice.org.uk

Updating the guideline

Literature searches were repeated for all of the evidence-based questions at the end of the GDG development process allowing any relevant papers published up until 16 April 2007 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Two years after publication of the guideline, NICE will ask a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update. If not, the guideline will be considered for update approximately 4 years after publication.

2.9 Disclaimer

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

The NCC-CC disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

2.10 Funding

The NCC-CC was commissioned by NICE to undertake the work on this guideline.

3 Key messages of the guideline

3.1 Key priorities for implementation

Offer structured education to every person and/or their carer at and around the time of diagnosis, with annual reinforcement and review. Inform people and their carers that structured education is an integral part of diabetes care.

Provide individualised and ongoing nutritional advice from a healthcare professional with specific expertise and competencies in nutrition.

When setting a target glycated haemoglobin (GHb):

- involve the person in decisions about their individual HbA1c target level, which may be above that of 6.5 % set for people with Type 2 diabetes in general
- encourage the person to maintain their individual target unless the resulting side effects (including hypoglycaemia) or their efforts to achieve this impair their quality of life
- offer therapy (lifestyle and medication) to help achieve and maintain the HbA1c target level
- inform a person with a higher HbA1c that any reduction in HbA1c towards the agreed target is advantageous to future health
- avoid pursuing highly intensive management to levels of less than 6.5 %.

Offer self-monitoring of plasma glucose to a person newly diagnosed with Type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon.

When starting insulin therapy, use a structured programme employing active insulin dose titration that encompasses:

- structured education
- continuing telephone support
- frequent self-monitoring
- dose titration to target
- dietary understanding
- management of hypoglycaemia
- management of acute changes in plasma glucose control
- support from an appropriately trained and experienced healthcare professional.

3.2 Algorithms

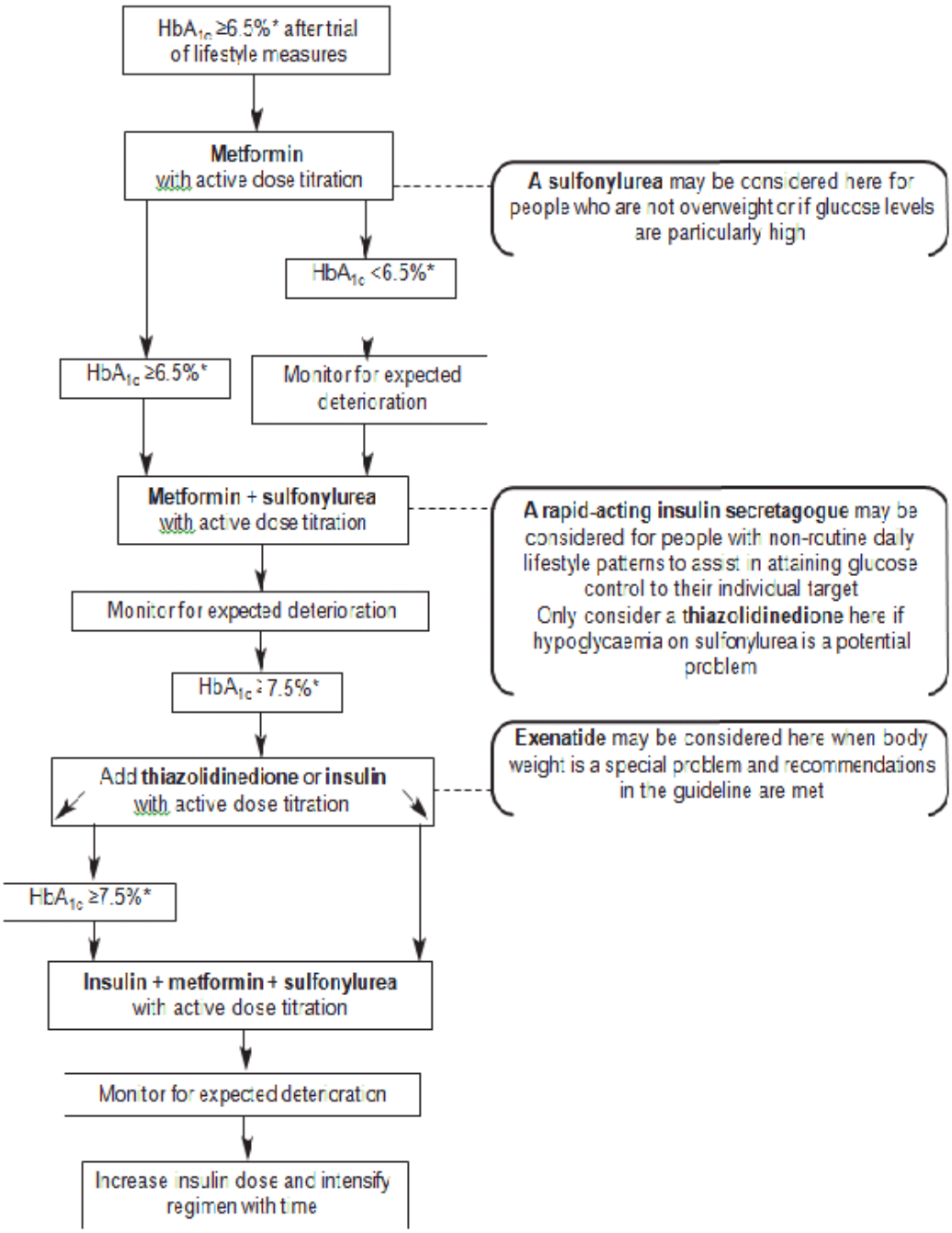

Figure 3.1 Scheme for the pharmacotherapy of glucose lowering in people with Type 2 diabetes
For details see recommendations on glucose lowering targets, clinical monitoring, use of oral agents, and use of insulin
* or as individually agreed

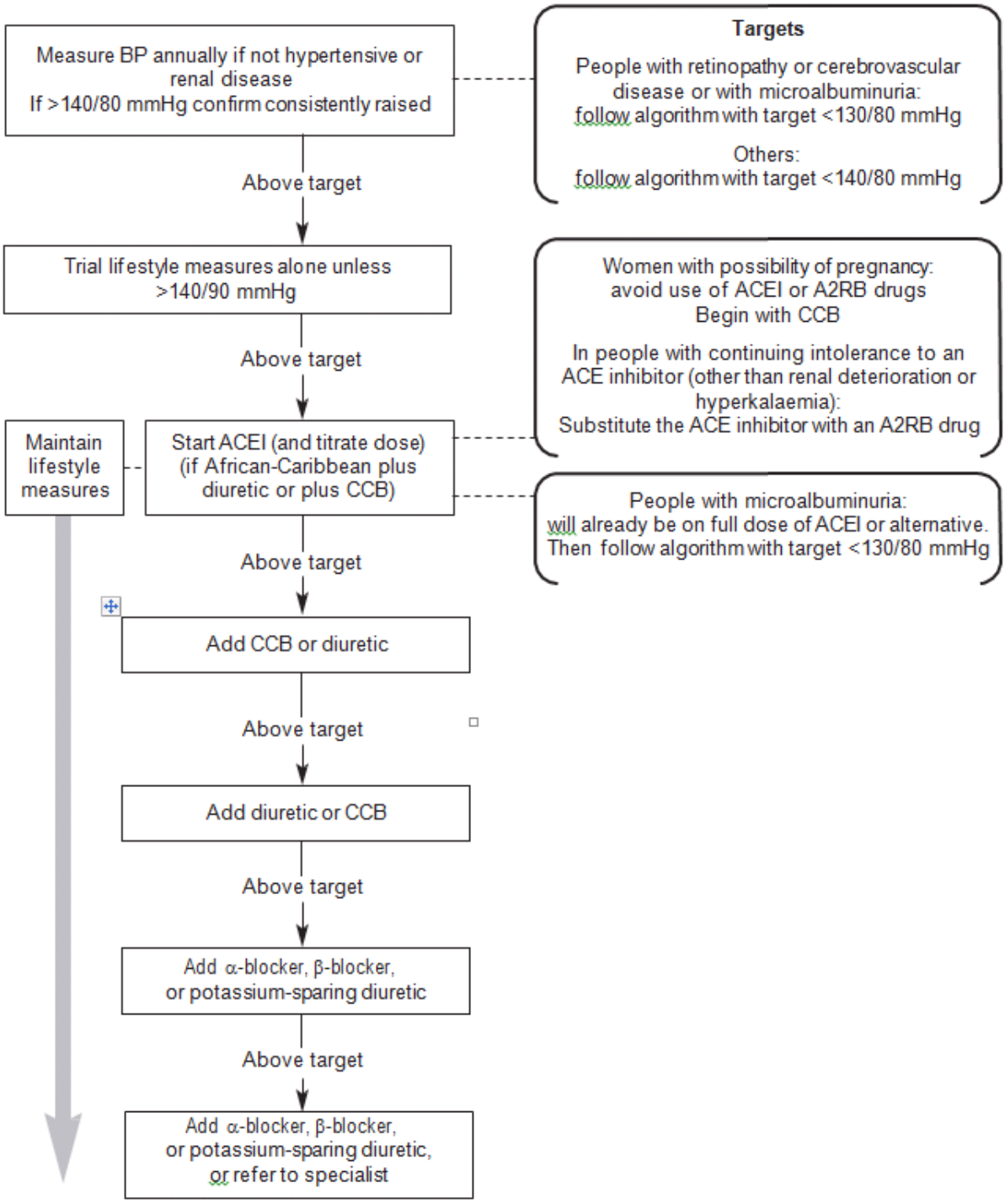

Figure 3.2 Scheme for the management of blood pressure (BP) for people with Type 2 diabetes
ACEI, angiotensin-converting enzyme inhibitor; A2RB, angiotensin 2 receptor blocker (sartan); CCB, calcium channel blocker

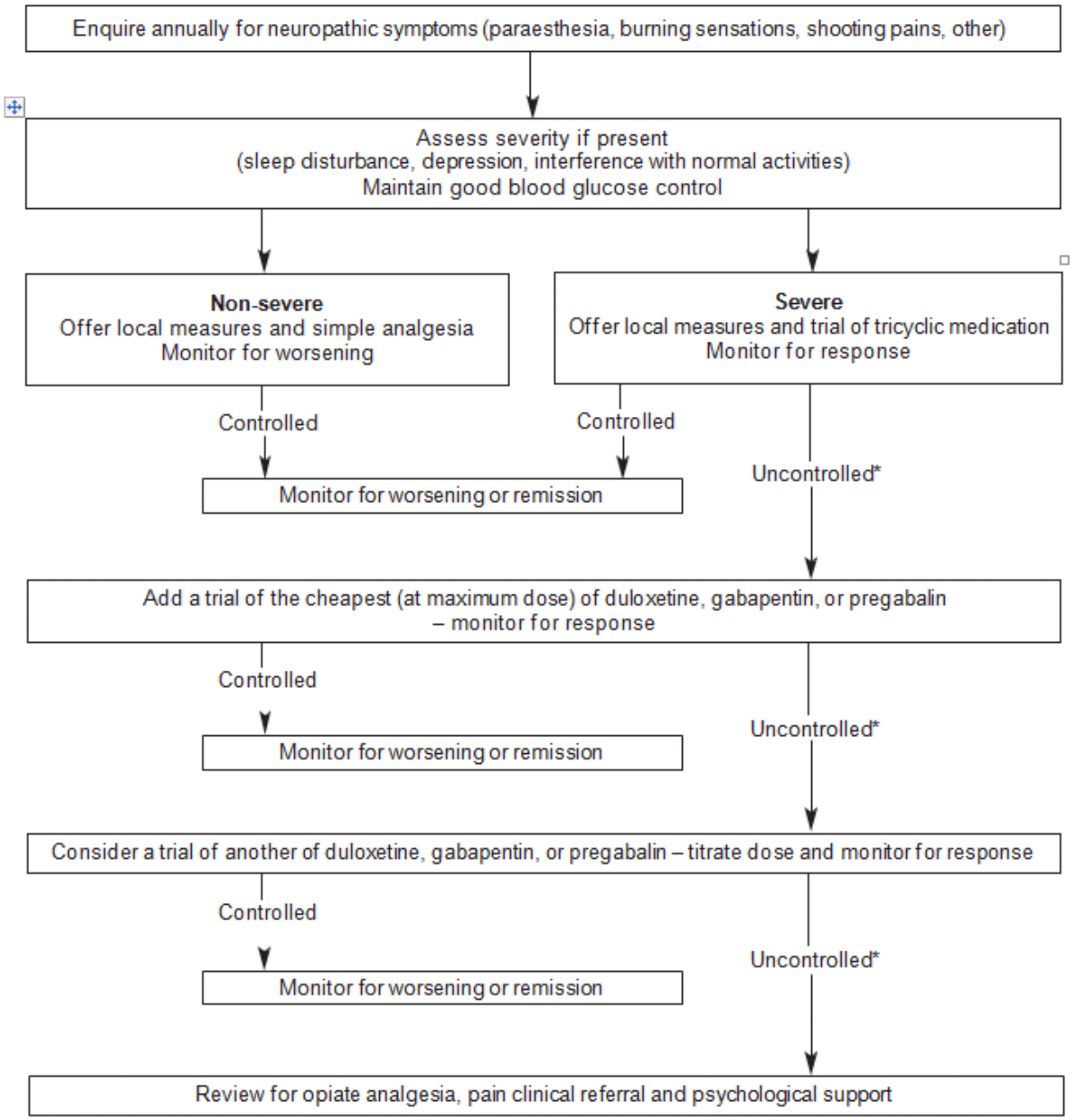

Figure 3.3 Diabetic symptomatic neuropathy management – a therapeutic summary
*Where neuropathic symptoms cannot be adequately controlled it is useful, to help individuals cope, to explain the reasons for the problem, the likelihood of remission in the medium term, the role of improved blood glucose control

4 Glossary and definitions

ACEI Angiotensin-converting enzyme inhibitor

ACR Albumin creatinine ratio

ADA American Diabetes Association

AER Albumin excretion rate – a measure of kidney damage due to diabetes (and other conditions) and a risk factor for arterial disease.

Albuminuria The presence of albumin and other proteins in urine.

Alpha-glucosidase inhibitors Group of drugs which inhibit the digestion of complex carbohydrates in the gut, and thus flatten the post-meal blood glucose excursion.

BMI Body mass index – a index of body weight corrected for height.

Cohort study A retrospective or prospective follow-up study. Groups of individuals to be followed up are defined on the basis of presence or absence of exposure to a suspected risk factor or intervention. A cohort study can be comparative, in which case two or more groups are selected on the basis of differences in their exposure to the agent of interest.

CKD Chronic kidney disease

Confidence interval (CI) A range of values which contains the true value for the population with a stated 'confidence' (conventionally 95%). The interval is calculated from sample data, and generally straddles the sample estimate. The 95% confidence value means that if the study, and the method used to calculate the interval, is repeated many times, then 95% of the calculated intervals will actually contain the true value for the whole population.

Cochrane review The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).

Concordance Concordance is a concept reflecting the extent to which a course of action agreed between clinicians and a person with diabetes is actually carried out; often but not solely used in the sense of therapeutic interventions or behavioural changes.

Cost-effectiveness analysis An economic study design in which consequences of different interventions are measured using a single outcome, usually in natural units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.

Cost-utility analysis A form of cost-effectiveness analysis in which the units of effectiveness are quality adjusted life years.

DCCT Diabetes Control and Complications Trial – a landmark study of the effects of intensification of diabetes care on development of microvascular complications.

Diabetes centre A generic term for a source of a unified multidisciplinary diabetes service.

Diabetes mellitus Chronic condition characterised by elevated blood glucose levels. Diabetes is of diverse aetiology and pathogenesis, and should not be regarded as a single disease. Predominant types are Type 1 diabetes and Type 2 diabetes, diabetes secondary to other pancreatic disease or other endocrine disease, and diabetes of onset in pregnancy.

Diabetes UK Self-help charity for people with diabetes in the UK, and a professional organisation for diabetes care.

Education In the context of this guideline, patient education in self- management of everyday diabetes issues like insulin therapy, dietary changes, self-monitoring of glucose level, physical exercise, coping with concurrent illness, how to avoid hypoglycaemia, complications, arterial risk control, jobs, travel, etc.

FBG Fasting blood glucose level or concentration

FPG Fasting plasma glucose level or concentration

Framingham equation A widely known and used calculation of arterial risk, derived from a long-term study in Framingham, Massachusetts. Not valid in people with Type 1 or Type 2 diabetes.

GDG Guideline Development Group

Glucose excursions Change in blood glucose levels especially after meals.

GFR Glomerular filtration rate – a measure of kidney function.

GHb Glycated haemoglobin – see HbA1c.

GI Gastrointestinal

HbA1c The predominant form of glycated haemoglobin, present in red blood cells, and formed when the normal haemoglobin A reacts non-enzymatically with glucose. As the reaction is slow and only concentration dependent, the amount of HbA1c formed is proportional only to the concentration of HbA and glucose. As HbA remains in the circulation for around 3 months, the amount of HbA1c present, expressed as a percentage of HbA, is proportional to the glucose concentration over that time.

HTA Health Technology Assessment, funded by the NHS Research and Development Directorate.

IDF International Diabetes Federation – a global federation of diabetes associations.

Incremental cost The cost of one alternative less the cost of another.

Incremental cost effectiveness ratio The ratio of the difference in costs between two alternatives to the difference in effectiveness between the same two alternatives. (ICER)

Insulin analogues A derivative of human insulin in which change of the amino-acid sequence alters duration of action after injection.

Insulin regimen A therapeutic combination of different insulin preparations, including time of injection and frequency during a day.

IHD Ischaemic heart disease

Meta-analysis A statistical technique for combining (pooling) the results of a number of studies that address the same question and report on the same outcomes to produce a summary result.

Metabolic syndrome Overweight (abdominal adiposity), insulin insensitivity, higher blood pressure, abnormal blood fat profile.

Methodological limitations Features of the design or reporting of a clinical study which are limitations known to be associated with risk of bias or lack of validity. Where a study is reported in this guideline as having significant methodological limitations, a recommendation has not been directly derived from it.

MI Myocardial infarction

Microalbuminuria A low but clinically significant level of albumin and other proteins in the urine.

NCC-CC The National Collaborating Centre for Chronic Conditions, set up in 2000 to undertake commissions from the NICE to develop clinical guidelines for the NHS.

NHS National Health Service – this guideline is written for the NHS in England and Wales.

NICE National Institute for Health and Clinical Excellence – a special health authority set up within the NHS to develop appropriate and consistent advice on healthcare technologies, and to commission evidence-based guidelines.

NPH insulin Neutral protamine Hagedorn insulin – a basal insulin, named after the Danish researcher Hans Christian Hagedorn, and developed in the 1940s. Synonymous with isophane insulin.

NS Not significant (at the 5% level unless stated otherwise).

NSC National Screening Committee (UK)

NSF National Service Framework – a nationwide initiative designed to improve delivery of care for a related group of conditions.

Observational study Retrospective or prospective study in which the investigator observes the natural course of events with or without control groups, for example cohort studies and case-control studies.

Odds ratio A measure of relative treatment effectiveness. An odds ratio of 1 means equality between the comparisons in the study, and higher numbers mean greater differences. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group.

PDE5 inhibitors Phosphodiesterase type 5 inhibitors, a class of drugs developed in recent years to treat erectile dysfunction.

PROCAM Prospective Cardiovascular Münster Heart Study – an epidemiological study performed in Germany.

Proteinuria The presence of protein in the urine.

p-values The probability that an observed difference could have occurred by chance. A p-value of less than 0.05 is conventionally considered to be 'statistically significant'.

Quality of life A term used to describe an individual's level of satisfaction with their life and general sense of well-being. It is often measured as physical, psychological and social well-being.

Quality of life-adjusted A measure of health outcome which assigns to each period of time year (QALY) a weight, ranging from 0 to 1, corresponding to the health-related quality of life during that period, where a weight of 1 corresponds to optimal health, and a weight of 0 corresponds to a health state judged equivalent to death; these are then aggregated across time periods.

RCT Randomised controlled trial. A trial in which people are randomly assigned to two (or more) groups – one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences

in outcomes to see how effective the experimental treatment was. Such trial designs help minimise experimental bias.

RR Relative risk

Sensitivity analysis A measure of the extent to which small changes in parameters and variables affect a result calculated from them. In this guideline, sensitivity analysis is used in health economic modelling.

Short-form 36 (SF-36) The SF-36 assesses functioning and well-being in chronic disease. Thirty-six items in eight domains are included, which cover functional status, well-being, and overall evaluation of health.

Specialist A clinician whose practice is limited to a particular branch of medicine or surgery, especially one who is certified by a higher medical educational organisation.

Stakeholder Any national organisation, including patient and carers' groups, healthcare professionals and commercial companies with an interest in the guideline under development.

Statistical significance …A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).

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.

Technology appraisal Formal ascertainment and review of the evidence surrounding a health technology, restricted in the current document to appraisals undertaken by NICE.

Thiazolidinediones A group of drugs which improve insulin sensitivity in people with reduced sensitivity to their own or injected insulin; presently the licensed drugs are both of the chemical group known as trivially 'glitazones' or PPAR-□□agonists.

Type 1 diabetes Insulin-deficiency disease, developing predominantly in childhood, characterised by hyperglycaemia if untreated, and with a consequent high risk of vascular damage usually developing over a period of decades.

Type 2 diabetes Diabetes generally of slow onset mainly found in adults and in association with features of the metabolic syndrome. Carries a very high risk of vascular disease. While not insulin dependent many people with the condition eventually require insulin therapy for optimal blood glucose control.

UAER Urinary albumin excretion rate

UKPDS United Kingdom Prospective Diabetes Study – a landmark study of the effect of different diabetes therapies on vascular complications in people with Type 2 diabetes.

WHO World Health Organization

5 Glucose control levels

5.1 Clinical monitoring of blood glucose levels

5.1.1 Clinical introduction

The risk of arterial disease and microvascular complications in people with diabetes are known to be related to the extent of hyperglycaemia with time. While the lifestyle, oral agent, and injectable therapies discussed in this guideline can improve blood glucose control, their efficacy is limited, as the underlying pathogenesis of diabetes worsens with time. As symptoms are not a reliable guide to blood glucose control in people on therapy, it is important to have an accurate means of measuring blood glucose control over time, to enable decision-making.

This section addresses the clinical questions as to the tests of blood glucose control best predictive of future vascular damage from diabetes, the nature of the relationship between test results and such vascular risk, how tests should be deployed in clinical practice, and how they might be interpreted.

5.1.2 Methodological introduction

The UKPDS is a large (N=3,867) landmark study with a 10-year follow-up period. It evaluated whether in people newly diagnosed with Type 2 diabetes more intense therapy to achieve tighter glycaemic control would result in a greater reduction in the incidence of microvascular and macrovascular complications than would conservative therapy. Due to the size and duration of this study, other studies published from 2001 onwards in this area were only considered if they had a sample size of at least N=2,000 people with Type 2 diabetes, or mixed Type 1 and 2 diabetes populations. Studies were not reviewed if they simply found significant associations between HbA1c and diabetes complications without giving further information about that association.

Published results from the UKPDS were included in this review if they specifically reported results on the relationship between HbA1c and microvascular and/or macrovascular complications. One prospective observational study[28] was identified which analysed the UKPDS glucose control results in terms of both macrovascular and microvascular complications.

A meta-analysis[29] was also identified which assessed the association between glycosylated haemoglobin and cardiovascular (CV) disease in people with diabetes. This included an analysis of 10 studies specifically of people with Type 2 diabetes. As some of the cohorts included in this analysis were participants in the UKPDS study, it is necessary to be alert to double-counting.

Other observational studies identified, which were not published results of the UKPDS study or included in the meta-analysis, considered the relationship between glycaemic control and CV and renal risk,[30] and between glycaemic control and heart failure

5.1.3 Health economic methodological introduction

One paper was identified which was excluded from further consideration as it was not possible to compare the costs between patients with good or poor control because the well-controlled patients were probably earlier in the course of the disease.[32] Two evaluations based on the UKPDS were identified that were considered to be of good quality.[33]

5.1.4 Evidence statements

- The risk of each of the microvascular and macrovascular complications of Type 2 diabetes and cataract extraction was strongly associated with hyperglycaemia as measured by updated mean HbA1c.
- There was no indication of a threshold for any complication below which risk no longer decreased, nor a level above which risk no longer increased.
-

Table 7.1 UKPDS study[28]
N=3,642 included in the analysis of relative risk
Level of evidence 2++

Microvascular/macrovascular complications or mortality	**1% reduction in updated mean HbA_{1c} was associated with reductions in risk of***
Any endpoint related to diabetes (MI, sudden death, angina, stroke, renal failure, lower extremity amputation or death from peripheral vascular disease, death from hyperglycaemia or hypoglycaemia, heart failure, vitreous haemorrhage, retinal photocoagulation, and cataract extraction)	21%, 95% CI 17% to 24% (p<0.0001)
For deaths related to diabetes (MI, sudden death, stroke, lower extremity amputation or fatal peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia)	21%, 95% CI 15% to 27% (p<0.0001)
All cause mortality	14%, 95% CI 9% to 19% (p<0.0001)
MI (fatal MI, non-fatal MI, and sudden death)	14%, 95% CI 8% to 21% (p<0.0001)
Stroke (fatal and non-fatal stroke)	12%, 95% CI 1% to 21% (p=0.035)
Peripheral vascular disease (lower extremity amputation or death from peripheral vascular disease)	43%, 95% CI 31% to 53% (p<0.0001)
Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or non-fatal renal failure)	37%, 95% CI 33% to 41% (p<0.0001)
Heart failure (non-fatal, without a precipitating MI)	16%, 95% CI 3% to 26% (p=0.016)
Cataract extraction	19%, 95% CI 11% to 26% (p<0.0001)
The adjusted incidence rates for any endpoint related to diabetes increased with each higher category of updated mean HbA_{1c}, with no evidence of a threshold and with a three-fold increase over the range of updated mean HbA_{1c} of less than 6%, to equal to, or more than, 10%.	

* Data adjusted for age at diagnosis of diabetes, sex, ethnic group, smoking, presence of albuminuria, systolic blood pressure, high and low density lipoprotein cholesterol and triglycerides

- There was an increase in CV risk with increasing levels of glycosylated haemoglobin in persons with Type 2 diabetes.

Table 7.2 Meta-analysis of prospective cohort studies[29]
N=10 studies in people with Type 2 diabetes
Level of evidence 2+

Cardiovascular complications or mortality	**Pooled RR for each 1 percentage point increase in glycosylated haemoglobin***
Total CV (combining 10 studies of coronary heart disease alone, stroke alone, and stroke and coronary heart disease combined)	1.18 (95% CI 1.10 to 1.26)
Coronary heart disease (combining five studies of MI, angina and IHD)	1.13 (95% CI 1.06 to 1.20)
Fatal coronary heart disease (combining five studies of fatal MI, angina and IHD)	1.16 (95% CI 1.07 to 1.26)
Cerebrovascular disease (combining three studies of fatal and non-fatal stroke)	1.17 (95% CI 1.09 to 1.25)
Peripheral arterial disease (combining three studies of lower extremity peripheral arterial disease, amputation and claudication)	1.28 (95% CI 1.18 to 1.39)

*All RR estimates in the pooled analyses were from the most fully adjusted multivariate model
IHD, ischaemic heart disease; RR, relative risk

- There was an independent progressive relationship between GHb and incident cardiovascular events, renal disease and death.

Table 7.3 Prospective observational study of participants in the Heart Outcomes Prevention Evaluation (HOPE) study[30]
N=3,529
Level of evidence 2+

Cardiovascular and renal complications	**A 1% absolute rise in updated glycated haemoglobin was associated with relative risks of***
Future CV events (the first occurrence of one or more of the following: non-fatal MI, stroke or CV death)	1.07, 95% CI 1.01 to 1.13 (p=0.014)
Death	1.12, 95% CI 1.05 to 1.19 (p=0.0004)
Hospitalisation for heart failure	1.20, 95% CI 1.08 to 1.33 (p=0.0008)
Overt nephropathy	1.26, 95% CI 1.17 to 1.36 (p=0.0001)
There was a consistent and progressive relationship between the GHb level (both baseline and updated) and the age and sex adjusted relative hazard of the above outcomes. All showed significant trends with the strongest relationships being seen with the updated GHb level	

*After adjusting for age, sex, diabetes duration, blood pressure, BMI, hyperlipidaemia and ramipril

- There was an independent graded association between glycaemic control and incidence of hospitalisation and/or death due to heart failure.

Table 7.4 Observational study of participants on the Kaiser Permanente Medical Care Program of Northern California diabetes registry[31]
N=48,858
Level of evidence 2+

Cardiovascular complications	**The relative risk associated with a 1% increase in HbA_{1c}***
Composite of hospitalisation for heart failure or death with heart failure as the underlying cause	1.08, 95% CI 1.05 to 1.12
A concentration of HbA_{1c} more than or equal to 10% relative to HbA_{1c} less than 7%, was associated with a 1.6 fold increased heart failure risk (for hospitalisation or death)	

* This model was adjusted for age, sex, ethnicity, education level, smoking, alcohol consumption, self-reported hypertension, obesity, cardioprotective medicine used at baseline, type of diabetes and treatment, duration of diabetes and incidence of MI during follow-up

5.1.5 Health economic evidence statements

The UKPDS included an analysis of intensive blood glucose control with metformin for overweight patients compared to conventional treatment primarily with diet. The study included 753 overweight (>120% ideal body weight) patients with newly diagnosed Type 2 diabetes from 15 hospital-based clinics in England, Scotland and Northern Ireland. Of these patients 342 were allocated to an intensive blood glucose control policy with metformin and 411 were allocated to conventional treatment, primarily with diet alone. The study was conducted from 1977 to 1991. The median follow-up period was 10.4 years.

In the conventional policy group the glycaemic goal was to obtain the lowest fasting plasma glucose (FPG) attainable with diet alone. In the intensive policy group the aim was a FPG of less than 6.0 mmol/l by increasing the dose of metformin from 500 to 2,550 mg a day as required. Use of metformin for intensive blood glucose control in overweight patients was found to confer a 32% risk reduction for any diabetes related endpoint and a 42% risk reduction for diabetes related deaths compared with a conventional policy.

In the 2001 cost-effectiveness analysis, intensive treatment with metformin cost on average £258 less than conventional treatment, and resulted in a longer life expectancy of 0.4 years.[34]

In the 2005 cost-utility analysis the discounted cost (6% discount rate) of an intensive blood glucose control policy with insulin or sulphonylureas was on average £884 more per patient and the discounted benefits gained were 0.15 quality of life-adjusted year (QALY), a cost per QALY gained of £6,028.[33]

The discounted cost of intensive blood glucose control policy with metformin in overweight patients was on average £1,021 less than the conventional policy and had a longer discounted life expectancy of 0.55 QALYs, making this intensive treatment strategy both cost-saving and more effective.[34]

5.1.6 From evidence to recommendations

There were a number of difficulties agreeing the level at which therapeutic interventions should begin or be enhanced. It was agreed that people with diabetes and the professionals advising them needed a reference level if optimum glucose control is to be obtained. It was noted that treat-to-target studies achieved much better outcomes than studies with less well defined aims.

The evidence base has not significantly moved on since the earlier guideline, except to support the conclusions of the UKPDS epidemiological analysis (that CV risk fell linearly well into the normal range of HbA1c). A single target figure is unhelpful as this may vary in individuals depending on the:

- quality of life that might have to be sacrificed in reaching the target
- extent of side effects
- resources available for management.

An individual requiring insulin for adequate control, who is at risk and prone to hypoglycaemia would have a higher personal target of glucose control than someone newly diagnosed who had adopted significant lifestyle changes.

Microvascular risk data suggests higher glucose control targets. This led to a stronger recommendation in the NICE/RCP Type 1 diabetes guideline for those at no added macrovascular disease risk. Most of those with Type 2 diabetes can be regarded as at high macrovascular risk, by reason of phenotype or age.

Cardiovascular risk can be reduced by 10–15% per 1.0 % reduction of HbA1c, the treatment effect and epidemiological analysis of UKPDS giving the same conclusions. Mean levels of close to 6.5 % were achieved in the first 5 years of the UKPDS in both the main glucose study and the obese ('metformin') study in the active treatment arms. The epidemiological analysis supports a linear fall in macrovascular risk down to 6.0 % or below, and this will largely reflect data from the more actively managed group.

However, expensive therapies or very intensive interventions are required to achieve glucose control in the normal range in most people with diabetes. Consequently a population target should not be any tighter than the HbA1c of 6.5 % previously chosen for those at macrovascular risk. Nearly all people with Type 2 diabetes are of high CV risk, usually in association with insulin insensitivity, but if not with age. Additionally there has been very recent concern (no evidence yet to review) about pursuing very intensive glucose control (target <6.0 %) in people

with higher CV risk and longer duration of diabetes, mostly on multiple insulin injection therapy.[35]

The GDG were made aware of the issue of postprandial plasma glucose control, and that it could be specifically targeted in some circumstances and with some interventions. A review of the literature in this regard had not been performed for the present guideline. However, the GDG were informed that an evidence-based guideline had been published by the IDF since completion of the current guideline draft, and that no RCTs addressing the question with true health outcomes as an endpoint had been identified. Accordingly a view to treat this aspect specifically relied on weaker evidence. Accordingly the GDG were content only to make recommendations on the identification of pre-meal and postprandial hyperglycaemia, and levels for intervention.

The GDG expressed concern that intervention levels for enhancement of therapy should not be confused with audit or reimbursement standards. These types of standards are set with much greater attention being paid to attainability.

5.1.7 Recommendations

R16 When setting a target glycated haemoglobin HbA1c:

- involve the person in decisions about their individual HbA1c target level, which may be above that of 6.5 % set for people with Type 2 diabetes in general

- encourage the person to maintain their individual target unless the resulting side effects (including hypoglycaemia) or their efforts to achieve this impair their quality of life
- offer therapy (lifestyle and medication) to help achieve and maintain the HbA1c target level
- inform a person with a higher HbA1c that any reduction in HbA1c towards the agreed target is advantageous to future health
- avoid pursuing highly intensive management to levels of less than 6.5 %.

R18 If HbA1c levels remain above target levels, but pre-meal self-monitoring levels remain well controlled (<7.0 mmol/l), consider self-monitoring to detect postprandial hyperglycaemia (>8.5 mmol/l), and manage to below this level if detected

R19 Measure HbA1c using high-precision methods and report results in units aligned with those used in DCCT Trial (or as recommended by national agreement after publication of this guideline).

6 Self-monitoring of plasma glucose

6.1.1 Clinical introduction

Self-monitoring is the only direct method by which a person with diabetes can be aware of their level of control of blood glucose. It has utility when used with therapies of erratic effect, those requiring considerable dose adjustment (notably insulin), and in those whose therapies put them at risk of hypoglycaemia. More controversial, except for people using insulin, is the use of self-monitoring to provide feedback on the impact of lifestyle measures on blood glucose control, and as part of the overall educational package designed to enhance self-care. Indirect monitoring using urine glucose tests is cheaper, but also delivers less information than plasma glucose monitoring.

This section addresses the clinical question of the role of self-monitoring of plasma glucose in people at different stages of the condition and on different therapies, and its integration with other key processes of care such as patient education.

6.1.2 Methodological introduction

Three recent systematic reviews[36–38] were identified which compared self-monitoring of blood glucose (SMBG) with usual care and/or with self-monitoring of urine glucose (SMUG) in patients with Type 2 diabetes not using insulin. One was a Cochrane review[38] of six RCTs without a meta-analysis. The same authors also published a second review[37] with the same studies including a meta-analysis. The third review was a meta-analysis of eight RCTs.[36] Although all of these reviews were of high methodological quality, this was not true of the studies included within them. In two reviews,[37,38] four out of six studies were found to be of low quality and in the other review,[36] five of the eight studies were judged to be of moderate risk of bias and three to be of high risk of bias. A further systematic review and meta-analysis included Type 2 diabetic patients that were on insulin treatment and used Bayesian methods to conduct a mixed treatment comparison.[39]

It should be noted that the two Cochrane reviews published by the same authors [37,38] did not perform a meta-analysis because they considered the studies they had identified to have 'clinical heterogeneity', in terms of baseline data of the patients and type of interventions between the studies. With regard to the interventions, the authors concluded that there were also discrepancies in monitoring frequency, training the patient in terms of the technique and educating the patient on how the data should be acted upon.

The meta-analysis by Jansen[39] scored the included studies for internal validity and adjusted for this in sensitivity analysis. This was also the only new study that compared the effects of urine versus blood self-monitoring on glycaemic control, albeit in an indirect comparison.

A protocol for a new 4-year UK trial in this area (the Diabetes Glycaemic Education and Monitoring (DiGEM) trial)[40] was identified and the results of this, once available, should clarify if and how to use SMBG, as part of a self-management programme. In one arm, a self-monitoring group will receive support in interpreting and applying the results of blood testing to enhance motivation and maintain adherence to diet, physical activity and medication regimens.

Two RCTs were identified which compared SMBG with no monitoring.[41,42] One study did not include insulin-treated patients.[42] The other included patients treated with insulin and the use of blood glucose monitoring in one arm of the study.[41]

Four cohort studies were also identified.[43–46] As noted in the previous guideline, it can be argued that limited credence can be given to observational study associations between blood glucose control and self-monitoring as those patients and healthcare professionals who

advocate self-monitoring may be the same people who are motivated to achieve better control.

One cross-sectional study[47] and one case-series [48] were also identified.

The GDG requested for a separate qualitative search to be conducted on this topic. This search identified two papers which considered self-monitoring from a patient perspective.[49,50] The papers reported results from the same qualitative Scottish study although the papers had slightly different aims. One explored the respective merits of urine testing and SMBG from the perspective of newly diagnosed patients with Type 2 diabetes[49] whilst the other explored the pros and cons of self-blood glucose monitoring from the patients' perspective.[50]

6.1.3 Health economics methodological introduction

One cost-effectiveness analysis was identified in the search.[51] It did not include enough detail on the costs and utilities to adequately interpret the results.

A cost analysis of implementing intensive control of blood glucose concentration in England identified increased frequency of home glucose tests as a main contributor to the total costs of intensive control.[52] It was estimated that the additional management costs of implementing intensive control policies would be £132 million per year, of which £42.2 million would be on home glucose tests. The sensitivity analysis results found that changes in the unit cost of home blood glucose strips (baseline cost £0.27, range tested £0.16–£0.40) in the proportion of patients already being managed intensively, and the costs of intensifying management, had the largest impact on the cost of implementation.

6.1.4 Evidence statements

(See the methodological introduction for commentary on systematic reviews of RCTs.)

Even though the Cochrane reviews[37,38] were not able to meta-analyse the data (due to clinical and methodological heterogeneity) the authors concluded that SMBG might be effective in improving glycaemic control in patients with Type 2 diabetes who are not using insulin. Authors also stated that a well designed large RCT assessing the benefits (including patient- related outcomes) of SMBG alongside patient education is required. **Level 1+**

The other review[36] concluded that, 'in the short term, and when integrated with educational advice, self-monitoring of blood glucose as an adjunct to standard therapy, may contribute to improving glycaemic control among non-insulin requiring Type 2 diabetes patients'. **Level 1+**

In an indirect analysis, Jansen[39] found a non-significant reduction in HbA1c of 0.3% when interventions with SMBG were compared with those associated with SMUG.

The study by Jansen also reported that interventions with SMBG were found to be more effective in reducing HbA1c than interventions without self-monitoring. The reduction in HbA1c was statistically significant and it was estimated to be around 0.4%. This effect was increased when regular feedback was added to the SMBG and was shown in both an insulin-treated Type 2 diabetes group, and in a group of Type 2 diabetes patients that included those being treated with oral agents. **Level 1+**

An RCT looking at the effects of an education manual[41] on blood glucose monitoring found that the greatest reduction in HbA1c occurred in the education manual group (–0.13±1.28%) compared with both the SMBG (–0.04±1.31%) and standard care (0.04±1.10%) groups. The authors did not report whether there was a significant difference between groups. **Level 1+**

A second multicentre RCT[42] found a significantly greater reduction in HbA1c in the SMBG compared to the non-SMBG group (p=0.0086). **Level 1+**

A retrospective cohort study performed in the USA (N=976) found that duration of SMBG (0–3 years) was not a significant predictor of HbA1c values in those with Type 2 diabetes on oral medication.[45] **Level 2+**

In a German retrospective cohort study of 1,609 patients with Type 2 diabetes, hazard ratios indicated that SMBG was associated with a 32% reduction in morbidity for combined macrovascular (MI and stroke) and microvascular (foot amputation, blindness or end-stage renal failure) non-fatal endpoints (HR=0.68, 95% CI 0.51–0.91, p=0.009). This was despite an increase of microvascular events, and a 51% reduction in mortality over the observation period (HR=0.49, 95% CI 0.31–0.78, p=0.003) where mean follow-up was 6.5 years. In those not receiving insulin, SMBG was associated with a 28% reduction in combined non-fatal endpoints (HR=0.72, 95% CI 0.52–0.99, p=0.0496) and a 42% reduction in mortality over the observation period (HR=0.58, 95% CI 0.35–0.96, p=0.035).[44] **Level 2+**

A retrospective cohort study of people with diabetes in a US medical care programme[43] found greater SMBG practice frequency among new users, which was associated with a graded decrease in HbA1c (relative to non-users) regardless of diabetes therapy (p<0.001). Changes in SMBG frequency among prevalent users were associated with an inverse graded change in HbA1c but only among pharmacologically-treated patients (p<0.0001). **Level 2+**

A study including patients from the Fremantle Diabetes Study (FDS) cohort[46] over 5 years of follow-up did not find any difference in HbA1c or in fasting plasma glucose, either overall or within treatment groups in patients who used SMBG than those who did not (p≥0.05). There were also no differences in HbA1c or FPG between SMBG adherent and non-adherent users by treatment group (p≥0.09). **Level 2+**

In a qualitative study performed in Scotland of newly diagnosed Type 2 diabetics, ‘patients reported strongly negative views of urine testing, particularly when they compared it with self-monitoring of blood glucose. Patients perceived urine testing as less convenient, hygienic and accurate than self-monitoring of blood glucose. Most patients assumed that blood glucose meters were given to those with a more advanced or serious form of diabetes. Patients often interpreted negative urine results as indicating that they did not have diabetes.[49]

A Scottish qualitative study sought newly diagnosed Type 2 diabetes patients’ perspectives on the pros and cons of SMBG.

Pros of self-monitoring:

- provides a heightened awareness of, and evidence of, the condition
- when readings are within advised guidelines and fluctuations are easily interpretable, patients emphasise the positive role that monitoring has in their diabetes management. Low readings are a high point giving personal gratification
- cultivates independence from health services and enhances self-regulation.

Cons of self-monitoring:

- potentially, self-monitoring can raise anxiety about readings
- blood glucose parameters were found to be problematic by patients when they felt they were receiving contradictory information about upper thresholds or no guidance about ideal parameters
- lack of awareness as to how to manage hyperglycaemia
- increased self-responsibility accompanied by increased self-blame and negative emotional reactions to high glucose readings
- counter-intuitive readings could be sources of distress and anxiety, in some cases adversely effecting adherence to diabetic regimens by promoting nihilistic attitudes

- healthcare professionals were not interested in readings.[50]

6.1.5 From evidence to recommendations

The newer meta-analyses did not add significantly to the views expressed in the previous Type 2 diabetes guideline. The findings of the ROSSO study[44] and the data from the large Kaiser Permanente cohorts4[3] added considerable confidence to the view that SMBG was an integral part of effective patient education packages and enabled the effective use of many other therapies and lifestyle interventions. The view in the previous guideline that self-monitoring of plasma glucose is not a stand-alone intervention was endorsed.

Concern was expressed over a number of issues surrounding the successful use of self-monitoring, and recognised that its cost meant that it had to be effectively deployed. It should only be supported in the context of a provision of a package of care, including structured education, from a primary or secondary diabetes care team. The initial education should be provided by a properly trained and skilled professional with understanding of the problems of the technology. Also, the skills of people with diabetes in using the technology should be the subject of regular quality assurance (together with the devices) perhaps as part of the regular annual review process. Devices should be calibrated to plasma glucose levels in line with 2006 WHO recommendations.

The importance of self-monitoring to the effective use of insulin therapy and for those at risk of hypoglycaemia through leisure or work activities (including driving) on oral medications was noted. The frequency of monitoring that is useful to someone with diabetes is highly individual and it is inappropriate to put an artificial restriction on this. The usefulness of self-monitoring, is dependent on the ability of users and health professionals to interpret the data particularly in the early stages of use by a person with diabetes, implying proper education and professional training on these aspects.

Qualitative studies from Scotland suggested that people with diabetes disliked monitoring of urine glucose compared to the self-monitoring of plasma glucose, and did not find it useful.

Hyperglycaemic complications were related to exposure to high glucose levels in plasma, and there were no major studies like the ROSSO and Kaiser studies for urine glucose monitoring. The evidence that plasma glucose monitoring could be replaced by urine glucose monitoring was found to be poor.

Although the DiGEM study was published after the evidence cut-off date, it had been identified as potentially important on the basis of earlier information. However, at review the GDG felt that a study which viewed self-monitoring as a stand-alone intervention, and not as an element of a full educational programme, could not properly inform the appropriate use of self- monitoring. The GDG further noted that people who might already have benefited from self- monitoring were excluded from participation.

Adverse effects of self-glucose monitoring (inconvenience, finger pricking) limited the use and cost-effectiveness of the technology. Obsessional and psychological problems relating to use of self-monitoring were rare in real clinical practice.

6.1.6 Recommendations

R22 Offer self-monitoring of plasma glucose to a person newly diagnosed with Type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon.

R23 Self-monitoring of plasma glucose should be available:

- **to those on insulin treatment**
- **to those on oral glucose lowering medications to provide information on hypoglycaemia**
- **to assess changes in glucose control resulting from medications and lifestyle changes**
- **to monitor changes during intercurrent illness**
- **to ensure safety during activities, including driving.**

R25 If self-monitoring is appropriate but blood glucose monitoring is unacceptable to the individual, discuss the use of urine glucose monitoring.

7 Oral glucose control therapies (1): metformin, insulin, secretagogues, an acarbose

7.1 Clinical introduction

Maintenance of glucose control to target levels is achieved in only very few people with Type 2 diabetes for more than a few months using lifestyle measures alone.[53,54] Oral glucose-lowering drugs are then indicated, and the choice, order and combination in which these are used will reflect evidence of:

- prevention of microvascular and arterial damage
- control of blood glucose levels
- assessment of the inconvenience
- risks of side effects.

Glucose control deteriorates continually with time in most people with Type 2 diabetes – it is not a chronic stable condition.[53,54] This is known to be due to progressive failure of insulin secretion.[55] Accordingly therapy has to be stepped up with time, one drug added to another until such time as only exogenous insulin replacement will suffice.

The evidence of efficacy and side effects differs between drug classes, and to a lesser extent between members of the same class. Since their introduction was over 40 years ago the cost of some generic drugs is low whilst newer drugs have inevitably incurred high development costs and are relatively expensive. Cost-effectiveness is then a relevant issue too. The parent guideline suggested the long established biguanides (metformin) and sulfonylureas as the usual choice of first- and second-line oral glucose-lowering therapy when indicated. These, and other insulin secretagogues working through the same mechanisms as sulfonylureas, are considered in this chapter, and the more expensive newer glucose-lowering drugs in the next chapter.

The clinical questions concern the order with which these oral glucose-lowering medications should be introduced and added to one another in different groups of people with Type 2 diabetes. Because such people vary in attributes (such as body weight) which can affect choice of medication, and because some medication side effects can have consequences for aspects of daily living (such as driving motor vehicles), blanket recommendations cannot be made for everyone with Type 2 diabetes.

7.2 Metformin

7.2.1 Methodological introduction

A large number of RCTs were identified in this area; included trials were limited to participants with Type 2 diabetes, a trial duration of at least 12 weeks and a sample size of 300 or more. Studies with smaller sample sizes were only included if there were no other larger studies for a particular comparison.

Two Cochrane reviews were identified.[56,57] One considered the effectiveness of metformin monotherapy compared with placebo or any active combination.[56] The other review included studies of metformin alone or in combination with other treatments compared with placebo or a range of other treatments, with the aim of reporting deaths due to lactic acidosis and non-fatal cases of lactic acidosis.[57] Similarly, an RCT was identified which compared serious

adverse events (AEs) and plasma lactate levels between metformin and non-metformin treated groups.[58]

We identified a further five RCTs which compared metformin monotherapy with pioglitazone,[59] glimepiride,[60] metformin plus rosiglitazone,[61] metformin and rosiglitazone as a fixed-dose combination,62 and metformin plus nateglinide.[63] Two of these studies had methodological limitations and were not considered further.[60,61]

In one RCT, metformin and biphasic insulin was compared with biphasic insulin alone.[64]

An additional RCT was identified and included which compared metformin immediate-release (MIR) with metformin extended-release (MXR).[65] The GDG subsequently felt that there might be relevant and important information in existence on the AE profile of these two formulations which had not been found during our search. Thus a focused call for evidence to all stakeholders was made. Following this, the GDG considered two RCTs (published in the same paper) which compared MXR against placebo,[66] and to a retrospective chart review comparing immediate- release and extended-release formulations.[67] Consideration was also given to four abstracts; however their usefulness is limited by the small number of patients included and the lack of detail inhibiting any assessment of study quality.[68–71]

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

7.2.2 Health economic methodological introduction

Five papers were identified in the literature search, of these three compared metformin mono- therapy with metformin in combination and so were thought to be more appropriate evidence for other questions.[72–74] One paper included a subgroup analysis of metformin monotherapy compared to nateglinide monotherapy, although the results of this analysis were not reported.[75] Two evaluations based on the UKPDS were identified that were considered to be of good quality.[33]

7.2.3 Evidence statements

Mortality and morbidity

In terms of mortality and morbidity, a Cochrane review[56] looked at the events listed in the Clinical Endpoint Analyses from the UKPDS[b] (UKPDS-34 1998). The systematic review found five studies providing data on mortality and/or morbidity outcomes (four RCTs in addition to the UKPDS).

In the UKPDS (median follow-up 10.7 years), among overweight (54% with obesity) participants allocated to intensive blood glucose control, metformin (N=342) showed a greater benefit than chlorpropamide, glibenclamide, or insulin (N=951) for any diabetes-related outcomes, and for all-cause mortality. For other outcomes including diabetes-related death, MI, stroke, peripheral vascular disease and microvascular, there were no significant differences between both comparison arms. **Level 1++**

In the same vein, the UKPDS found that overweight participants assigned to intensive blood glucose control with metformin (N=342) showed a greater benefit than overweight patients on conventional treatment (non-intensive blood glucose control, mainly with diet), (N=411), for any diabetes-related outcomes, diabetes-related death, all-cause mortality, and MI. For the rest of the outcomes such as stroke, peripheral vascular disease and microvascular, there were no significant differences between both comparison arms. **Level 1++**

b According to the Cochrane review, the UKPDS is the unique trial that has been specifically designed to determine whether tight glycaemia control decreases complications related to diabetes and increases life expectancy.

After pooling data from the four non-UKPDS trials, the Cochrane review did not find significant differences among comparisons either for all-cause mortality or for ischemic heart disease (study durations ranged from 24 weeks to 2 years). **Level 1++**

Table 9.1 Metformin mortality and morbidity studies

Study/comparison	Outcome	Effect size (RR)
UKPDS: metformin vs sulfonylureas or insulin	Any diabetes-related outcomes	0.78 (95% CI 0.65 to 0.94) p=0.009
	All-cause mortality	0.73 (95% CI 0.55 to 0.97) p=0.03
	Diabetes-related death	NS
	Myocardial infarction	NS
	Stroke	NS
	Peripheral vascular disease	NS
	Microvascular	NS
UKPDS: metformin vs conventional (non-intensive blood glucose control, mainly with diet)	Any diabetes-related outcomes	0.74 (95% CI 0.60 to 0.90) p=0.004
	Diabetes-related death	0.61 (95% CI 0.40 to 0.94) p=0.03
	All-cause mortality	0.68 (95% CI 0.49 to 0.93) p=0.01
	Myocardial infarction	0.64 (95% CI 0.45 to 0.92) p=0.02
	Stroke	NS
	Peripheral vascular disease	NS
	Microvascular	NS
Non-UKPDS trials: metformin vs comparison	All-cause mortality	NS
	Ischaemic heart disease	NS

Glucose control

Overall, the evidence appraised suggested that monotherapy with metformin produced significantly greater improvements in glycaemic control (i.e. HbA1c and FPG/fasting blood glucose (FBG)) when it was compared with placebo, diet and sulfonylureas. Head-to-head comparisons with other antidiabetic agents (i.e. alpha-glucosidase inhibitors, thiazolidinediones, meglitinides and insulin) and extended-release formulations of metformin, failed to show more benefit for glycaemic control than standard monotherapy with metformin. In addition metformin used in combination with different doses of nateglinide produce significantly lower glycaemic values than metformin monotherapy.

Body weight/ body mass index

Overall, the evidence demonstrated a significant difference in terms of body weight/BMI reduction favouring metformin monotherapy when compared with sulfonylureas, glitazones and insulin therapies. Non-significant differences were found in head-to-head comparisons between metformin against placebo, diet, alpha-glucosidase inhibitors, meglitinides and treatment with extend-release formulation of metformin. Combination of metformin and different doses of nateglinide produced a significant reduction in body weight when compared with metformin monotherapy. **Level 1+**

Lipid profile

Non-significant differences in terms of lipid profile were found when metformin was compared with placebo or meglitinides. **Level 1++**

Studies evaluating other comparisons found differences in specific lipid profile parameters.

When compared to diet, metformin significantly reduced total cholesterol (TC), however in a comparison with a □-glucosidase inhibitor, metformin significantly increased TC.[56] **Level 1++**

The meta-analysis of studies comparing metformin to sulfonylureas found significant benefits for metformin in terms of low-density lipoprotein cholesterol (LDL-C) and triglycerides.[56] **Level 1++**

In a comparison of metformin against insulin, significant benefits for metformin were found in terms of total and LDL-C levels but not high-density lipoprotein cholesterol (HDL-C).[56] **Level 1++**

In a study which compared metformin with pioglitazone,[59] pioglitazone was significantly more beneficial in terms of triglycerides and HDL-C, however metformin was more beneficial for LDL-C levels. The TC/HDL-C ratio did not differ significantly between the groups. **Level 1++**

A study which compared metformin monotherapy with metformin and nateglinide63 found no differences across the lipid profile between these two groups except for triglycerides which were reduced significantly in the metformin and nateglinide group (nateglinide 120 mg tablets thrice daily). **Level 1+**

Where MIR was compared with MXR treatment, lipid profiles were similar between groups (statistical significance not reported) except for triglycerides where the mean change from baseline in the immediate-release group was 1 mg/dL; but was 34 mg/dl in the MXR 1,000 mg arm, and 42 mg/dl in the MXR 1,500 mg arm.[65] **Level 1+**

Table 9.2 Metformin comparison studies

Comparison	Study	Change in HbA_{1c} (%)	FPG	Post load glucose/ PPBG/ PPGE	BMI (kg/m^2)	Body weight (kg)	TC	LDL	TG	HDL
Head-to-head comparisons										
Metformin vs placebo	Cochrane systematic review[56] 12 studies N=1,587	SMD –0.97 (95% CI –1.25 to –0.69)	SMD –0.87 (95% CI –1.13 to –0.61)	NE	NS	–	NS Four studies N=906	NS Four studies N=418	NS Three studies N=374	NS Four studies N=418
Metformin vs diet	Cochrane systematic review[56] Three studies N=914	SMD –1.06 (95% CI –1.89 to –0.22)	NS	NE	NS	–	SMD –0.59 (95% CI –0.90 to –0.27) Two studies N=161	NS One study N=61	NS Two studies N=161	NS One study N=61
Metformin vs alpha-glucosidase inhibitors	Cochrane systematic review[56] Two studies N=223	NS	NS	NE	NS	–	1.32 (95% CI 0.77 to 1.87) One study N=62	SMD One study N=62	NS One study N=62	NS NS One study N=62
Metformin vs sulfonylureas	Cochrane systematic review[56] 12 studies N=2,376	SMD –0.14 (95% CI –0.28 to –0.01)	SMD –0.16 (95% CI –0.27 to –0.05)	NE	SMD –0.45 (95% CI –0.80 to –0.10)	–	NS 10 studies N=1,150	SMD –0.29 (95% CI –0.52 to –0.07) Six studies N=793	SMD –0.22 (95% CI –0.43 to –0.02) 10 studies N=1,150	NS Eight studies N=1,069
Metformin vs meglitinides	Cochrane systematic review[56] Two studies N=413	NS	SMD –0.31 (95% CI –0.51 to –0.12)	NE	NS	–	NS One study N=56	NS One study N=56	NS One study N=56	NS One study N=56

continued

Table 9.2 Metformin comparison studies – *continued*

Comparison	Study	Change in HbA_{1c} (%)	FPG	Post load glucose/ PPBG/ PPGE	BMI (kg/m^2)	Body weight (kg)	TC	LDL	TG	HDL
Head-to-head comparisons – *continued*										
Metformin vs glitazones	Cochrane systematic review[56] Three studies N=260	SMD –0.28 (95% CI –0.52 to –0.03)	NS	NE	NS	–	NE	NE	NE	NE
	Metformin vs pioglitazone One study[59] N=1,199	NS	–0.3 mmol/l, p=0.016 in favour of pioglitazone	NE	NE	Mean body weight increased by 1.9 kg compared to a decrease of 2.5 kg with metformin*	NS (TC/HDL-C ratio)	+0.27 mmol/l change from baseline for pioglitazone vs –0.12 mmol/l metformin p=0.001	–0.61 mmol/l change from baseline for pioglitazone vs –0.3 mmol/l metformin p=0.001	+0.16 mmol/l change from baseline for pioglitazone vs +0.08 mmol/l metformin p=0.001
Metformin vs insulin	Cochrane systematic review[56] Two studies N=811	NS	NS	NE	SMD –0.91 (95% CI –1.44 to –0.37)	–	SMD –0.77 (95% CI –1.29 to –0.24) One study N=60	SMD –0.83 (95% CI –1.35 to –0.30) One study N=60	SMD NS One study N=60	SMD 0.65 (95% CI 0.13 to 1.17) One study N=60

continued

Table 9.2 Metformin comparison studies – *continued*

Comparison	Study	Change in HbA_{1c} (%)	FPG	Post load glucose/ PPBG/ PPGE	BMI (kg/m^2)	Body weight (kg)	TC	LDL	TG	HDL
Head-to-head comparisons – *continued*										
MIR vs MXR (MXR – 1,000 mg and 1,500 mg)	One study[65] N=217	NS	Mean FPG concentrations increased in all three treatment groups at week 24. The mean increases were smaller in the MXR groups compared with the MIR group (statistical significance not reported)	NE	NE	NS	Change from baseline MIR –1 mg/dl, MXR 1,000 +2 mg/dl and –3 mg/dl MXR 1,500*	Change from baseline –4 mg/dl with MIR and –6 mg/dl in both MXR groups*	Change from baseline MIR +1 mg/dl, MXR 1,000 + 34 mg/dl and +42 mg/dl MXR 1,500*	Change from baseline MIR +2 mg/dl, MXR 1,000 mg/dl and –1 mg/dl MXR 1,500*
Rosiglitazone/ metformin (FDC) vs metformin	One study[62] N=569	Treatment difference –0.22% (95% CI –0.36 to –0.09%, p=0.001)	–18.3 mg/dL 95% CI –23.5 to –13.2; p<0.0001 in favour of rosiglitazone/ metformin	NE	NE	There was a mean size effect increase from baseline in weight in the RSG/MET group (1.3 (0.22) kg) and a mean decrease in the MET group (–0.9 (0.26) kg)*	0.1% change from baseline for MET vs 10.7% RSG/ MET*	3.4% change from baseline for MET vs 14.5% RSG/ MET*	–8.5% change from baseline for MET vs 1.2% RSG/ MET*	–1.3% change from baseline for MET vs 4.1% RSG/ MET*

continued

Table 9.2 Metformin comparison studies – *continued*

Comparison	Study	Change in HbA_{1c} (%)	FPG	Post load glucose/ PPBG/ PPGE	BMI (kg/m^2)	Body weight (kg)	TC	LDL	TG	HDL
Head-to-head comparisons – *continued*										
Metformin vs metformin + nateglinide (60 mg and 120 mg)	One study[63] N=467	Nateglinide 60 mg –0.36%, p=0.003 nateglinide 120 mg –0.51%, p<0.001	–0.8 mmol/l (p=< 0.01) in favour of metformin + nateglinide 120 mg	NE	NE	0.9 kg increase was observed in the nateglinide 120 mg-group (over that in the metformin group) (p<0.001)	NS	NS	Metformin plus nateglinide 120 mg vs metformin (mean difference –0.2 p=0.042)	NS
Combinations										
Metformin + insulin biphasic vs insulin biphasic	One study[64] N=341	0.39%, p=0.007	NE	PPBG NS	NE	NS	NE	NE	NS	NS

MET, metformin; NE, not evaluated; NS, non-significant; PBG, postprandial blood glucose; PPGE, postprandial glucose excursion; RSG, rosiglitazone; SMD, standardised mean difference; TG, triglycerides
*Indicates statistical significance tests not reported/performed

Adverse events

Adverse events

The main differences across all the different treatment groups were:

- the high frequency of gastrointestinal (GI) complaints reported by metformin-treated patients
- the high frequency of hypoglycaemic events reported by sulfonylurea-treated patients
- the high number of episodes of oedema reported by glitazone-treated patients
- the high number of cases of upper respiratory infection in patients treated with meglitinides.

Level 1+

In the only RCT[65] directly comparing MIR and MXR, more diarrhoea, flatulence and abdominal pain were experienced in the extended-release group whilst more or equivalent proportions of patients, experienced nausea/vomiting, headache and dyspepsia/heartburn in immediate-release group (significance tests not performed). In placebo-controlled studies, patients on MXR always experienced more GI AEs than those on placebo.[66] **Level 1+**

A retrospective chart review[67] found a significantly reduced frequency of GI AE in a cohort of patients when they were switched from MIR to MXR. A cohort of patients taking metformin for the first time also experienced less GI AEs if they were commenced on MXR rather than the immediate-release formulation. **Level 2+**

Table 9.3 Metformin adverse events

Comparison	Study	Size effect
Head-to-head comparisons		
Metformin vs placebo	Cochrane systematic review[56]	Hypoglycaemia NS GI discomfort NS Diarrhoea Two studies N=639 3.09 (95% CI 1.58 to 6.07)
Metformin vs diet	Cochrane systematic review[56]	Hypoglycaemia One study N=811 4.21 (95% CI 1.40 to 12.66)
Metformin vs alpha-glucosidase inhibitors	Cochrane systematic review[56]	GI discomfort Two studies N=223 0.26 (95% 0.07 to 0.91)
Metformin vs glitazones	Cochrane systematic review[56]	NE
Metformin vs pioglitazone	One study[59] N=1,199	Diarrhoea* Metformin 11.1% Pioglitazone 3.2% Oedema* Metformin 1.7% Pioglitazone 4.5%

continued

Table 9.3 Metformin adverse events – *continued*

Comparison	Study	Size effect
Head-to-head comparisons – *continued*		
MIR vs MXR (MXR – 1,000 mg and 1,500 mg)	One study[65] N=217	Hypoglycaemia* Metformin MIR 1.4% Metformin MXR 1,000 mg 1.3% For other AEs* (Metformin IR 500 mg BD vs Metformin XR 1,000 mg od) Diarrhoea 3% vs 5% Flatulence 1% vs 4% Abdominal pain 1% vs 4% Nausea/vomiting 4% vs 3% Headache 4% vs 4% Dyspepsia/heartburn 6% vs 3%
MXR 1,000 mg (protocol 1) or 500–2,000 mg (protocol 2) vs placebo	Two studies[66]	Protocol 1 All-cause AEs were reported by 59.5% of patients treated with placebo and by 63.5% of patients treated with MXR For GI AEs (placebo vs MXR) Abdominal pain 5.1% vs 7.5% Diarrhoea 5.1% vs 6.9% Nausea/vomiting 3.8% vs 9.4% Protocol 2 All-cause AEs were reported by 59.5% of patients treated with placebo and by 65.85% of patients treated any dosage of MXR For GI AEs (placebo vs MXR) Abdominal pain 2.6% vs 5.1% Diarrhoea 3.4% vs 12.9% Nausea/vomiting 1.7% vs 8.2%
MIR (mean dose 1,282 mg) vs MXR (mean dose 1,258 mg)	One cohort study[67]	Overall in the MXR vs MIR cohorts: frequency of any GI AEs within the first year of treatment NS. Patients switched from MIR to MXR: Frequency of any GI AEs 26.45% on MIR vs 11.71% after switching to MXR; p=0.0006) Frequency of diarrhoea 18.05% vs 8.29%; p=0.0084) Comparison of patients new to metformin treatment with either MIR or MXR % of patients reporting a GI AE during the first year of treatment with MIR 19.83% vs 9.23% MXR (p=0.04) Frequency of diarrhoea (13.5% vs 3.08, p=0.0169)

continued

Table 9.3 Metformin adverse events – *continued*

Comparison	Study	Size effect
Head-to-head comparisons – *continued*		
Rosiglitazone/metformin (FDC) vs metformin	One study[62] N=569	Hypoglycaemia* Metformin 0.4% Rosiglitazone/metformin 1% Diarrhoea* Metformin 14% Rosiglitazone/metformin 6% Oedema* Metformin 1% Rosiglitazone/metformin 3%
Metformin vs metformin + nateglinide (60 mg and 120 mg)	One study[63] N=467	Hypoglycaemia* Placebo group 3.9% Nateglinide 60 mg 8.4% Nateglinide 120 mg 15.6% Diarrhoea* Placebo group 7.9% Nateglinide 60 mg 5.8% Nateglinide 120 mg 5.6% Upper respiratory infection* Placebo group 4.6% Nateglinide 60 mg 9.7% Nateglinide 120 mg 8.1%

* Indicates statistical significance tests not reported/performed

Lactic acidosis

A Cochrane review[57] looked at the risk of lactic acidosis in patients treated with metformin. There were no cases of fatal or non-fatal lactic acidosis reported. **Level 1+**

In addition, one RCT[58] did not find a significant difference in plasma lactate levels between metformin-treated patients and patients treated with other antidiabetic agents. **Level 1+**

7.2.4 Health economics evidence statements

The UKPDS included an analysis of intensive blood glucose control with metformin for overweight patients compared to conventional treatment primarily with diet. The study included 753 overweight (more than 120% ideal body weight) patients with newly diagnosed Type 2 diabetes from 15 hospital-based clinics in England, Scotland and Northern Ireland. Of these patients 342 were allocated to an intensive blood glucose control policy with metformin and 411 were allocated to conventional treatment, primarily with diet alone. The study was conducted from 1977 to 1991. The median follow-up period was 10.4 years.

In the conventional policy group the glycaemic goal was to obtain the lowest FPG attainable with diet alone. In the intensive policy group the aim was a FPG of less than 6.0 mmol/l by increasing the dose of metformin from 500 to 2,550 mg a day as required. Use of metformin for intensive blood glucose control in overweight patients was found to confer a 32% risk reduction for any diabetes-related endpoint and a 42% risk reduction for diabetes-related deaths compared with a conventional policy.

Resource use was routinely collected as part of the study. Non-inpatient resource use data was collected using a questionnaire distributed between January 1996 and September 1997. The incremental costs reported in the analysis have the study protocol driven costs removed. These were replaced with a pattern of clinic visits reflecting general practitioner and specialist clinical opinion on the implementation of intensive policy.

Where a patient was still alive at the end of the follow-up, a simulation model was used to estimate the time from end of follow-up to death. It was assumed that there would be no continuation of benefit of therapy beyond the trial period in both evaluations.

The data was used in a cost-effectiveness analysis[34] and a cost–utility analysis.[33] Both evaluations showed intensive blood glucose control with metformin for overweight patients to be cost-saving compared to conventional treatment.

In the cost-utility analysis, within trial costs and projected costs were included. In the cost-effectiveness analysis only costs incurred during the trial period were included.

Table 9.4 Results: Clarke (2001)[34]

	Mean cost per patient (1997 cost year)		Mean cost difference (95% CI) per patient
	Conventional	Metformin	
Total costs, 3% discount per year	£6,878	£6,607	–£271 (–£1,345, £801)
Total costs, 6% discount per year	£5,893	£5,635	–£258 (–£1,171, £655)

Table 9.5 Results: Clarke (2001)[34]

	Mean (95% CI) life expectancy (years) per patient		Mean difference (95% CI) per patient
	Conventional	Metformin	Difference
Not discounted	21.3	22.3	1.0 (–0.0,2.1)
3% discount per year	15.1	15.7	0.6 (0.0,1.2)
6% discount per year	11.3	11.7	0.4 (0.0, 0.8)

Table 9.6 Results: Clarke (2005)[33]

	Mean cost per patient (2004 cost year)		Mean cost difference (95% CI) per patient
	Conventional	Metformin	
Total cost of treatment (3.5%)	£16,941	£15,290	–£1,021 (–£4,291, £2,249)
Total cost of treatment (6%)	£12,798	£11,792	–£1,006 (–£3,251, £1,239)

Table 9.7 Results: Clarke (2005)[33]

	Mean (95% CI) QALY per patient		Mean difference (95% CI) per patient
	Conventional	Metformin	
Mean QALYs per patient (not discounted)	16.44	17.32	0.88 (–0.54, 2.29)
3.5% discount rate	–	–	0.55 (–0.10, 1.20)
6% discount rate	–	–	0.40 (–0.01, 0.80)

In the cost-effectiveness model with costs and effects discounted at a 6% rate, there was a 71% probability that metformin would prove to be cost-saving compared with a conventional policy.[34]

If additional costs of intensive policy with metformin were 50% more than assumed in the baseline estimates then the cost per life-year gained would be £948.

In the cost-utility model there was a 77% probability that metformin would prove to be cost-saving compared with a conventional policy.[33] Sensitivity analyses were performed for anti-diabetic therapy cost (±50%); standard practice costs (±50%); cost of complications (±50%); utility of one when free of complications; no treatment benefit and continuing benefit beyond the trial. Metformin was consistently shown to be a cost-reducing intervention.

7.3 Insulin secretagogues

7.3.1 Methodological introduction

A large volume of RCTs were identified in this area as the sulfonylurea and meglitinide drug classes include nine different agents (chlorpropamide, glibenclamide, gliclazide, glimepiride, glipizide, gliquidone, tolbutamide, nateglinide and repaglinide). Head-to-head comparisons with metformin were excluded as this is addressed in a previous question. Comparisons with the thiazolidinediones (the glitazones) were also excluded, as this will be addressed as part of a separate evidence review (see section 10.2).

Twenty-one studies were identified, four of which were excluded due to methodological limitations.[76–79]

Table 9.8 The various comparisons made in the included RCTs	
	Reference
Nateglinide vs placebo	80,81
Repaglinide vs placebo	82
Repaglinide vs nateglinide	83
Repaglinide vs glimepiride	84
Repaglinide vs glipizide	85
Repaglinide vs glibenclamide	8
Repaglinide + bedtime NPH vs gliclazide + bedtime NPH	87
Nateglinide + metformin vs repaglinide + metformin	88
Nateglinide + metformin vs glibenclamide + metformin	89
Nateglinide + metformin vs gliclazide + metformin	90
Nateglinide + metformin vs nateglinide vs metformin	91
Nateglinide + insulin glargine vs placebo + insulin glargine	92
Gliclazide modified release vs glimepiride	93
Gliclazide modified release vs gliclazide immediate release	94
Glimepiride vs metformin vs glimepiride + metformin	95
Glibenclamide vs insulin lispro	96

One cohort study on UKPDS data compared patients treated with diet alone vs sulfonylurea vs metformin vs insulin monotherapy.[97]

There is a paucity of studies for some comparisons, for example there are no head-to-head studies of the sulfonylureas (excluding studies of gliclazide-modified release) and only one study which compares a meglitinide with a sulfonylurea.[84]

Differing study populations, dose and titration regimens may limit direct comparison between studies.

7.3.2 Health economic methodological introduction

Thirteen papers were identified in the literature search. Of these, three were considered of good quality and relevant to the guideline. Two UKPDS papers were identified; a cost-utility analysis[33] and a cost-effectiveness[98] analysis of intensive blood glucose control.

Metformin monotherapy was compared with nateglinide plus metformin in the UK.[74]

7.3.3 Evidence statements

Metiglinides (repaglinide and nateglinide) vs placebo

Overall, metiglinides produced a significantly greater glycaemic control and a higher incidence of hypoglycaemic events when compared with placebo. No differences were found in terms of body weight and lipid profile.

Table 9.9 Nateglinide (120 mg) vs placebo
1 study[81] N=47
Level of evidence 1+

HbA1c	Nateglinide –3.6% Placebo +5.6% p=0.02			
FPG	NS			
Post load glucose/PPBG	NE			
Lipid profile	**TC** NS	**LDL** NS	**TG** NS	**HDL** NS
Body weight/BMI	**BMI** NE	**Body weight** NE		
AEs	AE data not reported			

Table 9.10 Nateglinide (30, 60, 120 mg) vs placebo
1 study[80] N=675
Level of evidence 1+

HbA_{1c}	Nateglinide relative to placebo (–0.26±0.05, –0.31±0.04, –0.39±0.05 for 30 mg, 60 mg and 120 mg respectively) were significant (p<0.001)			
FPG	Modest but statistically significant and dose-related reduction of FPG relative to placebo (p<0.001 vs placebo for all dose strengths)			
Post load glucose/PPBG	NE			
Lipid profile	**TC** NE	**LDL** NE	**TG** NE	**HDL** NE
BMI/body weight	**BMI** NE	**Body weight** NS		
AEs	Hypoglycaemia There was a dose-related increase in symptomatic hypoglycaemia but the incidence of confirmed hypoglycaemia in nateglinide-treated patients was much lower than symptomatic hypoglycaemia			

	Symptomatic	**Confirmed**
Placebo	4.9%	(1.2%)
30 mg nateglinide	12%	(2.4%)
60 mg nateglinide	11.4%	(4.0%)
120 mg nateglinide	22.8%	(5.3%)

Table 9.11 Repaglinide vs placebo
1 study[82] N=408
Level of evidence 1+

HbA_{1c}	Final HbA_{1c} levels were significantly greater for repaglinide monotherapy than nateglinide monotherapy (–1.57 vs –1.04%, p=0.002)			
FPG	Significantly greater efficacy for repaglinide than nateglinide (–57 vs –18 mg/dl, p<0.001			
Post load glucose/PPBG	NS			
Lipid profile	**TC** NE	**LDL** NE	**TG** NE	**HDL** NE
BMI/body weight	**BMI** NE	**Body weight** Mean weight gains from baseline to study end were +1.8 kg for repaglinide and +0.7 kg for nateglinide, p=0.04		
AEs	The most common AEs (3–10% of patients in both groups) were upper respiratory tract infection, sinusitis, constipation, arthralgia, headache and vomiting but there was no notable difference in the pattern between the two groups Hypoglycaemia There were 7% of repaglinide patients who had minor hypoglycaemic episodes and 0% for nateglinide (this is 0.016 events per patient per months for repaglinide vs 0 for nateglinide p=0.3, NS)			

Repaglinide vs nateglinide

When repaglinide was compared with nateglinide in people with Type 2 diabetes previously treated with diet and exercise:

- repaglinide and nateglinide had similar postprandial glycaemic effects. However, repaglinide was more effective than nateglinide in reducing HbA1c and FPG values
- a greater weight gain (p=0.04) was seen in repaglinide-treated patients when compared to
- nateglinide-treated patients
- hypoglycaemic events were more frequently reported by patients receiving repaglinide (non-significant difference between the two groups).

Table 9.12 Repaglinide vs nateglinide 1 study[83] N=150 **Level of evidence 1+**				
HbA_{1c}	Final HbA_{1c} levels were 0.99% lower in the repaglinide group than in the placebo group ($p<0.001$)			
FPG	There was a mean 1.44 mmol/l greater reduction in the repaglinide group compared with the placebo group ($p<0.001$)			
Post load glucose/PPBG	NE			
Lipid profile	**TC** NE	**LDL** NE	**TG** NE	**HDL** NE
BMI/body weight	**BMI** NE	**Body weight** NS		
AEs	The overall tolerability of repaglinide was similar to placebo excluding hypoglycaemic events Hypoglycaemia 17% of patients in the repaglinide group and 3% in the placebo group reported minor episodes of hypoglycaemia 3 repaglinide patients reported a total of 4 major hypoglycaemic events			

Meglitinides vs sulfonylureas

In head-to-head comparisons with sulfonylureas, metiglinides failed to demonstrate better glucose control and led to a similar number of hypoglycaemic events. No significant differences were observed in terms of lipid profile and body weight reduction.

Table 9.13 Repaglinide vs glimepiride 1 study[84] N=132 **Level of evidence 1+**				
HbA_{1c}	NS			
FPG	NS			
Post load glucose/PPBG	PPG levels were significantly lower with repaglinide compared with glimepiride ($p<0.01$)			
Lipid profile	**TC** NS	**LDL** NS	**TG** NS	**HDL** NS
BMI/body weight	**BMI** NS	**Body weight** NS		
AEs	AE data not reported			

Table 9.14 Repaglinide vs glipizide
1 study[85] N=256
Level of evidence 1+

HbA_{1c}	Statistically significant difference between HbA_{1c} changes from baseline in the two treatment groups in favour of repaglinide (0.19% vs 0.78%, difference –0.59%, p<0.05)			
FPG	Statistically significant difference between FPG changes in the two treatment groups in favour of repaglinide (0.5 mmol/l vs 1.3 mmol/l, difference –0.9 mmol/l, p<0.05)			
Post load glucose/PPBG	NE			
Lipid profile	**TC** NS	**LDL** NS	**TG** NS	**HDL** NS
BMI/body weight	**BMI** NE	**Body weight** NS		
AEs	A total of 20 patients in the repaglinide group and nine in the glipizide group reported AEs other than hypoglycaemia. The most common were nausea and fatigue Hypoglycaemia The number of patients experiencing minor hypoglycaemic events was similar in the repaglinide and glipizide groups (15% vs 19% respectively)			

Table 9.15 Repaglinide vs glibenclamide
1 study[86] N=175
Level of evidence 1+

HbA_{1c}	NS			
Fasting glucose	Glibenclamide caused a significantly greater decrease than repaglinide (p<0.001)			
PPG peak and 2 hour PPG levels	Repaglinide caused a significantly greater decrease in peak glucose than glibenclamide (p<0.001) AUC 0–2h decreased significantly more among patients receiving repaglinide (p=0.01)			
Lipid profile	**TC** NS	**LDL** NE	**TG** NS	**HDL** NS
BMI/body weight	**BMI** NE	**Body weight** NE		
AEs	Hypoglycaemic events; repaglinide (9%) and glibenclamide (13%)			
CIMT	CIMT regression was observed in 52% of patients receiving repaglinide and in 18% of those receiving glibenclamide (p<0.01)			
Inflammatory markers IL-6 and C-reactive protein	IL-6 and C-reactive protein decreased more in the repaglinide group than in the glibenclamide group (p=0.04 and p=0.02 respectively)			

AUC, area under curve; CIMT, carotid intima-media thickness

Gliclazide modified release vs gliclazide

When a modified-release version of gliclazide was compared with the immediate-release version of gliclazide in people with Type 2 diabetes who had been on diet control or on treatment with oral hypoglycaemic agents:

- both versions were associated with significant reductions in HbA1c (non-significant difference between the two groups). FPG decreased significantly on gliclazide MR but not on gliclazide (non-significant difference between the two groups)
- no clinically significant changes were seen in terms of lipid profile (non-significant difference between the two groups)
- hypoglycaemic events were only reported by patients receiving gliclazide MR (9%) (non-significant difference was reported between the two groups).

Table 9.16 Gliclazide MR vs gliclazide
1 study[94] N=63
Level of evidence 1+

HbA_{1c}	NS			
FPG	NS			
Post load glucose/PPBG	NE			
Lipid profile	**TC** NE	**LDL** NE	**TG** NE	**HDL** NE
BMI/body weight	**BMI** NE	**Body weight** NS		
AEs	In the gliclazide MR group, the most common adverse effects reported by patients were abdominal pain (9%) and pharyngitis (9%), while in the gliclazide group the most common adverse effect was neuropathy (14%) Hypoglycaemia Three patients (9.3%) experienced five mild hypoglycaemic episodes in the gliclazide MR treatment group. No suspected hypoglycaemic episodes were observed in the gliclazide treatment group			

Gliclazide MR vs glimepiride

When a modified-release version of gliclazide was compared with glimepiride in people with Type 2 diabetes being treated with diet alone or with either metformin or alpha-glucosidase inhibitors:

- both interventions were equally effective in terms of glycaemic control (alone or in combination with metformin or alpha-glucosidase inhibitors)
- gliclazide MR had a better safety profile than glimepiride.

Table 9.17 Gliclazide MR vs glimepiride 1 study[93] Level of evidence 1+				
HbA_{1c}	NS			
FPG	NS			
Post load glucose/PPBG	NE			
Lipid profile	**TC** NS	**LDL** NS	**TG** NS	**HDL** NS
BMI/body weight	**BMI** NE	**Body weight** gliclazide MR: 83.1 to 83.6 kg glimepiride: 83.7 to 84.3 kg*		
AEs	Hypoglycaemia Hypoglycaemia with blood glucose <3 mmo/l occurred significantly less frequently (p=0.003) in the gliclazide MR group (3.7%) compared with the glimepiride group (8.9%) with an odds ration of 2.5 (95% CI, 1.4 to 4.7)			
* Indicates statistical significance tests between groups were not reported/performed				

Insulin lispro vs glibenclamide

When insulin lispro was compared with glibenclamide in people with Type 2 diabetes who had been treated with oral antidiabetic (OAD) therapy, but not insulin:

- both regimes produced comparable effects in the control of glycaemia with respect to HbA1c. However, treatment with insulin lispro resulted in smaller postprandial blood glucose excursions compared to oral treatment with glibenclamide
- no significant differences were observed between the treatment groups regarding hypoglycaemic episodes and other AEs.

Table 9.18 Insulin lispro vs glibenclamide 1 study[96] N=143 Level of evidence 1+				
HbA_{1c}	NS			
FPG	NE			
Post load glucose/PPBG	The change in mean overall blood glucose excursions from baseline to endpoint was –1.0±1.5 mmol/l in the insulin lispro-treatment group and –0.3±1.5 mmol/l in the glibenclamide group, (p=0.013)			
Lipid profile	**TC** NE	**LDL** NE	**TG** NE	**HDL** NE
BMI/body weight	**BMI** NE	**Body weight** NS		
AEs	AEs No significant difference between groups Hypoglycaemia No significant difference between groups			

Bedtime NPH + repaglinide vs bedtime NPH + gliclazide

When repaglinide was compared with gliclazide (both drugs in combination with bedtime NPH) in Type 2 diabetes patients inadequately controlled with oral hypoglycaemic therapy:

- both interventions were associated with significant reductions in HbA1c and FPG (non-significant difference between the two groups)
- weight gain during the treatment period was similar in both groups
- no significant differences were observed between the treatment groups regarding hypoglycaemic episodes and other AEs.

Table 9.19 Bedtime NPH + repaglinide vs bedtime BPH + gliclazide
1 study[87] N=80
Level of evidence 1++

HbA_{1c}	NS			
FPG	NS			
Post load glucose/PPBG	N			
Lipid profile	**TC** NE	**LDL** NE	**TG** NE	**HDL** NE
BMI/body weight	**BMI** NE	**Body weight** NS		
AEs	AEs A total of 70 AEs were recorded throughout the study, 38 in the insulin/gliclazide and 32 in the insulin/repaglinide group. Hypoglycaemia No significant difference between groups			

Nateglinide + metformin vs gliclazide + metformin

Nateglinide in combination with metformin was compared with gliclazide and metformin, to compare the effects on glycaemic control in patients with Type 2 diabetes:

- no significant difference was seen between the groups in terms of HbA1c
- the nateglinide group demonstrated better PPG control.

Table 9.20 Nateglinide + metformin vs gliclazide + metformin
1 study[91] N=262
Level of evidence 1+

HbA_{1c}	NS			
FPG	NS			
Post load glucose/PPBG		**Nateglinide + metformin**	**Gliclazide + metformin**	**p-value**
	Max PPG excursion (mmol/l)	–0.71±0.22	–0.10±0.23	p=0.037
	30 minute postprandial insulin (pmol/l)	98.9±12.1	32.5±12.56	p<0.001
	2 hour postprandial insulin (pmol/l)	83.9±16.6	39.6±17.8	p=0.047
	2 hour postprandial insulin excursion (pmol/l)	75.5±16.0	30.2±16.6	p=0.033
Lipid profile	**TC** NE	**LDL** NE	**TG** NE	**HDL** NE
BMI/body weight	**BMI** NE	**Body weight** NS		
AEs	Suspected drug-related AEs Nateglinide arm 6.9% Gliclazide arm 7.1% NS			

Glimepiride + metformin vs glimepiride vs metformin

When glimepiride in combination with metformin was compared with monotherapy of each drug in Type 2 diabetes patients inadequately controlled by metformin monotherapy:

- combination treatment was more effective than either drug alone in terms of glycaemic control
- combination therapy was more effective than either drug in reducing TC levels
- metformin alone resulted in a significantly lower BMI than either glimepiride alone, or the combination
- the incidence of hypoglycaemic episodes was significantly higher in the combination treatment group than in either of the monotherapy groups.

Table 9.21 Glimepiride vs metformin vs glimepiride + metformin
1 study[95] N=372
Level of evidence 1++

HbA_{1c}	Combination treatment (glimepiride + metformin) was significantly more efficient in reducing HbA_{1c} levels than: glimepiride alone (difference in mean change 1.04% 95% CI 0.81 to 1.27%; p<0.001) metformin alone (difference in mean change 0.92% 95% CI 0.63 to 1.21%; p<0.001) There was no significant difference between metformin or glimepiride monotherapy in terms of HbA_{1c}			
FPG	Combination treatment was significantly more effective than either monotherapy in reducing FBG (p<0.001) There was no significant difference between metformin or glimepiride monotherapy in terms of FPG			
Post load glucose/PPBG	Combination treatment was significantly more effective than either monotherapy in reducing PPBG (p<0.001) Treatment with glimepiride was significantly more effective than metformin in reducing PPBG (p<0.001)			
Lipid profile	**TC** Combination was significantly more effective than glimepiride alone (p<0.001) in reducing TC levels, although there was no significant difference between the combination and metformin alone	**LDL** NS	**TG** NS	**HDL** NS
BMI/body weight	**BMI** Treatment with metformin resulted in a significantly lower BMI than either glimepiride alone (p<0.001) or the combination treatment (p<0.002); however there was NS difference between the glimepiride and combination treatment groups	**Body weight** NE		
AEs	AEs were experienced by 105 patients **N (%)** Metformin 22 (29%) Glimepiride 38 (25%) G + M 45 (31%) Hypoglycaemia The incidence of symptomatic episodes was significantly higher in the combination treatment group than in either of the monotherapy groups (22% of patients vs 11% of patients in the metformin group and 13% of patients in the glimepiride group, p=0.039) Diarrhoea was more commonly reported in the metformin group than in the other two treatment groups (7% of patients vs 1% of patients in the glimepiride group and 3% of patients in the combination group)			

Nateglinide + metformin vs nateglinide vs metformin vs placebo

When nateglinide in combination with metformin was compared with monotherapy of each treatment and placebo in drug naive patients with Type 2 diabetes:

- nateglinide, metformin and combination therapy (nateglinide + metformin), were associated with significant reductions in HbA1c, FPG and PPGE (an additive effect was seen with combination therapy)
- the incidence of GI AEs was higher in patients receiving combination therapy and metformin than in those receiving placebo and nateglinide
- the incidence of hypoglycaemic episodes was higher in the combination treatment group than in either of the monotherapy groups.

Table 9.22 Nateglinide vs metformin vs nateglinide + metformin
1 study[91] N=401
Level of evidence 1+

HbA_{1c}	Changes from baseline			
	Placebo	(⊗ = +0.3±0.1%)		
	Nateglinide	(⊗ = –0.8±0.1%)		
	Metformin	(⊗ = –0.8±0.1%)		
	Combination therapy	(⊗ = –1.6±0.1%)		
FPG	Changes from baseline			
	Placebo	not change		
	Nateglinide	(⊗ = –1.1±0.3 mmol/l)		
	Metformin	(⊗ = –1.2±0.3 mmol/l)		
	Combination therapy	(⊗ = –2.3±0.3 mmol/l)		
Post load glucose/PPBG	Changes from baseline			
	Placebo	(⊗ = –0.5±0.2 mmol/l)		
	Metformin	(⊗ = –1.0±0.2 mmol/l)		
	Nateglinide	(⊗ = –1.9±0.2 mmol/l)		
	Combination therapy	(⊗ = –2.3±0.2 mmol/l)		
Lipid profile	**TC**	**LDL**	**TG**	**HDL**
	NE	NE	NE	NE
BMI/body weight	**BMI**	**Body weight**		
	NE	NS changes from baseline for		
		combination therapy	(⊗ = +0.2±0.4 kg)	
		placebo	(⊗ = –0.2±0.4 kg)	
AEs	No serious AEs judged to be related to study medication			
	GI			
	The percentage of patients randomised to combination therapy experiencing one or more GI AE (27%) was essentially identical to that of those receiving metformin monotherapy (27.9%), and approximately twofold that of patients receiving placebo and nateglinide monotherapy (14.4% and 16.3% respectively)			
	Incidence of symptomatic hypoglycaemia in patients receiving combination therapy=29%			
	Incidence of confirmed hypoglycaemia in drug naive patients receiving combination therapy 3.4% (with all considered to be mild)			

Nateglinide + insulin glargine vs placebo + insulin glargine

The effect of adding nateglinide to therapy with insulin glargine in adults with Type 2 diabetes previously treated with insulin and with poor blood glucose control.

- Adding nateglinide improved blood glucose control in the early part of the day after breakfast and lunch.
- Adding nateglinide did not provide good blood glucose control overall.

Table 9.23 Nateglinide + insulin vs placebo + insulin glargine
1 study[91] N=55
Level of evidence 1+

HbA_{1c}	NS			
Post load glucose/PPBG	Self-monitored blood glucose concentrations (mmol/l) were significantly lower in the nateglinide group only at certain times of the day.			
	Time	**Difference in mmol/l (95% CI)**	**p-value**	
	After breakfast	–2.3 (–4.4, 0.2)	0.030	
	Before lunch	–2.5 (–4.6, –0.3)	0.029	
	After lunch	–2.3 (–4.6, –0.4)	0.021	
Lipid profile	**TC**	**LDL**	**TG**	**HDL**
	NE	NE	NE	NE
BMI/body weight	**BMI**	**Body weight**		
	NE	NS		
AEs	NS			

Diet vs sulphonylurea vs insulin

This cohort study investigated the incidence of hypoglycaemia in patients treated with diet alone, sulphonylurea, metformin or insulin monotherapy. The results on metformin are not discussed here as they are considered in a separate question.

Table 9.24 Diet vs sulphonylurea vs insulin
1 study[97] N=5,063
Level of evidence 2+

HbA_{1c}	NE			
FPG	NE			
Post load glucose/PPBG	NE			
Lipid profile	**TC** NE	**LDL** NE	**TG** NE	**HDL** NE
BMI/body weight	**BMI** NE	**Body weight** NE		
AEs	Annual percentage (95% CI) of patients reporting at least one hypoglycaemic episode in relation to therapy			
	Therapy	**Grades 1–4 hypoglycaemia**	**Grades 2–4 hypoglycaemia**	
	Diet alone	0.8 (0.6 to 1.0)	0.1 (0.1 to 0.2)	
	Sulphonylurea	7.9 (5.1 to 11.9)	1.2 (0.4 to 3.4)	
	Basal insulin alone	21.2 (14.6 to 29.8)	3.8 (1.2 to 11.1)	
	Basal + prandial insulin	32.6 (21.8 to 45.6)	5.5 (2.0 to 14.0)	

Hypoglycaemia was defined on the following scale: 1) transitory symptoms not affecting normal activity 2) temporarily incapacitated but patient able to control symptoms without help 3) incapacitated and required assistance to control symptoms without help 4) required medical attention or glucagon injection

7.3.4 Health economic evidence statements

Sulfonylurea monotherapy

Conventional glucose control, mainly through diet was compared to more intense blood glucose control with insulin or sulfonylureas in the UKPDS. Intensive treatment was cost-saving with the resource use according to the trial protocol. Using standard clinical resource use, intensive treatment had an incremental cost-effectiveness ratio (ICER) of £1,166 per event- free year gained within the trial period (6% discount rate, 1997 cost year).[98]

In a further cost-utility analysis published in 2005 intensive blood glucose control with insulin or sulfonylurea was found to have a cost-effectiveness ratio of £6,028 per QALY gained compared to conventional glucose (2004 cost year, 3.5%).[33]

Combination therapy

Metformin monotherapy (1,500 mg/day) was compared with nateglinide (360 mg/day) plus metformin (1,500 mg/day) in a UK setting. A hypothetical population based on US data was used. The mean baseline HbA1c level was 8.4%. The duration of diabetes was not stated, although a pre-model period of 7 years was included. The resulting cost per QALY was £8,058 (1999 cost year, 3% discount rate).[74]

7.4 Acarbose

7.4.1 Methodological introduction

A Cochrane review[99] and eight RCTs[100–107] compared monotherapy acarbose or other combination OAD drugs, with other OAD drug regimens or placebo. Studies were excluded unless they were of at least 12-weeks duration. Two of the RCTs[100,107] were excluded due to methodological limitations.

The Cochrane review[99] identified 30 RCTs in a search performed in April 2003 which compared acarbose monotherapy with placebo, sulfonylureas, metformin or nateglinide. The additional six RCTs included in this analysis compared acarbose with placebo when both groups were also treated with metformin,[104] with sulphonylureas,[105,106] or with insulin,[103] and there were also comparisons between acarbose and pioglitazone[101] and acarbose and sulfonylurea.[102]

Although a substantial amount of evidence has been found in this area, several different drug combinations and comparisons, differing dosing and titration regimens and the differing populations included in the studies, limit direct comparison between studies. Additionally, some study results may not be generalisable to a UK population of people with Type 2 diabetes. For example, the study by Lin[106] was undertaken in a Chinese population with a mean BMI of 25 kg/m^2.

7.4.2 Health economic methodological introduction

Three papers were identified from the literature search. All three were excluded. One was an analysis of adherence to oral antihyperglycaemic medication conducted in the US. This was not an economic analysis, and the comparison of costs was of patients with diabetes compared to patients with diabetes and cardiovascular disease.[108]

One paper was a cost-effectiveness analysis with an outcome of prevention of progression to Type 2 diabetes, which is outside of the scope of these guidelines.[109]

The final paper identified was a cost-effectiveness analysis. The focus was on quality of life in older patients. Not enough description was given of the treatments, referring only to oral medication with no further details.[110]

7.4.3 Evidence statements

The evidence appraised suggested that acarbose (used as monotherapy or in combination) failed to demonstrate better glycaemic control when compared with other oral agents. Treatment with acarbose did not demonstrate superiority over other oral agents when lipid profile and body weight were evaluated.

Reports of adverse effects were higher in the acarbose groups across all studies.[99,101–106] The main difference between the treatment groups was the high frequency of GI complaints reported by acarbose-treated patients. Flatulence was reported in all acarbose arms ranging from 28.6% to 57.5% of all patients.

Table 9.25 HbA_{1c}

Comparison	Study	Change in HbA_{1c} (%)
Acarbose vs placebo	Cochrane systematic review[99] 28 studies N=2,831	–0.77, 95% CI –0.90 to –0.64
Acarbose vs metformin	Cochrane systematic review[99] One study N=62	NS
Acarbose vs sulfonylurea	Cochrane systematic review[99] Eight studies N=596	NS
	One study[102] N=219	Greater reduction in HbA_{1c} in the glimepiride group (2.5±2.2%) compared with the acarbose group (1.8±2.2%, p=0.014)
Acarbose vs pioglitazone	One study[101] N=271	Greater reduction for the patients treated with pioglitazone compared with those treated with acarbose (p<0.001)
Acarbose vs nateglinide	Cochrane systematic review[99] One study N=179	NS
Acarbose + metformin vs placebo + metformin	One study[104] N=83	LSM* difference between the treatment arms of 1.02%, 95% CI 0.543 to 1.497%, p=0.0001
Acarbose + sulfonylurea vs placebo + sulfonylurea	One study[106] N=69	The difference in the mean endpoints between the two treatment groups was –1.05%, 95% CI –1.69 to –0.41, p=0.0018
	One study[105] N=373	LSM difference –0.54%, CI –0.86 to –0.22; p=0.001)
Insulin + acarbose vs insulin + placebo	One study[103] N=112	Comparison between the treatment groups showed a difference of –0.69%, 95% CI –1.18 to –0.20; p=0.008

*Adjusted least square mean
LSM, least square mean; NS, non-significant; PP, postprandial

Table 9.26 Fasting blood glucose

Comparison	Study	Change in FBG (mmol/l)
Acarbose vs placebo	Cochrane systematic review[99] 28 studies N=2,838	–1.09, 95% CI –1.36 to –0.83
Acarbose vs metformin	Cochrane systematic review[99] One study N=62	NS
Acarbose vs sulfonylurea	Cochrane systematic review[99] Eight studies N=596	0.69, 95% CI 0.16 to 1.23
	One study[102] N=219	The reduction was greater in the glimepiride-treated patients (2.6±2.6 mmol/l) than in the acarbose-treated patients (1.4±2.8 mmol/l, p=0.004)
Acarbose vs pioglitazone	One study[101] N=271	The decrease was significantly greater with pioglitazone than acarbose. (–56.41±73.6 vs –22.54±65.86, p=0.001)*
Acarbose vs nateglinide	Cochrane systematic review[99] One study N=175	NS
Acarbose + metformin vs placebo + metformin	One study[104] N=83	LSM** 1.132, 95% CI 0.056 to 2.208; p=0.0395. This was an increase at endpoint in both groups: 0.34±0.42 for acarbose compared to 1.48±0.39 for placebo
Acarbose + sulfonylurea vs placebo + sulfonylurea	One study[106] N=69	NS
	One study[105] N=373	LSM** difference –14.8 mg/dl, 95% CI –27.3 to –2.4, p=0.0195
Insulin + acarbose vs insulin + placebo	One study[103] N=112	NS

* This study evaluated FPG
**Adjusted least square mean

Table 9.27 Post-load blood glucose

Comparison	Study	Change in post-load blood glucose (mmol/l)
Acarbose vs placebo	Cochrane systematic review[99] 22 studies N=2,238	–2.32, 95% CI –2.73 to –1.92.
Acarbose vs metformin	Cochrane systematic review[99] One study N=62	–0.42 95% CI –0.79 to –0.05
Acarbose vs sulfonylurea	Cochrane systematic review[99] Eight studies N=596	NS
	One study[102] N=219	3.1±3.1 mmol/l glimepiride vs 1.7±3.5 mmol/l acarbose, p=0.004 (decreased glucose response to breakfast)
Acarbose vs pioglitazone	One study[101] N=271	NE
Acarbose vs nateglinide	Cochrane systematic review[99]	NE
Acarbose + metformin vs placebo + metformin	One study[104] N=83	NE
Acarbose + sulfonylurea vs placebo + sulfonylurea	One study[106] N=69	–2.49 mmol/l, 95% CI –4.01 to –0.96, p=0.002
	One study[105] N=373	LSM of –33.4 mg/dl, 95% CI –49.2 to –17.7, p=<0.0001
Insulin + acarbose vs insulin + placebo	One study[103] N=112	–34 mg/dl 95% CI –63 to –5, p=0.029) Change in 2 hours PP=NS

Table 9.28 Body mass index/body weight

Comparison	Study	BMI (kg/m^2)	Body weight (kg)
Acarbose vs placebo	Cochrane systematic review[99]	14 studies N=1,430 –0.17, 95% CI –0.25 to –0.08	NS
Acarbose vs metformin	Cochrane systematic review[99]	NE	One study N=62 NS
Acarbose vs sulfonylurea	Cochrane systematic review[99]	Four studies N=230 NS	Five studies N=397 NS
	One study[102] N=219	NE	Acarbose change from baseline: 1.9±3.9 (p=0.001) Glimepiride change from baseline: 0.4±5.2 (NS)
Acarbose vs pioglitazone	One study[101] N=271	NE	Increased with pioglitazone treatment (1.23±5.42) and decreased with acarbose (–2.09±3.58,p<0.001)

continued

Table 9.28 Body mass index/body weight – *continued*

Comparison	Study	BMI (kg/m²)	Body weight (kg)
Acarbose vs nateglinide	Cochrane systematic review[99]	NE	One study N=169 –0.68 95% –1.30 to –0.06
Acarbose + metformin vs placebo + metformin	One study[104] N=83	NE	NS
Acarbose + sulfonylurea vs placebo + sulfonylurea	One study[106] N=69	NE	NS
	One study[105] N=373	NE	NE
Insulin + acarbose vs insulin + placebo	One study[103] N=112	NE	NS

Table 9.29 Lipid profile

Comparison	Study	TC	LDL	TG	HDL	VLDL
Acarbose vs placebo	Cochrane systematic review[99]	NS	NS	NS	NS	NE
Acarbose vs metformin	Cochrane systematic review[99]	One study N=62 –0.94, 95% CI –1.66 to 0.22	One study N=62 –0.94 95% –1.52 to 0.36	NS	NS	NE
Acarbose vs sulfonylurea	Cochrane systematic review[99]	NS	NS	NS	NS	NE
	One study[102] N=219	NE	NE	NE	NE	NE
Acarbose vs pioglitazone	One study[101] N=271	NS	NS	Greater mean decrease with pioglitazone (p<0.001)	Greater mean increase with pioglitazone (p<0.001)	Greater mean decrease with pioglitazone (p=0.037)
Acarbose vs nateglinide	Cochrane systematic review[99]	NE	NE	NE	NE	NE
Acarbose + metformin vs placebo + metformin	One study[104] N=83	NE	NE	NE	NE	NE
Acarbose + sulfonylurea vs placebo + sulfonylurea	One study[106] N=69	NS	NS	NS	NS	NS
	One study[105] N=373	NS	NE	NS	NS	NE
Insulin + acarbose vs insulin + placebo	One study[103] N=112	NS	NS	NS	NS	NE

Table 9.30 Adverse effects

Comparison	Study	Effect size
Acarbose vs placebo	Cochrane systematic review[99] Four studies N=1,442	Occurrence of AEs: OR=3.37, 95% CI 2.6 to 4.36 Occurrence of GI AEs: OR=3.30, 95% CI 2.31 to 4.71
Acarbose vs metformin	Cochrane systematic review[99] One study N=62	OR=15.00, 95% CI 3.06, 73.58
Acarbose vs sulfonylurea	Cochrane systematic review[99] One study N=145	Occurrence of AEs: OR=3.95, 95% CI 2.00 to 7.80 Occurrence of GI AEs: OR=7.70, 95% CI 3.64 to 16.31
	One study N=219	52% glimepiride vs 81% acarbose, p=0.001.* Hypoglycaemic episodes were experienced by 18% of the glimepiride group and 1.9% of the acarbose group (there were no severe episodes requiring external help)
Acarbose vs pioglitazone	One study[101] N=271	Adverse effects occurred in 10.1% patients receiving pioglitazone, and in 39.7%) patients receiving acarbose**
Acarbose vs nateglinide	Cochrane systematic review[99] One study N=179	Occurrence of AEs: 1.92, 95% CI 1.05 to 3.5 Occurrence of GI effects: OR=3.22, 95% CI 1.66 to 6.24
Acarbose + metformin vs placebo + metformin	One study[104] N=83	75% of patients in the acarbose group reported side effects, compared to 55.8% of placebo patients. The main difference between the treatment groups was the higher frequency of GI complaints (Flatulence: Acarbose= 57.5% Placebo=27.9%)
Acarbose + sulfonylurea vs placebo + sulfonylurea	One study[106] N=69	48.5% of the patients in the acarbose group reported at least one adverse side effect, compared with 12.5% of the placebo group. The incidence of GI side effects was especially high in the acarbose group (flatulence 33% vs 6.3%, abdominal pain 9.1% vs 0.0)
	One study[105] N=373	33.3% of patients in the acarbose arm (reported AEs) versus 16% in the placebo group. Flatulence: reported by 26.2% in the acarbose group compared with 10.6% in the placebo.
Insulin + acarbose vs insulin + placebo	One study[103] N=112	44.6% patients in the acarbose group reported 46 drug-related events and 36.4% patients in the placebo group had 40 drug-related events. Incidence of side effects was similar in the two treatment groups, except for flatulence (acarbose 28.6% placebo 16.4%)

* The AE in glimepiride-treated patients were predominantly hypoglycaemic episodes, whereas GI symptoms prevailed in the acarbose group

** Pioglitazone: including six cases of edema (in five females and one male). Acarbose: mainly abdominal distension/flatulence which was reported by 46 patients

7.5 Oral glucose control therapies; from evidence to recommendations

7.5.1 Metformin

None of the newer evidence altered the priority given to metformin cited in the previous guideline. Although the specific cardioprotective effects of metformin suggested by the UKPDS study were open to challenge from some of the very recent studies, this was not on the basis of strong outcome data. Large observational studies from Canada and Scotland [111,112] appeared to support the widespread advantage of metformin over sulfonylureas, but the A Diabetes Outcome Progression Trial (ADOPT) study did not. The cardioprotective gains shown in the UKPDS and in the Scottish study far outweighed the concerns over lactic acidosis (provided renal function was adequate) in people with mild to moderate hepatic and cardiac disease. Nearly all the data related to overweight people, and there was little to guide metformin use in the normal weight person without extrapolation of the evidence. However, the overwhelming majority of people with Type 2 diabetes are overweight; in making this judgement however attention has to be paid to differences between ethnic groups.

The studies confirmed the glucose-lowering benefits of metformin in combination with all other available glucose-lowering medications. The widespread use of the previous recommendations in regard of levels of serum creatinine for reduction and discontinuing therapy was acknowledged. The complete substitution of estimated glomerular filtration rate (eGFR) for serum creatinine is not possible because of uncertainty surrounding methods of eGFR calculation in many people with Type 2 diabetes.

An evidence call on the use of extended-release metformin preparations did not find that their use in unselected patients reduced GI side effects. Differences in cost, and lack of other documented benefit, led to the conclusion that these therapies should be used only where intolerance to the immediate-release preparation had been documented.

7.5.2 Insulin secretagogues

Insulin secretagogues include the sulfonylureas and the rapid-acting insulin secretagogues (nateglinide and repaglinide).

The evidence base for the insulin secretagogues was more extensive than ascertained for the parent guideline. However, in many of the papers in which they are compared to other drugs they were being used as the comparator therapy rather than the investigated therapy. New evidence did not lead to new conclusions about the role of these drugs in clinical management, either from the point of view of efficacy or safety. Sulfonylureas proved as efficacious as newer comparator therapies in reducing surrogate outcomes (principally HbA1c) highlighting that they still have a role in modern management of Type 2 diabetes. In the ADOPT study[54] the sulfonylurea glibenclamide controlled HbA1c as effectively as rosiglitazone or metformin as monotherapy for the first 3 years, but persistence of glucose control after this time was worse. Cardiovascular outcomes were, if anything, better with the sulfonylurea.

There was little new evidence on comparative hypoglycaemia within the class, although the tighter blood glucose targets achieved in modern practice was leading to an overall increase in risk. With the relative demise in use of glibenclamide in the UK, hypoglycaemia was not regarded as a problem for most people, though sulfonylureas were regarded as a problem in some occupations (e.g. vocational drivers).

Where medication adherence is a concern the case for the general use of once daily or long-acting sulfonylurea preparations was supported.

The rapid-acting insulin secretagogues (meglitinides) also appeared to be efficacious in people with Type 2 diabetes, though the evidence for comparability of nateglinide to sulfonylureas was less certain. While the flexible use of these drugs in mealtime regimens appeared appealing for some people with diabetes, the multiple dosing requirements had inhibited uptake in clinical practice. These drugs are more expensive than sulfonylureas. Accordingly the GDG saw no reason to make general recommendation for their use in preference to the sulfonylureas, or to change the previous recommendations.

7.5.3 α-glucosidase inhibitors

The newer evidence did not add significantly to the previous understanding of the role of α-glucosidase inhibitors in the management of Type 2 diabetes, except in so far as the evidence suggested that the efficacy and intolerance problems were similar in oriental ethnic groups to Europids. Lower glucose-lowering efficacy, a higher rate of intolerance and dropout from therapy, and relative expense compared to generic metformin and sulfonylureas were noted. However, hypoglycaemia is not a problem when this drug is used as monotherapy, though through glucose lowering it may enhance the hypoglycaemic potential of other medications.

ORAL GLUCOSE CONTROL THERAPIES; RECOMMENDATIONS

For oral agent combination therapy with insulin please refer to chapter 11.

Metformin

1. **Start metformin treatment in a person who is overweight or obese (tailoring the assessment of body weight associated risk according to ethnic group*[c]) and whose blood glucose is inadequately controlled (see recommendation 16) by lifestyle interventions (nutrition and exercise) alone. (26)**

2. **Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight. (27)**

3. **Continue with metformin if blood glucose control remains or becomes inadequate (see recommendation 16) and another oral glucose-lowering medication (usually a sulfonylurea) is added. (28)**

4. **Step up metformin therapy gradually over weeks to minimise risk of gastrointestinal side effects. Consider a trial of extended absorption metformin tablets where gastrointestinal tolerability prevents continuation of metformin therapy. (29)**

5. **The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that:**
   - **5.1. due consideration can be given to the cardiovascular-protective effects of the drug**
   - **5.2. an informed decision can be made on whether to continue or stop the metformin.**

Insulin secretagogues

6. **Consider a sulfonylurea as an option for first-line glucose lowering-therapy if:**

[c] Please see the NICE Obesity guideline (CG43) www.nice.org.uk/guidance/index.isp?action= byID86=11000

6.1. **the person is not overweight**

6.2. **the person does not tolerate or is contraindicated**

6.3. **a rapid response to therapy is required because of hyperglycaemic symptoms.**

7. **Add a sulfonylurea as second-line therapy when blood glucose control remains, or becomes, inadequate (see recommendation 16) with metformin.**

8. **Continue with a sulfonylurea if blood glucose control remains, or becomes, inadequate (see recommendation 16) and another oral glucose-lowering medication is added. (34)**

9. **Prescribe a sulfonylurea with a low acquisition cost (but not glibenclamide) when an insulin secretagogue is indicated (see recommendation 32 and 33).**

10. **When drug concordance is a problem, offer a once daily, long-acting sulfonylurea.**

11. **Educate a person being treated with an insulin secretagogue, particularly if renally impaired, about the risk of hypoglycaemia.**

Rapid-acting insulin secretagogues

12. **Consider offering a rapid-acting insulin secretagogue to a person with an erratic lifestyle. (38)**

Acarbose

13. **Consider acarbose for a person unable to use other oral glucose-lowering medications. (39)**

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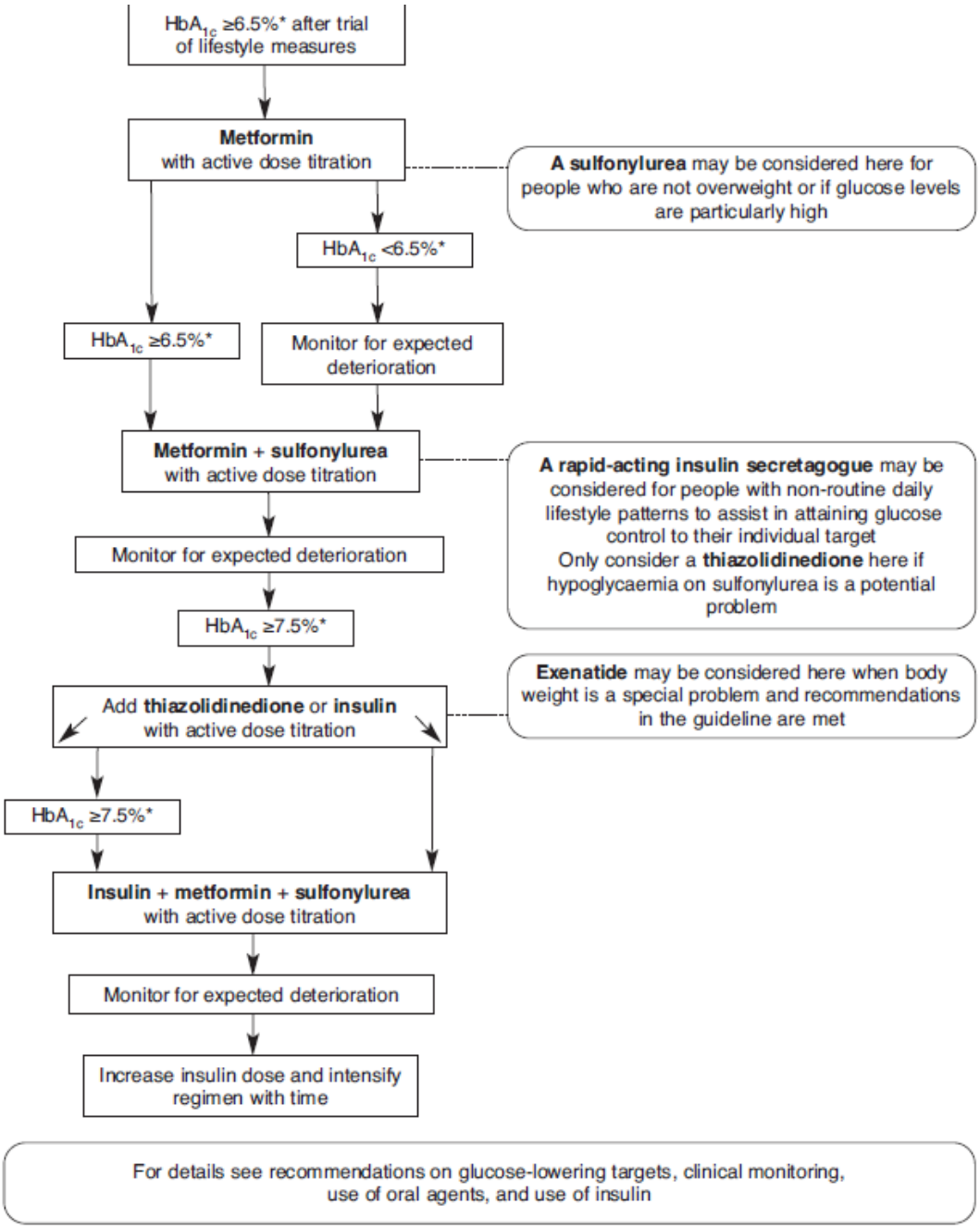

Figure 9.1 Scheme for the pharmacotherapy of glucose lowering in people with Type 2 diabetes
For details see recommendations on glucose lowering targets, clinical monitoring, use of oral agents, and use of insulin
* or as individually agreed

8 Oral glucose control therapies (2): other oral agents and exenatide

8.1 Clinical introduction

Maintenance of glucose control to target levels is achieved in only very few people with Type 2 diabetes for more than a few months using lifestyle measures, and as described in the previous chapter metformin and sulfonylureas are then generally used to assist in achieving glucose control targets.

However, as also discussed above, glucose control continues to deteriorate with time in most people with Type 2 diabetes, due to progressive failure of insulin secretion.[43–45] Accordingly other therapies need to be added with time, until such time as only exogenous insulin replacement will suffice. Other therapies may also be useful where metformin and sulfonylureas are contraindicated or not tolerated.

The newer oral agent therapies and exenatide are inevitably more expensive than the older ones and evidence of efficacy and side effects less well documented or more controversial. In the case of one class of drugs, the gliptins (GLP-1 enhancers), licensing during the finalisation of the guideline, and a paucity of published evidence at the time, has meant deferral of consideration of their role to a future guideline update.

The clinical questions concern the order with which these oral glucose-lowering medications should be introduced and added to one another in different groups of people with Type 2 diabetes. Because such people vary in attributes (such as body weight and insulin sensitivity) which can affect choice of medication, and because some medication side effects can have consequences for aspects of daily living (such as driving motor vehicles), blanket recommendations cannot be made for everyone with Type 2 diabetes.

8.2 Thiazolidinediones (glitazones)

8.2.1 Methodological introduction

A NICE technology appraisal (TA)[113] previously reviewed the evidence available up to April 2002 and made recommendations on the use of the glitazones (pioglitazone and rosiglitazone) in Type 2 diabetes. This guideline updates the appraisal and the GDG considered whether the appraisal recommendations should be changed in the light of new evidence.

Recommendations from the 2003 NICE TA:

‘For people with Type 2 diabetes, the use of a glitazone as second-line therapy added to either metformin or a sulfonylurea – as an alternative to treatment with a combination of metformin and a sulfonylurea – is not recommended except for those who are unable to take metformin and a sulfonylurea in combination because of intolerance or a contraindication to one of the drugs. In this instance, the glitazone should replace in the combination the drug that is poorly tolerated or contraindicated.

The effectiveness of glitazone combination therapy should be monitored against treatment targets for glycaemic control (usually in terms of haemoglobin A1c (HbA1c level) and for other cardiovascular risk factors, including lipid profile. The target HbA1c level should be set between 6.5% and 7.5%, depending on other risk factors.’

Rosiglitazone

Rosiglitazone is now licensed for use as monotherapy, combination therapy with metformin or a sulfonylurea, or as part of triple therapy with metformin and a sulfonylurea in the UK. Combination therapy with insulin is not licensed at present. As from January 2008 the European Medicines Agency (EMEA)[114] states that[d] 'rosiglitazone is indicated in the treatment of Type 2 diabetes mellitus:

- as monotherapy in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance
- as dual oral therapy in combination with:
  - metformin in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
  - a sulfonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite monotherapy with a sulfonylurea
- as triple oral therapy in combination with metformin and a sulfonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy.'
- Rosiglitazone is also available in two combination tablet formats (with metformin and also with glimepiride).

Studies reporting cardiovascular outcomes

A recent meta-analysis studying rosiglitazone's cardiovascular (CV) safety was identified.[115] This meta-analysis is based on 42 clinical trials of rosiglitazone, as compared either with other therapies for Type 2 diabetes or with placebo. The prespecified primary endpoints of interest were MI and death from CV causes. The meta-analysis includes nearly 30 trials for which the only available source was a clinical trial registry maintained by GlaxoSmithKline (GSK) since 2004.

A clinical trial reporting an unplanned interim analysis of the CV endpoints of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study was also identified.[116] The primary endpoint of the RECORD trial consists of an aggregate of time to first hospitalisation for a CV event or death from CV causes.

A further review of meta-analyses looking at the glitazones CV safety was undertaken in order to clarify the concerns in relation to the apparent risk of MI in patients treated with rosiglitazone. Five meta-analyses [117–121] and one Cochrane systematic review[122] were identified. Among the five meta-analyses, three were looking at rosiglitazone,[118,119,121] one at pioglitazone[117] and one at both glitazones agents.[120] EMEA, US Food and Drug Administration (FDA), and the Medicines and Healthcare products Regulatory Agency (MHRA) statements on glitazones were also reviewed along with an independent FDA meta-analysis on rosiglitazone presented at the FDA joint advisory committee on 30 July 2007.

d The European Medicines Agency (EMEA) have issued recent updates for rosiglitazone contained in the 'Update Summary of Product Characteristics' (SPC) dated: (a) 30 May 2007 to inform prescribers about new safety information concerning bone fractures following analysis of a long-term efficacy and safety study (ADOPT); (b) 21 November 2007 removing the contraindication for the use of rosiglitazone in combination with insulin with a warning regarding the risk of this combination; (c) 24 January 2008 to inform prescribers that the use of rosiglitazone in patients with IHD and/or peripheral arterial disease is not recommended. A new contraindication was also adopted stating that rosiglitazone must not be used in patients with acute coronary syndrome, such as angina or some types of MI.

Studies reporting surrogate outcomes

Seventeen RCTs were identified which compared rosiglitazone as monotherapy or in combination with other oral antidiabetic agents, with other oral antidiabetic agents and/or placebo.[54,61,62,123–136]

One RCT was not considered as part of the evidence due to methodological limitations.[61] Two studies comparing the combination of rosiglitazone and insulin therapy with other glucose- lowering medications were excluded because this combination is not currently licensed in the UK.[137,138]

Two additional studies looking at the addition of insulin glargine or rosiglitazone to the combination therapy of sulfonylurea plus metformin in insulin-naive patients were also identified.[139,140]

Studies were only included if sample sizes were equal to, or more than, 300; unless this meant the omission of a particular comparison.

Only one small study131 (N=95) was identified which compared metformin and rosiglitazone with metformin and a sulfonylurea. Such a comparison is useful in the consideration of whether rosiglitazone could displace sulfonylureas second line (added to metformin).

Three studies were found looking at the newer rosiglitazone fixed-dose combination (FDC) tablet of rosiglitazone combined with metformin.62,134,135 No study was found for the fixed-dose combination of rosiglitazone and glimepiride.

Pioglitazone

Pioglitazone is now licensed for use as monotherapy, combination therapy with metformin or a sulfonylurea, as part of triple therapy with metformin and a sulfonylurea, or in combination therapy with insulin. As from September 2007 the EMEA[114] states that, 'pioglitazone is indicated in the treatment of Type 2 diabetes mellitus:

- as monotherapy in patients (particularly overweight patients) inadequately controlled by diet and exercise for whom metformin is inappropriate because of contraindications or intolerance
- as dual oral therapy in combination with:
  - metformin in patients (particularly overweight patients) with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
  - a sulfonylurea, only in patients who show intolerance to metformin or for whom metformin is contraindicated, with insufficient glycaemic control despite maximal tolerated dose of monotherapy with a sulfonylurea
- as triple oral therapy in combination with:
  - metformin and a sulfonylurea, in patients (particularly overweight patients) with insufficient glycaemic control despite dual oral therapy
- pioglitazone is also indicated for combination with insulin in Type 2 diabetes mellitus patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.'

A Cochrane review[141] was identified which searched for pioglitazone RCTs of at least 24-weeks duration published up until August 2006. The review identified 22 studies including comparisons of pioglitazone monotherapy with placebo, pioglitazone monotherapy with any other OAD medication, and pioglitazone in combination with any other OAD medication or insulin, compared with any other OAD medication or insulin.

Most studies were of 6-months duration and investigated HbA1c and lipid parameters as primary outcomes. Only one study of mean follow-up duration 34.5 months included mortality

and morbidity outcomes within composite endpoints.[142] There was some controversy surrounding the results of this study however, in particular due to debate as to whether the main secondary endpoint was specified a-priori or whether this was the result of a post hoc analysis.[143,144]

Due to study heterogeneity, it was only possible to perform meta-analysis for the adverse event (AE) outcome 'oedema'.

The Cochrane systematic review noted at the moment of its publication, that there were five ongoing studies (Action to Control Cardiovascular Risk in Diabetes (ACCORD), Bypass Angio- plasty Revascularization Investigation 2 Diabetes (BARI-2D), Carotid Intima-media Thickness in Atherosclerosis using Pioglitazone (CHICAGO) study, Pioglitazone Effect on Regression and Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE), and Peroxisome Proliferator-activated Receptor study (PPAR)) which, according to the review, may contribute important information to future understanding of the role of pioglitazone in Type 2 diabetes.

Seven studies which compared pioglitazone as monotherapy or in combination with other OAD agents, with other OAD agents and/or placebo were identified in the re-runs.[145–151] One RCT was not considered as part of the evidence due to methodological limitations.[149]

Two of the studies identified by the re-runs were substudies of the Prospective Pioglitazone Clinical Trial In Macrovascular Events (PROactive) trial which assessed the effects of pioglitazone on mortality and macrovascular morbidity in patients with Type 2 diabetes and a previous MI or previous stroke.[150,152] Three other pioglitazone-based studies were identified as relevant from the re-runs.[145,146,148]

As noted in the rosiglitazone section a further review of meta-analyses published up to December 2007 looking at the glitazones CV safety was undertaken. In relation to pioglitazone two meta-analyses were identified as relevant: a meta-analysis analysing pioglitazone studies[117] and one looking at both glitazones agents.[120]

Thiazolidinediones and the risk of oedema

One meta-analysis[153] was identified assessing the overall risk for developing oedema secondary to glitazones (rosiglitazone and pioglitazone).

8.2.2 Health economic methodological introduction

The 2003 TA found no published economic studies on either pioglitazone or rosiglitazone and the economic evidence was based on the manufacturer submitted economic evaluations. The indications included were pioglitazone and rosiglitazone in oral combination treatment with either metformin or a sulfonylurea.[154]

The economic model submitted for pioglitazone was reviewed for the original 2001 TA.[155] The model compared pioglitazone combination therapy (added to either sulfonylureas or metformin) compared with other combination therapies or changing to insulin. The key results were removed from the 2004 TA because they were submitted in confidence.

The model submitted for rosiglitazone compared rosiglitazone plus a sulfonylurea, or metformin to other CTs or changing to insulin.

Seven other papers were identified of which only one was considered relevant. Beale et al.156 conducted a cost-effectiveness analysis of rosiglitazone in a population of obese and overweight Type 2 diabetes patients in the UK.

In the re-run of the literature search a further paper was identified comparing pioglitazone with rosiglitazone in the UK.[157]

An economic model was constructed based upon the UKPDS outcomes model to inform the GDG deliberations with regard to choice of glitazones or exenatide as third-line therapy in comparison to other third-line options. This is presented in appendix C available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

8.2.3 Evidence statements

8.2.3.1 Rosiglitazone

Cardiovascular outcomes

One meta-analysis[115] concluded that rosiglitazone was associated with a significant increase in the risk of MI and a borderline significant finding for death from CV causes (see tables 10.1 and 10.2).[e]

Table 10.1 Rosiglitazone meta-analysis: myocardial infarction data

MI	Rosiglitazone group	Control group	Odds ratio	p value
Small trials	44/10,280	22/6,105	1.45 95 CI% 0.88 to 2.39	0.15
DREAM	15/2,635	9/2,634	1.65 95 CI% 0.74 to 3.68	0.22
ADOPT	27/1,456	41/2,895	1.33 95 CI% 0.80 to 2.21	0.27
Overall	86	72	1.43 95 CI% 1.03 to 1.98	0.03

Table 10.2 Rosiglitazone meta-analysis: death from cardiovascular causes data

Death from CV causes	Rosiglitazone group	Control group	Odds ratio	p value
Small trials	25/6,557	7/3,700	2.40 95 CI% 1.17 to 4.91	0.02
DREAM	12/2,365	10/2,634	1.20 95 CI% 0.52 to 2.78	0.67
ADOPT	2/1,456	5/2,854	0.80 95 CI% 0.17 to 3.86	0.78

Findings from an interim report of the RECORD study[f116] were inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalisation or death from CV causes. The report concluded that rosiglitazone was associated with a significant increase in the risk of congestive heart failure (CHF) (see table 10.3).

e Another pharma-sponsored meta-analysis showed a similar higher risk of MI for rosiglitazone (odds ratio, 1.31; 95% CI 1.01 to >1.70). This meta-analysis was submitted to the US Food and Drug Administration (FDA) in 2006.

f The RECORD trial is scheduled to end when there is a median of 6 years of follow-up; the mean follow-up reported in the interim analysis is 3.75 years.

Table 10.3 RECORD study: 3.75 years results

Endpoint	RSG group	Control group	HR	p
Hospitalisation or death from CV events	217	202	1.08 95% CI 0.89 to 1.31	0.43
Death from CV events	29	35	0.83 95% CI 0.51 to 1.36	0.46
MI	43	37	1.16 95% CI 0.75 to 1.81	0.50
CHF	38	17	2.24 95% CI 1.27 to 3.97	0.006

RSG, rosiglitazone

Overall, the interim results of the RECORD trial do not provide any assurance of the safety of treatment with rosiglitazone in terms of the risk of myocardial ischaemic events.

Studies identified as part of the further review of the evidence published up to December 2007 (rosiglitazone and pioglitazone – meta-analyses and systematic reviews)

None of the 18 rosiglitazone trials analysed by the Cochrane systematic review[122] included mortality or morbidity as a primary or secondary endpoint. The review stated that active glucose-lowering agents like metformin, glibenclamide, or glimepiride resulted in similar reductions of HbA1c compared to rosiglitazone treatment. The only outcome that could be subjected to meta-analysis was oedema whose incidence was significantly raised in patients receiving rosiglitazone (OR 2.27, 95% CI 1.83 to 2.81). The systematic review concluded that new studies should focus on patient-oriented outcomes to clarify the benefit–risk ration of rosiglitazone therapy.

Three of the four rosiglitazone meta-analyses reported a statistically significant increase in the RR of myocardial ischaemic events among patients taking rosiglitazone (see table 10.4). In addition, the meta-analysis by Singh[119] concluded that among patients with Type 2 diabetes, rosiglitazone use for at least 12 months is associated with a significantly increased risk of heart failure, without a significantly increased risk of CV mortality.

Table 10.4 Rosiglitazone meta-analyses (June–December 2007)

Meta-analysis	Event	Rosiglitazone	Control	Odds/hazard ratio	p value
GSK (2007)[412]	MI	171/8,604	85/5633	1.31 95% CI 1.01 to 1.72	<0.05
FDA (2007)[413]	Any ischemia	171/8,604	85/5633	1.4 95% CI 1.1 to 1.8	0.02
Singh (2007)[119]	MI	94/6,421	83/7,870	1.42 95% CI 1.06 to 1.91	0.02

One additional meta-analysis on rosiglitazone[118] reanalysed the data set of 42 trials considered originally by Nissen and Wolski[115] by using various modelling and weighting

statistical methods (e.g. inclusion of trials with zero events). The authors concluded that the risk for MI and death from CV disease for diabetic patients taking rosiglitazone is uncertain. They also advocate for new long-term patient-oriented outcome studies on rosiglitazone to clarify its safety.

A meta-analysis of 19 pioglitazone trials[117] (with the PROactive study being the largest study included) reported that treatment with pioglitazone was associated with a significantly lower risk of death, MI, or stroke. Pioglitazone was also associated with a significantly higher risk of serious heart failure (see table 10.5).

Table 10.5 Pioglitazone meta-analyses (June–December 2007)

Meta-analysis	Event	Pioglitazone	Control	Odds/hazard ratio	p value
Lincoff (2007)[117]	Death/MI/stroke	375/8,554	450/7,836	0.82 95% CI 0.72 to 0.94	0.005
	Death/MI	309/8,554	357/7,836	0.85 95% CI 0.73 to 0.99	0.04
	Serious heart failure	200/8,554	139/7,836	1.41 95% CI 1.14 to 1.76	0.002

A further meta-analysis[120] looking at the risk of CHF and CV death in patient with pre-diabetes and Type 2 diabetes treated with glitazones reported a significantly higher risk of developing heart failure in those treated with rosiglitazone or pioglitazone compared with controls (RR 1.72 95% CI 1.21 to 2.42, p=0.002). By contrast, the study reported that the risk of CV death was not increased with either of the two glitazones.

8.2.3.2 Glycaemic control

Head-to-head comparisons

Two studies comparing different monotherapies concluded that glycaemic control (HbA1c and FPG values) was similar when rosiglitazone was compared with glibenclamide.[128,129] A third study evaluating monotherapies with rosiglitazone, glibenclamide and metformin in a 4-year clinical trial, concluded that in the long term, rosiglitazone-treated patients experienced a significantly longer durability in terms of reduction of HbA1c and FPG levels.[54]

Combination therapy

Rosiglitazone used in combination with metformin, a sulfonylurea, repaglinide or insulin, significantly improved glycaemic values (HbA1c and FPG) compared to these agents or rosiglitazone used as monotherapy (with or without placebo). This was also true in cases where the monotherapy was uptitrated.

Other studies comparing the addition of rosiglitazone to either metformin or a sulfonylurea with the combination of metformin and a sulfonylurea failed to demonstrate significant between-treatment differences in terms of glycaemic control (HbA1c and FPG).

8.2.3.3 Triple therapy

Two studies [139,140] compared the addition of rosiglitazone to the combination of sulfonylurea and metformin with the addition of insulin glargine. HbA1c improvements from baseline were similar in both groups with no significant difference between the groups. However, one study[139] found that when baseline HbA1c was more than 9.5%, the reduction of HbA1c with

insulin glargine was significantly greater than with rosiglitazone. Both studies revealed significantly greater reductions in FPG levels in the insulin glargine group.

Fixed-dose combination

Fixed-dose combination of rosiglitazone and metformin produced significantly greater reductions in HbA1c and FPG values when compared to rosiglitazone and metformin used as monotherapies. This was also true in cases where the monotherapy was uptitrated.[62,134,135]

8.2.3.4 Rosiglitazone vs pioglitazone

Only one study compared metformin used in combination with rosiglitazone with treatment with metformin and pioglitazone. The study did not find significant differences between the groups in terms of HbA1c and FPG values.[133]

Table 10.6 HbA_{1c} outcomes

Comparison	Study	Change in HbA_{1c} %
Rosiglitazone vs repaglinide vs repaglinide & rosiglitazone	One study[125] N=252 1+	Greater reduction for combination therapy (–1.43%) than for repaglinide monotherapy (–0.17%) or rosiglitazone (–0.56%) (p<0.001 for combination vs either monotherapy). p≤0.001 for combination vs either monotherapy
Rosiglitazone vs glibenclamide	One study[128] N=203 1	Comparable at endpoint*
	One study[129] N=598 1+	NS
Rosiglitazone vs glibenclamide vs metformin	One study[54] N=4,360	After 6 months, the rate of increase in HbA_{1c} was greatest in the glibenclamide group, which had annual increases of 0.24%, intermediate in the metformin group, which had annual increases of 0.14%; and least in the rosiglitazone group, which had increases of 0.07%, (p<0.001)
Rosiglitazone + sulfonylurea vs placebo + sulfonylurea	One study[124] N=227 1+	The HbA_{1c} reduction with RSG + SU was significantly different from uptitrated SU alone (–0.79%, p<0.0001)
Rosiglitazone + sulfonylurea vs sulfonylurea	One study[127] N=348 1+	The RSG and SU group showed a decrease in HbA_{1c} 9.1% to 7.9%, mean change –1.1, 95% CI –1.37 to –0.89, from baseline. HbA_{1c} increased slightly in the control group. The difference between the treatment groups was significant, (p=0.0001)
Rosiglitazone + gliclazide vs gliclazide uptitration	One study[132] N=471 1+	HbA_{1c} was reduced by ≥0.7% 65% of patients in the combination treatment group compared to 21% in the uptitrated gliclazide group, (p<0.0001)
Rosiglitazone + glibenclamide vs glibenclamide uptitration	One study[130] N=340 1+	Combination therapy reduced HbA_{1c} by 0.81% compared with glibenclamide monotherapy, (p<0.0001)
Rosiglitazone + metformin vs glimepiride + metformin	One study[131] N=95 1+	NS
	One study[123] N=99 1+	NS
Rosiglitazone + metformin vs glibenclamide + metformin	One study[126] N=389 1+	NS
Rosiglitazone + metformin or sulfonylurea vs metformin + sulfonylurea	One study[136] N=1,122 1+	NS

continued

Table 10.6 HbA_{1c} outcomes – *continued*

Comparison	Study	Change in HbA_{1c} %
Rosiglitazone + sulfonylurea + metformin vs insulin glargine + sulfonylurea + metformin	One study[139] N=217 1+	Improvements from baseline were similar in both groups (–1.66% vs –1.51% for glargine and rosiglitazone respectively) with no significant difference between the groups, (p=0.14) In patients with HbA_{1c} glargine resulted in significantly greater A_{1C} reduction compared with rosiglitazone, (p<0.05)
Insulin glargine + sulfonylurea + metformin vs rosiglitazone + sulfonylurea + metformin	One study[140]	NS
Rosiglitazone/metformin (FDC) vs metformin uptitrated	One study[62] N=569 1++	The treatment difference was –0.22% (95% CI –0.36 to –0.09, p=0.001) in favour of the FDC
Rosiglitazone/metformin (FDC) vs metformin monotherapy	One study[135] N=526	At week 32 there was a reduction from baseline in mean HbA_{1c} in the RSG/MET group from 7.2±0.6 to 6.7±0.8% compared with 7.2±0.6 to 6.8±0.9% in the MET group, (p=0.0357)
Rosiglitazone/metformin (FDC) vs rosiglitazone vs metformin	One study[134] N=468 1+	At week 32, reductions in HbA_{1c} were observed in all the treatment groups. The greatest mean reduction, 2.3%, was observed in the RSG/MET group from a baseline of 8.9±1.1% to 6.6±1.0% at study end. This reduction was significantly greater when compared with the 1.8% reduction in the MET group (p=0.0008) and 1.6% in the RSG group (p<0.0001)
Metformin + pioglitazone 15 mg OD vs metformin + rosiglitazone 4 mg OD	One study[133] N=96 1+	NS

*Significance tests not performed
MET, metformin; RSG, rosiglitazone; SU, sulfonylurea

Table 10.7 Fasting plasma glucose/fasting blood glucose outcomes

Comparison	Study	Change in FPG/FBG
Rosiglitazone vs repaglinide vs repaglinide and rosiglitazone	One study[125] N=252 1+	Greater for combination therapy (–5.2 mmol/l, –94 mg/dl) than for repaglinide monotherapy (–3.0 mmol/l, –54 mg/dl) or rosiglitazone monotherapy (–3.7 mmol/l, –67 mg/dl) p≤0.001 for combination vs either monotherapy
Rosiglitazone vs glibenclamide	One study[128] N=203 1+	Mean FPG decreased from 236.4 to 161.1 mg/dl for rosiglitazone and from 245.5 to 188.3 mg/dl for glibenclamide*
	One study[129] N=598	The difference (0.6 mmol/l) between the mean FPG reduction with rosiglitazone 8 mg/d (–2.3 mmol/l) and glibenclamide (–1.7 mmol/l) was statistically significant (95% CI –15.4 to –0.6, p=0.03)

continued

Table 10.7 Fasting plasma glucose/fasting blood glucose outcomes – *continued*

Comparison	Study	Change in FPG/FBG
Rosiglitazone vs glibenclamide vs metformin	One study[54] N=4,360	After 6 months, the rate of increase in FPG levels was greatest in the glibenclamide group, which had annual increases of 0.31 mmol/l; intermediate in the metformin group, which had annual increases of 0.15 mmol/l; and least in the rosiglitazone group, which had increases of 0.04 mmol/l, (p<0.001)
Rosiglitazone + sulfonylurea vs placebo + sulfonylurea	One study N=227 1+	FPG was reduced with RSG + SU but increased with uptitrated SU alone The difference between treatment groups was statistically significant (–2.09 mmol/l, p<0.0001)
Rosiglitazone + sulfonylurea vs sulfonylurea	One study N=348 1+	The RSG and SU group showed a decrease in mean FPG (199 to 166 mg/dl, mean change –38.4, 95% CI –47.1 to –19.7) from baseline. Mean FPG increased slightly in the control group. The difference between the treatment groups was significant (p=0.0001)
Rosiglitazone + gliclazide vs gliclazide uptitration	One study[132] N=471 1+	FPG was reduced by 3.0 mmol/l (p=0.0001) in the rosiglitazone plus gliclazide group compared to the uptitrated gliclazide group after 26 weeks
Rosiglitazone + glibenclamide vs glibenclamide uptitration	One study[130] N=340 1+	Combination therapy reduced FPG by 2.4 mmol/l compared with glibenclamide monotherapy (p<0.0001)
Rosiglitazone + metformin vs metformin + glimepiride	One study[131] N=95 1+	NS
	One study[123] N=99 1+	NS
Rosiglitazone + metformin vs glibenclamide + metformin	One study[126] N=389 1+	NS
Rosiglitazone + metformin or sulfonylurea vs metformin + sulfonylurea	One study[136] N=1,122 1+	NS
Rosiglitazone + sulfonylurea + metformin vs insulin glargine + sulfonylurea + metformin	One study[139] N=217 1+	FPG decreased significantly from baseline to endpoint in both groups; however, greater reductions occurred in the insulin glargine group than in the rosiglitazone group (–3.60±0.23 vs –2.57±0.22 mmol/l) p=0.001
Insulin glargine + sulfonylurea + metformin vs rosiglitazone + sulfonylurea + metformin	One study[140]	Patients in the glargine group experimented a significantly greater reduction in FPG levels when compared with the rosiglitazone group (glargine –3.60±0.23 mmol/l; rosiglitazone –2.57±0.22 mmol/l p=0.001)
Rosiglitazone/metformin (FDC) vs metformin uptitrated	One study[62] N=569 1++	The treatment difference was –18.3 mg/dl (95% CI –23.5 to –13.2; p<0.0001) in favour of the FDC

continued

Table 10.7 Fasting plasma glucose/fasting blood glucose outcomes – *continued*

Comparison	Study	Change in FPG/FBG
Rosiglitazone/metformin (FDC) vs metformin monotherapy	One study[135] N=526	At week 32 the reduction in FPG from baseline was greater in the RSG/MET group. The proportion of participants achieving a FPG target of <7.0 mmol/l at week 32 was 56% in the RSG/MET group compared with 38% in the MET group (odds ratio = 2.33, p<0.0001)
Rosiglitazone/metformin (FDC) vs rosiglitazone vs metformin	One study[134] N=468 1+	At week 32 the greatest mean decrease in FPG was seen with RSG/MET. This difference in FPG reduction was clinically and statistically significant compared with the 2.8 mmol/l reduction in the MET group (p<0.0001) and the 2.6 mmol/l reduction in the RSG (p< 0.0001)
Metformin + pioglitazone 15 mg OD vs metformin + rosiglitazone 4 mg OD	One study[133] N=96 1+	NS

* Significance testing not performed

Lipid profile

Overall, treatment with rosiglitazone (used as monotherapy, dual therapy, fixed-dose combination or triple therapy) was associated with significantly larger increases in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) compared to other therapies.[g] In addition, rosiglitazone was associated with a significantly greater use of lipid-lowering therapy.

The study comparing rosiglitazone and pioglitazone showed that patients in the pioglitazone add- on to metformin group experienced significant reductions (p≤0.05) in TC, low-density lipoprotein (LDL) and triglyceride (TG) levels when compared to those receiving rosiglitazone + metformin. High-density lipoprotein (HDL) levels were significantly higher (p≤0.05) in patients treated with pioglitazone + metformin when compared to patients in the rosiglitazone add-on to metformin group.

Table 10.8 Lipid profile outcomes* (changes from baseline)

Comparison	Study	TC	LDL	TG	HDL
Rosiglitazone vs repaglinide vs repaglinide and rosiglitazone	One study[125] N=252 1+	+8% +1% +5%	+9% +1% +6%	–8% +4% –4%	+7% 0% +7%
Rosiglitazone vs glibenclamide	One study[128] N=203 1+	NE	+7.7 mg/dl –8.9 mg/dl	–2.8 mg/dl –13.8 mg/dl	+7.7 mg/dl
	One study[129] N=598 1+	+0.7 mmol/l –0.1 mmol/l	+0.4 mmol/l –0.1 mmol/l	NS	+0.17 mmol/l –0.08 mmol/l

continued

g For TGs and HDL-C no clear pattern emerged.

Table 10.8 Lipid profile outcomes* (changes from baseline) – *continued*

Comparison	Study	TC	LDL	TG	HDL
Rosiglitazone vs glibenclamide vs metformin	One study[54] N=4,360	Not reported	RSG 104 mg/dl GLI 99.3 mg/dl MET 96.5 mg/dl	RSG 163.5 mg/dl GLI 171.7 mg/dl MET 166.5 mg/dl	RSG 51.8 mg/dl GLI 48.9 mg/dl MET 50.5 mg/dl
Rosiglitazone + sulfonylurea vs placebo + sulfonylurea	One study[124] N=227	+6.2% –1.7%	+3.3% –1.3%	+9.5% –5.4%	+2.7% +1.6%
Rosiglitazone + sulfonylurea vs sulfonylurea	One study[127] N=348 1+	+14 mg/dl –2 mg/dl	+5 mg/dl –5 mg/dl	NE	+4 mg/dl +2 mg/dl
Rosiglitazone + gliclazide vs gliclazide uptitration	One study[132] N=471	+8.8% +1.2%	+10.9% 0%	+7.7% +3.5%	+6.8% 0%
Rosiglitazone + glibenclamide vs glibenclamide uptitration	One study[130] N=340 1+	+7.7% –5%	+7.0% –6.7%	–5.8% –1.9%	+15.8% +14.6%
Rosiglitazone + metformin vs metformin + glimepiride	One study[131] N=95 1+	NE	NE	NE	NE
	One study[123] N=99 1+	+7 mg/dl (R+M) –15 mg/dl (M+G)	+4 mg/dl (R+M) –16 mg/dl (M+G)	–57 mg/dl (R+M) –41 mg/dl (M+G)	0 mg/dl (R+M) +1 mg/dl (M+G)
Rosiglitazone/metformin (FDC) vs metformin uptitrated	One study[62] N=569 1++	FDC –0.1% MET –10.7%	FDC +3.4% MET +14.5%	FDC –1.2% MET –8.5%	FDC +4.1% MET –1.3%
Rosiglitazone/metformin (FDC) vs metformin monotherapy	One study[135] N= 526	FDC +4.1% MET –5.9%	FDC +2.8% MET –8.8%	FDC +1.9% MET –6.2%	FDC +7.9% MET +2.6%
Rosiglitazone/metformin (FDC) vs rosiglitazone vs metformin	One study[134] N=468 1+	FDC –2.2% RSG +5.3% (p=0.0006 vs FDC) MET –9% (p=0.009 FDC)	FDC –0.2% RSG +4.5% (p=0.16 vs FDC) MET -10.7% (p=0.016 vs FDC)	FDC –18.7% RSG –4.8% (p=0.005 vs FDC) MET -15.4% (p=0.5 vs FDC)	FDC +5.8% RSG +3.1% (p=0.25 vs FDC) MET 0% vs (p=0.01 vs FDC)

continued

Table 10.8 Lipid profile outcomes* (changes from baseline) – *continued*

Comparison	Study	TC	LDL	TG	HDL
Rosiglitazone + SU or metformin vs metformin + SU	One study[136] N=1,122 1+	RSG + M vs M + SU Difference 0.53 mmol/l p<0.001 RSG+ SU vs SU + M Difference 0.56 mmol/l p=0.001	RSG + M vs M + SU Difference 0.30 mmol/l p no reported RSG+ SU vs SU + M Difference 0.48 mmol/l p no reported	RSG + M vs M + SU Difference 0.26 mmol/l p=0.16 RSG+ SU vs SU + M Difference 0.06 NS	RSG + M vs M + SU Difference 0.06 mmol/l p=0.001 RSG+ SU vs SU + M Difference 0.01 NS
Rosiglitazone + sulfonylurea + metformin vs insulin glargine + sulfonylurea + metformin	One study[139] N=217 1+	Insulin glargine: (196 to 186 mg/dl vs rosiglitazone: 196 to 215 mg/dl (–4.4 vs +10.1%) respectively p=0.0001)	Insulin glargine: (117 to 115 mg/dl vs rosiglitazone 106 to 120 mg/dl (–1.4 vs +13.1%) respectively p=0.0004)	Insulin glargine: (217 to 176 mg/dl vs rosiglitazone 241 to 252 mg/dl (–19.0 vs +4.6%) respectively p=0.0011)	Insulin glargine: unchanged but increased with rosiglitazone (+4.4%, p=0.0407)
Metformin + pioglitazone 15 mg OD vs metformin + rosiglitazone 4 mg OD	One study[133] N=96 1+	–0.49 mmol/l +0.21 mmol/l	–0.20 mmol/l +0.08 mmol/l	–0.48 mmol/l –0.03 mmol/l	+0.10 mmol/l –0.03 mmol/l

* Significance testing not performed

Body weight/body mass index

Across most of the studies treatment with rosiglitazone was associated with a significant increase in body weight/BMI.

Table 10.9 Weight/body mass index

Comparison	Study	Change in weight/BMI
Rosiglitazone vs repaglinide vs repaglinide and rosiglitazone	One study[125] N=252 1+	Mean change +2.3 kg +1.6 kg +4.4 kg*
Rosiglitazone vs glibenclamide	One study[128] N=203 1+	Mean body weight increased by 3.4 kg with glibenclamide and by 5 kg with rosiglitazone*
	One study[129] N=598 1+	Mean body weight increased by 1.9 kg with glibenclamide and by 2.9 kg with rosiglitazone

continued

Table 10.9 Weight/body mass index – *continued*

Comparison	Study	Change in weight/BMI
Rosiglitazone vs glibenclamide vs metformin	One study[54] N=4,360	Over a period of 5 years, the mean weight increased in the rosiglitazone group (change from baseline, 4.8 kg; 95% CI 4.3 to 5.3) but decreased in the metformin group (–2.9 95% CI –3.4 to –2.3 kg). In the glibenclamide group, weight gain occurred in the first year (1.6 kg; 95% CI 1.0 to 2.2), then remained stable. p values were significant for the treatment differences (RSG vs MET and RSG vs GLI)
Rosiglitazone + sulfonylurea vs placebo + sulfonylurea	One study[124] N=227 1+	Body weight increased by 4.3 kg with RSG + SU compared with a decrease of 1.2 kg with uptitrated SU alone*
Rosiglitazone + sulfonylurea vs sulfonylurea	One study[127] N=348 1+	NE
Rosiglitazone + gliclazide vs gliclazide uptitration	One study[132] N=471 1+	A significant increase in body weight was observed in patients receiving rosiglitazone plus gliclazide versus uptitrated gliclazide (3.4 kg, p=0.0001)
Rosiglitazone + libenclamide vs glibenclamide uptitration	One study[130] N=340 1+	Treatment with rosiglitazone + glibenclamide increased body weight by a mean of 3.1 kg. There was a small and non-significant increase in body weight of 0.14 kg compared with baseline in the uptitrated glibenclamide group*
Rosiglitazone + metformin vs metformin + glimepiride	One study[131] N=95 1+	NS (BMI)
	One study[123] N=99 1+	NS (BMI)
Rosiglitazone + metformin vs glibenclamide + metformin	One study[126] N=389 1+	At trial end, there were comparable increases in body weight in both treatment groups compared with baseline, with a mean weight gain of 1.94±4.63 kg with RSG + MET compared with 1.50±3.53 kg with GLY + MET
Rosiglitazone/metformin (FDC) vs metformin uptitrated	One study[62] N=569 1++	There was a mean (SE) increase from baseline in weight in the RSG/MET group (1.3 (0.22) kg) and a mean decrease in the MET group (-0.9 (0.26) kg)*
Rosiglitazone/metformin (FDC) vs metformin monotherapy	One study[135] N=526	Patients receiving RSG/MET experienced weight gain (0.01±0.3 kg) compared with a decrease of 1.9±0.3 kg in the MET group (p<0.0001 for difference)
Rosiglitazone/metformin (FDC) vs rosiglitazone vs metformin	One study[134] N=468 1+	Mean weight was reduced –2.9±4.4 kg with MET and increased 1.5±5.9 kg with RSG. There was no overall change in mean body weight with RSG/MET. Significant treatment differences in weight between RSG/MET and MET (p<0.001) and RSG/MET and RSG (p=0.01) were observed

continued

Table 10.9 Weight/body mass index – *continued*

Comparison	Study	Change in weight/BMI
Rosiglitazone + SU or metformin vs metformin + SU	One study[136] N=1,122 1+	Increases in body weight were observed in both arms of the metformin stratum; however, this increase was greater with rosiglitazone (+2.3 kg) than sulfonylurea (1.1 kg), p=0.003 In the sulfonylurea stratum there was a significant increase in body weight with rosiglitazone (+3.4 kg) compared with a slight decrease with metformin (–0.9 kg) p<0.001
Rosiglitazone + sulfonylurea + metformin vs insulin glargine + sulfonylurea + metformin	One study[139] N=217 1+	Rosiglitazone-treated patients gained more weight (3.0±0.4 kg) than those on insulin glargine (1.7±0.4 kg) (p=0.02)
Metformin + pioglitazone 15 mg OD vs metformin + rosiglitazone 4 mg OD	One study[133] N=96 1+	NS

* Significance testing not performed

Quality of life

When the addition of rosiglitazone to the combination of sulfonylurea and metformin (triple therapy) was compared to the addition of insulin glargine, significantly greater improvements were reported across several health-related quality of life outcomes (e.g. symptom score, mood symptoms, perception of general health) by patients in the glargine group compared to those in the rosiglitazone group.

Adverse events

Apart from the CV data described earlier in this chapter, the evidence appraised suggested that patients treated with rosiglitazone experienced a significantly higher incidence of oedema and anaemia. Similarly, rosiglitazone was associated with a significant risk of distal fractures in women patients.

Table 10.10 Adverse events

Comparison	Study	Change in AE
Rosiglitazone vs repaglinide vs repaglinide and rosiglitazone	One study[125] N=252 1+	Minor hypoglycaemia NS
Rosiglitazone vs glibenclamide	One study[128] N=203 1+	The absolute number and percentage of patients with at least one AE was similar between the two groups* Rosiglitazone-treated patients had more reports of oedema and anaemia (6.7% each) than patients in the glibenclamide group (1 and 2%)* Signs and symptom of hypoglycaemia were reported more commonly in glibenclamide-treated patients (7.1%) than in rosiglitazone-treated patients (1.9%)*

continued

Table 10.10 Adverse events – *continued*

Comparison	Study	Change in AE
	One study[129] N=598 1+	The most commonly reported AE was hypoglycaemia, which occurred in 25 patients (12.1%). Oedema was more common with rosiglitazone 8 mg/d (17 patients, 8.9%) than with rosiglitazone 4 mg/d (7 patients, 3.5%) or glibenclamide (4 patients, 1.9%) Small dose-dependant and statistically significant reductions in haemoglobin and haematocrit were observed in the rosiglitazone 4 mg/d (0.48 g/dl and 1.92% respectively) and rosiglitazone 8 mg/d (0.98 g/dl and 3.33% respectively) groups
Rosiglitazone vs glibenclamide vs metformin	One study[54] N=4,360	CV events: CV events were reported in 62 patients in the rosiglitazone group, 58 in the metformin group, and 41 in the glibenclamide group For all investigator reported CHF events, 22 occurred in the rosiglitazone group (1.5%), 19 in the metformin group (1.3%), and nine in the glibenclamide group (0.6%). The hazard ratio for CHF in the rosiglitazone group, as compared with the metformin group, was 1.22 (95% CI 0.66 to 2.26, p=0.52); the hazard ratio for the rosiglitazone group, as compared with the glibenclamide group, was 2.20 (95% CI, 1.01 to 4.79; p=0.05) Anaemia: Treatment with rosiglitazone was associated with a significantly decreased hematocrit, as compared with both metformin and glibenclamide (p<0.001 for both comparisons) Fractures: A higher rate of fractures was seen in the group receiving rosiglitazone More women in the rosiglitazone group had upper limb fractures involving the humerus and hand. Lower limb fractures were primarily increased in the foot GI: Rosiglitazone was less frequently associated with GI side effects than was metformin (p<0.001) Hypos: Fewer patients in the rosiglitazone group than in the glibenclamide group had hypoglycaemia (p<0.001)
Rosiglitazone + sulfonylurea vs placebo + sulfonylurea	One study[124] N=227 1+	Oedema was more frequent with RSG + SU (23 vs 9%)* There was no difference in the incidence of CHF between groups* The incidence of symptomatic hypoglycaemia was similar in the two treatment groups*
Rosiglitazone + sulfonylurea vs sulfonylurea	One study[127] N=348 1+	Hypoglycaemia occurred in 19 cases in the RSG and SU group and two in the SU alone group (p<0.001)

continued

Table 10.10 Adverse events – *continued*

Comparison	Study	Change in AE
Rosiglitazone + gliclazide vs gliclazide uptitration	One study[132] N=471 1+	The % of patients reporting on-therapy AEs in the rosiglitazone + gliclazide group (71%) was higher than in the uptitrated gliclazide group (59%)* Incidence of hypoglycaemia was 6% total; 1% severe in the rosiglitazone + gliclazide group and 2% total; 0.4% severe in the uptitrated gliclazide group* More patients in the combination group experienced oedema (11% vs 3%)*
Rosiglitazone + libenclamide vs glibenclamide uptitration	One study[130] N=340 1+	Incidence of hypoglycaemia was 18.5% in the rosiglitazone + glibenclamide group and 4.1% in the uptitrated glibenclamide group Incidence of oedema was 9.5% in the rosiglitazone + glibenclamide group and 2.5% in the uptitrated glibenclamide group*
Rosiglitazone + metformin vs metformin + glimepiride	One study[131] N=95 1+	Between group difference in terms of patients who had adverse effects: NS
Rosiglitazone + metformin vs glibenclamide + metformin	One study[126] N=389 1+	There was one death due to a serious AE (acute MI), which occurred in the RSG + MET group and was judged unlikely to be related to study medication The incidence of hypoglycaemia was 12.4% (23/124) with GLY + MET compared with 1.0% (2/133) of patients with RSG + MET Peripheral oedema was reported by 5.4% (11/133) of patients with RSG + MET compared with 2.2% (4/124) with GLY + MET The incidence of anaemia was 4.4% (9/133) and 1.1% (2/124) with RSG + MET and GLY + MET respectively
Rosiglitazone/metformin (FDC) vs metformin uptitrated	One study[62] N=569 1++	GI disorders were the most common leading to withdrawal in 5% of the MET group and 3% in the RSG/MET group 1% of patients in the RSG/MET group and 0.4% in the MET group reported on-therapy hypoglycaemia The incidence of diarrhoea was 14% in the MET group and 6% with RSG/MET. This was 9% and 6% for abdominal pain respectively Oedema was reported in 3% who received RSG/MET and in 1% in the MET group*

continued

Table 10.10 Adverse events – *continued*

Comparison	Study	Change in AE
Rosiglitazone/metformin (FDC) vs metformin monotherapy	One study[135] N=526	The overall proportion of participants with GI AEs was similar in both groups (33%); however, there was a reduced incidence of diarrhoea (8 vs 18%) in the RSG/MET group compared with the MET group Hypoglycaemia was reported in 17 participants (7%) in the RSG/MET group compared with 10 participants (4%) in the MET group. Six participants (2%) in the RSG/MET group vs none in the MET group had oedema Four participants (2%) in the RSG/MET vs none in the MET group had ischaemic events (two cases of angina pectoris, one myocardial ischemia, and one MI and coronary artery insufficiency) There were greater reductions in mean haemoglobin a haematocrit over 32 weeks in the RSG/MET group (Hb –0.75±0.007 g/dl, Hct –0.02±0.002%) compared with the MET group (Hb –0.34±0.07 g/dl, Hct –0.01±0.002%). The difference between the groups was significant for both parameters (p<0.0001)
Rosiglitazone/metformin (FDC) vs rosiglitazone vs metformin	One study[134] N=468 1+	Five events of IHD were reported. One in the RSG/MET group, two in the MET group and two in the RSG group Oedema was comparable between the RSG/MET (6%) and RSG groups (7%), but lower in the MET group (3%) There were no reports of CHF or pulmonary oedema The incidence of GI AE was similar with RSG/MET (47%) and MET (51%), but was less frequent with RSG (37%) Self-reported hypoglycaemic symptoms were similar across treatment groups (12% RSG/MET; 9% MET; 8% RSG)
Rosiglitazone + SU or metformin vs metformin + SU	One study[136] N=1,122 1+	Not reported
Rosiglitazone + sulfonylurea + metformin vs insulin glargine + sulfonylurea + metformin	One study[139] N=217 1+	AE possibly related to the study medication occurred significantly more among patients on rosiglitazone than on insulin glargine (28.6 vs 6.7% respectively, p<0.0001) Peripheral oedema occurred only in the rosiglitazone group, whereas no patient on insulin glargine reported oedema (12.5 vs 0% respectively, p<0.001) Hypoglycaemia: Confirmed hypoglycaemic events at plasma glucose <3.9 mmol/l were slightly greater with insulin glargine (N=57) (rosiglitazone, N=47, p=0.0528). Confirmed symptomatic hypoglycaemic events at plasma glucose <2.8 mol/l were greater in the insulin glargine-treated group (insulin glargine, N=26; rosiglitazone, N=14, p<0.0165) More patients in the insulin glargine group had confirmed nocturnal hypoglycaemia of <3.9 mmol/l (insulin glargine, N=29; rosiglitazone, N=12; p=0.02) and <2.8 mmol/l (insulin glargine, N=10; rosiglitazone, N=3; p<0.05) than in the rosiglitazone group. The calculated average rate per patient-year of a confirmed hypoglycaemic event (defined as <70 mg/dl), after adjusting for BMI, was 7.7 (95% CI 5.4 to 10.8) and 3.4 (2.3 to 5.0) events for insulin glargine and rosiglitazone respectively (p=0.0073)

continued

Table 10.10 Adverse events – *continued*

Comparison	Study	Change in AE
Metformin + pioglitazone 15 mg OD vs metformin + rosiglitazone 4 mg OD	One study[133] N=96 1+	No CV events reported In the pioglitazone arm, two patients has AST and ALT values that increased to 1.5 times the upper limit of normal (<40 U/l), but these values normalised after 15 days

*Significance tests not performed

8.2.3.5 Pioglitazone

Cardiovascular outcomes[h]

The systematic review[141] found only one study[158] evaluating mortality and morbidity as endpoints outcomes. As the primary composite endpoint, the PROactive study explored the incidence of the following outcomes from the time of randomisation.

- All-cause mortality.
- Non-fatal MI (including silent MI).
- Stroke.
- Acute coronary syndrome (ACS).
- Endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle.

The study concluded that for this composite endpoint there were no statistically significant differences between the pioglitazone and placebo group: the hazard ratio (HR) was 0.90 (95% CI 0.80 to 1.02, p=0.095). In the same vein, the individual components of the primary composite endpoint did not disclose statistically significant differences between intervention and control groups. **Level 1++**

Of all secondary endpoints only the so-called 'main' secondary endpoint 'time to the first event of the composite endpoint of death from any cause, MI (excluding silent MI) and stroke' indicated a statistical significant difference between pioglitazone and placebo (HR 0.84, 95% CI 0.72 to 0.98, p=0.027). **Level 1++**

A subgroup analysis[i] of the PROactive study[150] was identified by the re-runs. It analysed the effect of pioglitazone on recurrent MI in 2,445 patients with Type 2 diabetes and previous MI. The study found no significant differences in the primary or main secondary endpoints defined in the main PROactive study,[j] and the individual endpoints of the primary composite. In addition, the subgroup analysis suggest that patients treated with pioglitazone had a statistically significant beneficial effect on the pre-specified endpoint of fatal and non-fatal MI (28% risk reduction (RR), p=0.045) and ACS (37% RR; p=0.035) compared to those treated with placebo. **Level 1+**

This study also showed that the incidence of CHF was significantly higher in patients receiving pioglitazone as compared to placebo-treated individuals (13.5 vs 9.6%, p=0.003). The incidence of serious CHF (requiring hospitalisation) was also significantly higher in the pioglitazone group (7.5% vs 5.2%, p=0.022). **Level 1+**

Another subgroup analysis[k] of the PROactive study[152] was also identified by the re-runs. This analysis evaluated outcomes stratified for patients who entered the study with (N=984) and without previous stroke (N=4,254). In the patients with previous stroke, there were no significant differences in the primary or main secondary endpoints as defined in the main PROactive analysis, but there was a trend of benefit (HR 0.78, 95% CI 0.60 to 1.02, p=0.0670) for the primary endpoint. In patients with no previous stroke, there were no significant differences between pioglitazone and placebo for any of the endpoints defined in the main PROactive analysis. **Level 1+**

h See rosiglitazone section for further evidence published up to December 2007.

i The main limitation of this analysis is that it includes both pre-specified and post-hoc endpoints. It is an analysis of a subgroup of a larger study, and randomisation was not stratified by history of MI.

j Primary endpoint: time to death, non-fatal MI, ACS, cardiac intervention (PCI/CABG), stroke, leg amputation, revascularisation in the leg. Secondary endpoint: time to the first event of the composite endpoint of death from any cause, MI (excluding silent MI), and stroke. Individual components of the primary endpoint and CV mortality were specified as secondary outcomes.

k The main limitation of this analysis is that it includes both pre-specified and post-hoc endpoints It is an analysis of a subgroup of a larger study, and randomisation was not stratified by history of MI.

8.2.3.6 Surrogate outcomes

HbA1c

The systematic review concluded that active glucose-lowering compounds like metformin, glibenclamide, gliclazide or glimepiride resulted in similar reductions of HbA1c compared to pioglitazone treatment. (Due to heterogeneity this outcome could not be subjected to meta-analysis.) **Level 1++**

A head-to-head RCT[151] comparing pioglitazone monotherapy with glimepiride monotherapy reported no significant difference in the HbA1c values between the two treatment groups until week 48. By the end of the study (week 72) there was an absolute difference between the two treatment groups of 0.32% favouring pioglitazone-treated patients (p=0.002). **Level 1+**

A 2-year follow-up study[148] reported no significant differences in terms of HbA1c when patients receiving metformin and pioglitazone were compared with those treated with metformin + gliclazide. **Level 1+**

A study comparing the addition of different doses of pioglitazone (30 and 45 mg) to stable insulin therapy in patients with poorly controlled Type 2 diabetes[146] found that mean HbA1c levels decreased significantly from baseline to week 24 in both groups: 1.2 from 9.9% and 1.5 from 9.7% in the pioglitazone 30- and 45-mg groups respectively (p<0.0001 for each relative to baseline; p=0.011, 30 vs 45 mg). **Level 1+**

One RCT comparing the currently licensed combination of pioglitazone and insulin with insulin plus placebo[145] found that after 6 months there was a significantly higher decrease in HbA1c levels in patients treated with insulin and pioglitazone (difference –0.55; p<0.002).[l] **Level 1+**

Fasting plasma glucose

A 2-year follow-up study[148] showed a statistically significant difference in FPG between the pioglitazone add-on to metformin group and the gliclazide add-on to metformin group at week 104 (–1.8 vs –1.1 mmol/l, p<0.001). **Level 1+**

The study comparing the addition of different doses of pioglitazone (30 and 45 mg) to stable insulin therapy in patients with poorly controlled Type 2 diabetes did not find significant differences in the decrease of FPG levels from baseline between the two groups.[146] **Level 1+**

One RCT comparing the combination of pioglitazone and insulin with insulin plus placebo[145] reported at 6 months a significant difference in terms of FPG favouring the pioglitazone + insulin combination (difference 1.80 mmol/l, p<0.002). **Level 1+**

Lipid profile

An RCT[151] comparing pioglitazone monotherapy with glimepiride monotherapy reported that by the end of the study (week 72) pioglitazone-treated patients showed significantly higher HDL levels (difference 0.16 mmol/l, p<0.001).

A 2-year follow-up study[148] reported a statistically significant percentage difference between the pioglitazone add-on to metformin group and the gliclazide add-on to metformin from baseline to last value for TG (–23% vs –7%, p<0.001), HDL-C (22% vs 7%, p<0.001) and LDL-C (2 vs –6%, p<0.001). **Level 1+**

l At baseline the mean HbA1c value for the PIO+INS group was 8.85%. This improved to 8.11% at endpoint (p<0.002). In the PLB+INS group, the mean HbA1c value at baseline (8.79%) was unchanged at endpoint (8.66%).

The study comparing the addition of different doses of pioglitazone (30 and 45 mg) to stable insulin therapy in patients with poorly controlled Type 2 diabetes did not find significant differences in terms of lipid profile between the two groups. **Level 1+**

The RCT comparing the combination of pioglitazone and insulin with insulin plus placebo did not find significant differences in LDL and TG levels. However, after 6 months patients receiving pioglitazone and insulin had significantly higher levels of HDL (difference 0.13, p<0.002).[m 145] **Level 1+**

Body weight

According to the systematic review, 15 studies evaluated body weight and observed an increase up to 3.9 kg after pioglitazone treatment, seven studies described a rise in BMI up to 1.5 kg/m^2. (Due to heterogeneity this outcome could not be subjected to meta-analysis.) **Level 1++**

A 2-year follow-up study[148] reported a mean increase from baseline of 2.5 kg in the pioglitazone add-on to metformin group and 1.2 kg in the gliclazide add-on to metformin at week 104. **Level 1+**

A study comparing the addition of different doses of pioglitazone (30 and 45 mg) to stable insulin therapy reported that a statistically significant dose response for weight gain was observed at all time points. A mean increase in mean body weight was observed in both treatment groups: 2.94 and 3.38 kg in the 30- and 45-mg groups respectively, (p<0.001 for both groups).[146] **Level 1+**

A study comparing the combination of pioglitazone and insulin with insulin plus placebo reported a mean increase in body weight with PIO + INS of 4.05 kg, and a mean increase with PLB + INS of 0.20 kg.[145] **Level 1+**

Adverse events

The review concluded that the percentage of overall and serious AEs was comparable between intervention and control groups. The review also noted a somewhat higher discontinuation rate following pioglitazone administration especially in comparison to monotherapy with other OAD drugs. However, true numbers were difficult to evaluate due to study protocols defining withdrawals because of lack of efficacy as a serious AE. **Level 1++**

Oedema

The systematic review found that specific AE oedema was evaluated in 18 of the 22 studies. Overall, 11,565 participants provided data on the occurrence of oedema. The total number of events was 842 in the pioglitazone and 430 in the control groups. Pooling of the 18 studies revealed a RR of 2.86 (95% CI 2.14 to 3.18, p<0.00001). **Level 1++**

Hypoglycaemia

The systematic review found data on hypoglycaemic episodes in 11 of the 22 included studies. The review concluded that compared to active monotherapy control, pioglitazone treatment resulted in somewhat lower rates of hypoglycaemia. However, if pioglitazone was combined with insulin more hypoglycaemic incidents happened.

The review highlighted that the biggest trial[158] which compared pioglitazone versus placebo in combination with a variety of other glucose-lowering drugs reported hypoglycaemia rates

m The mean HDL level of the PIO + INS group at baseline (1.23 mmol/l) increased significantly at endpoint (1.35 mmol/l, p<0.002). The mean HDL level of the PLB + INS group at baseline (1.24 mmol/l) was unchanged at endpoint (1.21 mmol/l).

of 27.9% after pioglitazone and 20.1% after placebo combinations. Severe hypoglycaemic events were rarely reported.

(Due to heterogeneity hypoglycaemia could not be subjected to meta-analysis.) **Level 1++**

Other adverse events

The review found six studies reporting a more pronounced (sometimes dose related) decrease of haemoglobin after pioglitazone intake in comparison to other active compounds or placebo. Haemoglobin reductions ranged between 0.5 and 0.75 g/dl. **Level 1++**

The 2-year follow-up study[148] reported that there were more symptoms of hypoglycaemia (11.5% vs 2.2%) and GI disorders (5.1% vs 3.8%) in the gliclazide group but less aggravated CHF (0.6% vs 1.6%) and oedema (3.5% vs 7.6%) than in the pioglitazone group. **Level 1+**

A study comparing the addition of different doses of pioglitazone (30 and 45 mg) to stable insulin therapy reported that in both groups, hypoglycaemia was the most commonly reported drug-related AE (37 and 43% of patients respectively), followed by lower limb oedema (13 and 12%), weight gain (7 and 13%) and aggravated oedema in patients with oedema at baseline (4 and 3%). Frequency of CV AEs related to study group was low and comparable between groups (1.2 and 0.6% for the 30- and 45-mg groups respectively). Drug-related CHF was reported for three patients receiving pioglitazone 30 mg (one possibly related and two probably related) and one patient receiving 45 mg (possibly related).[146] **Level 1+**

A study comparing the combination of pioglitazone and insulin with insulin plus placebo[145] showed that there were 90 (63.4%) reported incidences of subjective hypoglycaemic episodes for PIO + INS and 75 (51.0%) for PLB + INS ($p<0.05$). There was no difference between the treatment groups for clinical hypoglycaemia. The study also reported 20 cases of oedema with PIO + INS and five cases with PLB + INS. No CV events reported. **Level 1+**

Glitazones and the risk of oedema

A meta-analysis[153] revealed a twofold increase in the RR of oedema secondary to thiazolidinedione therapy compared to placebo, oral antihyperglycaemic agents, or insulin. The pooled odds ratio was 2.26 (95% CI 2.02 to 2.53, $p<0.00001$) the increased risk of oedema was present in both monotherapy and combination therapy studies. **Level 1+**

The same meta-analysis suggested that rosiglitazone was associated with a more pronounced risk for oedema than pioglitazone. The calculated adjusted indirect comparison of rosiglitazone to pioglitazone based on all included studies yielded an approximate threefold higher risk of oedema with rosiglitazone, (2.74 (2.33 to 3.14)). When only placebo controlled studies of pioglitazone (1.18 (0.61 to 2.28), $p<0.063$) and rosiglitazone (3.58 (2.11 to 6.10), $p<0.00001$) were considered, the risk was still greater with rosiglitazone. The calculated adjusted indirect comparison of rosiglitazone to pioglitazone using only placebo controlled trials was 3.03 (2.15 to 3.91). The omission of all open-label trials also pointed towards an increased risk with rosiglitazone (3.64 (2.56 to 5.17)), over pioglitazone (2.18 (1.72 to 2.75), $p<0.00001$). **Level 1+**

8.2.4 Health economic evidence statements

The submission for the TA[154] looked at adding rosiglitazone to sulfonylurea or metformin compared with other CTs or changing to insulin. The efficacy data was unreported in the TA because it was submitted as commercial in confidence.

For patients who failed on metformin monotherapy:

- metformin plus a sulfonylurea compared to metformin plus rosiglitazone, led to an ICER of £9,972 per QALY

- metformin plus sulfonylurea, and when this combination failed, metformin plus rosiglitazone compared to metformin plus rosiglitazone started straight after metformin monotherapy failure, led to an ICER of £11,857 per QALY.

In the TA[154] sensitivity analysis was included that appears to have been conducted by the TA group. The sensitivity analysis indicated that some of the scenarios were very sensitive to changes in key effectiveness variables. Small changes in the effect of rosiglitazone on □-cell function and insulin sensitivity induced large changes in the cost per QALY ratios. When the impact of rosiglitazone on insulin sensitivity and □-cell function was varied, in the comparison of metformin plus a sulfonylurea and metformin plus rosiglitazone, rosiglitazone was dominated by the sulfonylurea in combination therapy (metformin plus sulfonylurea is more effective and less expensive).

The NICE 2003 guidance[113] found that in patients in whom monotherapy with either metformin or a sulfonylurea had failed, the use of combination therapy with a glitazone and either metformin or a sulfonylurea was not likely to be cost-effective when compared with the combination of metformin and a sulfonylurea.

Metformin plus sulfonylurea was compared with metformin plus rosiglitazone in patients who had failed on metformin alone in the cost-effectiveness analysis conducted by Beale et al.[156]

Table 10.11 Incremental cost-effectiveness ratios rounded to nearest £100

Patient group	Incremental cost per life year gained	Incremental cost per QALY
Obese	£21,300	£16,700
Overweight	£20,000	£11,600

The baseline results showed the combination of metformin plus rosiglitazone to be cost-effective compared to metformin plus sulfonylurea. Sensitivity analysis was performed on the threshold level of HbA1c at which patients were switched, the discount rate, and the mean BMI at diagnosis. Varying these parameters had little effect on the cost-effectiveness ratio. The effectiveness of rosiglitazone was not varied even though the data was taken from a variety of sources and were not necessarily from studies looking at rosiglitazone in combination with metformin.

In the Tilden et al.[157] analysis the glitazones were given after failure on metformin monotherapy. The study was based on a RCT which found no difference in the treatments on change in HbA1c or BMI. Pioglitazone was found to reduce TC: HDL, whereas rosiglitazone was found to increase this ratio. The analysis found that pioglitazone was more effective and cheaper than rosiglitazone. The results were insensitive to changes in key variables and pioglitazone remained dominant.

In contrast to these earlier analyses, the glitazones were appraised as a third-line treatment in patients who were not controlled on metformin plus sulfonylurea. Details are given in appendix C available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247.

As a broad summary of our results:

- rosiglitazone was consistently dominated by human insulin (both less effective and more expensive)
- pioglitazone was dominated in the base case, but was found cost-effective when some patient characteristics were changed (initial TC and initial systolic blood pressure (SBP))
- pioglitazone was estimated to yield a greater QALY gain at lower cost than rosiglitazone

- adjusting the initial SBP to reflect increased CV risk led to both glitazones being dominated by human insulin.

8.3 Gliptins (GLP-1 enhancers): dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors)

The GDG considered including sitagliptin and insulin detemir in this guideline; however, they were advised by NICE not to do so. NICE is undertaking a rapid update of recommendations in this guideline on second- and third-line drugs for managing blood glucose, which will cover these drugs. The updated guideline will be published early in 2009. For more information see www.nice.org.uk and search for 'Type 2 diabetes newer agents'.

8.4 Exenatide: GLP-1 mimetics

8.4.1 Methodological introduction

There were eight studies identified in this area, all were RCTs. Three were large, multicentre studies which compared doses of 5 µg and 10 µg exenatide with placebo for participants taking differing OAD treatments.[159–161]

These three studies had an extension open-label phase; this included those who had originally been randomised to have the exenatide treatment, they were invited to continue into this phase of the study. This drug is recently licensed; therefore this extension phase has been included as relevant, though there were methodological issues with it.[162]

One paper compared four differing doses of exenatide (2.5 µg, 5 µg, 7.5 µg and 10 µg) with placebo for participants treated with diet/exercise or a stable dose of metformin.[163]

There were two papers which compared exenatide with insulin glargine,[164,165] these studies by necessity are open-label; the other appraised studies were triple-blinded.

An open-label, non-inferiority RCT compared exenatide (5 µg bid for 4 weeks and 10 µg thereafter) with biphasic insulin aspart (twice daily doses titrated for optimal control).[166]

Finally, one paper compared the addition of exenatide to a glitazone with treatment with glitazone and placebo.[167]

It should be noted that the four triple-blinded studies were undertaken prior to exenatide gaining a therapeutic licence in the US.

Exenatide is indicated for treatment of Type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies.[168]

8.4.2 Health economic methodological introduction

One published analysis was identified by Ray et al.[169] which compared exenatide to insulin glargine in patients who had failed on metformin and sulfonylurea. The analysis was set in the UK but no perspective was given.

An economic model was constructed based upon the UKPDS outcomes model to inform the GDG deliberations with regard to choice of glitazones or exenatide as third-line therapy in comparison to other third-line options. This is presented in appendix C available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

8.4.3 Evidence statements

Exenatide 5 µg and 10 µg compared with placebo

Three studies, all multicentre and triple-blinded based in the US used this comparison, total N=1,446.[159–161] For participants treated with sulfonylureas (N=377), those treated with metformin (N=336), and those treated with both (N=733), exenatide caused significant reductions in HbA1c, FPG (at the higher 10 µg dose), postprandial glucose and body weight. **Level 1++**

Table 10.12 Exenatide 5 µg and 10 µg compared with placebo

	Sulfonylurea-treated participants[159]		Metformin-treated participants[160]		Metformin- and sulfonylurea-treated participants[161]	
	5 µg	10 µg	5 µg	10 µg	5 µg	10 µg
HbA_{1c}	–0.46±0.12% vs placebo 0.12±0.09% p≤0.0002	–0.86±0.11% vs placebo 0.12±0.09% p≤0.0002	Decrease compared with placebo p<0.001	Decrease compared with placebo p<0.001	–0.55±0.07% vs placebo 0.23±0.07% p<0.0001	–0.77±0.08% vs placebo 0.23±0.07% p<0.0001
Baseline HbA_{1c} >7%	N=31 reached ≤7% vs N=9 for placebo p<0.0001	N=41 reached ≤7% vs N=9 for placebo p<0.0001	N=27 reached ≤7% vs N=11 for placebo p<0.01	N=41 reached ≤7% vs N=11 for placebo p<0.01	24% reached ≤7% vs 7% for placebo p<0.0001	30% reached ≤7% vs 7% for placebo p<0.0001
Baseline HbA_{1c} >9%	–0.58±0.24% vs placebo 0.13±0.17% p<0.05	–1.22±0.19% vs placebo 0.13±0.17% p<0.05			Significant decreases compared with an increase with placebo p≤0.0002	Significant decreases compared with an increase with placebo p≤0.0002
Baseline HbA_{1c} ≤9%	–0.39±0.12% vs placebo 0.11±0.12% p<0.01	–0.65±0.12% vs placebo 0.11±0.12% p<0.01			Significant decreases compared with an increase with placebo p<0.0001	Significant decreases compared with an increase with placebo p<0.0001
FPG	NS	–0.6±0.3 mmol/l vs placebo 0.4±0.3 mmol/l p<0.05	NS	Difference 10 µg and placebo averaged –1.4 mmol/l p=0.0001	–0.5±0.2 mmol/l, vs placebo 0.8±0.2 mmol/l p<0.0001	–0.6±0.2 mmol/l vs placebo 0.8±0.2 mmol/l p<0.0001
Postprandial glucose			Significant reductions compared with placebo p=0.03	Significant reductions compared with placebo p=0.004	Significant reductions compared with placebo p=0.0001	Significant reductions compared with placebo p=0.0001

continued

Table 10.12 Exenatide 5 µg and 10 µg compared with placebo – *continued*

	Sulfonylurea-treated participants[159]		Metformin-treated participants[160]		Metformin- and sulfonylurea-treated participants[161]	
	5 µg	10 µg	5 µg	10 µg	5 µg	10 µg
Body weight	NS	–1.6±0.3 kg/m vs placebo –0.6±0.3 kg/m^2 p<0.05	–1.6±0.4 kg vs placebo –0.3±0.3 kg p≤0.05	–2.8±0.5 kg vs placebo –0.3±0.3 kg	–1.6±0.2 kg vs placebo –0.9±0.2 kg p≤0.01	–1.6±0.2 kg vs placebo –0.9±0.2 kg p≤0.01
Insulin	NS	NS	NS	NS		
Proinsulin	NS	–16 pmol/l (CI –26.1 to –6.0) vs placebo p<0.01	NS	NS		
Lipids	Small reduction vs placebo p<0.05	Small reduction vs placebo p<0.05				
Hypoglycaemia	Mild-to-moderate 14% (3% with placebo)	Mild-to-moderate 36% (3% with placebo)	Mild-to-moderate 4.5% (5.3% with placebo)	Mild-to-moderate 5.3% (the same as placebo)	19.2% – one case of severe hypoglycaemia, the remaining were mild-to-moderate (12.6% for placebo)	Mild-to-moderate 27.8% (12.6% for placebo)
AEs	Nausea 39% (7% with placebo)	Nausea 51% (7% with placebo)	Nausea 36% (23% with placebo)	Nausea 45% (23% with placebo)	Nausea 39.2% (20.6% with placebo)	Nausea 48.5% (20.6% with placebo)
Discontinuation	24.0% (7.2% with placebo)	29.5% (7.2% with placebo)	24.0% (39.8% with placebo)	29.5% (39.8% with placebo)	15.9% (23.9% with placebo)	17.8% (23.9% with placebo)

8.4.3.1 Open-label extension phase

The three RCTs in the table above [159–161] had a further open-label extension phase of 52 weeks, which was open to those participants who had been originally randomised to exenatide, N=668, analysis completed on N=314.[162] This study showed that at the end of 82 weeks that the reductions in HbA1c and in FPG which had been identified at the end of week 30 were maintained to week 82.

The reduction in body weight was progressive to week 82, week 30 the body weight changes for the 10 µg BD dose were –1.6 to –2.8 kg, at week 82 the change from baseline was –4.4±0.3 kg (95% CI: –3.8 to –5.1 kg), or 4.4% of baseline body weight. Higher levels of weight reduction were noted in those participants who had had a higher BMI at baseline; participants with baseline BMI <25 had a mean weight reduction of 2.9% of baseline body weight, those with a baseline BMI of ≥40 had a mean reduction of 5.5% of baseline body weight.

8.4.3.2 Exenatide 2.5 µg, 5 µg, 7.5 µg and 10 µg BD doses compared with placebo

This phase II study compared four doses of exenatide with placebo in participants treated either with diet modification and exercise alone or a stable dose of metformin, N=156.[163]

HbA1c

There was a decrease in HbA1c compared with an increase with placebo (0.1±0.1%), for all doses: 2.5 µg (–0.3±0.1%), 5 µg (–0.4±0.1%), 7.5 µg (–0.5±0.1%), 10 µg (–0.5±0.1%), p<0.01.

Fasting blood glucose

There was a decrease in FBG compared with an increase with placebo (6.8±4.1 mg/dl), for all doses: 2.5 µg (–20.1±5.2 mg/dl), 5 µg (–21.2±3.9 mg/dl), 7.5 µg (–17.7±4.8 mg/dl), 10 µg (–17.3±4.4 mg/dl), p<0.01.

Body weight

Reductions in body weight with exenatide were significant for the 7.5 µg (–1.4±0.3kg) and 10 µg (–1.8±0.3 kg) groups, p<0.01, compared with the placebo group who were weight neutral.

Subgroup analysis

This used data from the 5 µg and 10 µg groups and considered those treated with diet/exercise compared with those treated with metformin. This found that the effects of exenatide were similar in both groups for HbA1c, FPG and body weight.

Adverse events and discontinuation

40.7% of participants taking exenatide had nausea (6.5% severe nausea) compared with 12.1% of those taking the placebo (3.0% severe nausea). The nausea appeared to be dose dependent as it had a higher occurrence in the higher dose groups; 2.5 µg (23.3%), 5 µg (25.8%), 7.5 µg (61.3%) and 10 µg (51.6%). **Level 1+**

8.4.3.3 Exenatide vs insulin glargine

The phase III study compared exenatide and insulin glargine in participants who had not achieved adequate glycaemic control with a combination of metformin and sulfonylurea at maximally effective doses, with N=551 participants.[164]

HbA1c

Exenatide was as effective as insulin glargine in improving glycaemic control with both groups showing a reduction of 1.11% from baseline. The percentage of participants who achieved the target HbA1c of 7% or less were also similar, 46% for exenatide and 48% for insulin glargine.

Fasting plasma glucose

Those taking insulin glargine showed a greater reduction in FPG than those receiving exenatide (–2.9 vs –1.4 mmol/l), p<0.001. Significantly more of the insulin glargine group (21.6%) achieved a FPG of less than 5.6 mmol/l compared with 8.6% in the exenatide group (p<0.001).

Self-monitored blood glucose

Mean daily self-monitored glucose levels were similar between the treatments, however, those using insulin glargine had lower glucose levels at fasting (p<0.001), before meals (pre-lunch p=0.023; pre-dinner p=0.006), at 3.00 am (p<0.001) and evening (p<0.001) compared with exenatide.

Adverse events and discontinuation

There were higher incidences of the most frequent AEs of nausea and vomiting in the exenatide group (57.1% and 17.4% respectively) compared with insulin glargine (8.6% and 3.7%).

Overall rates of hypoglycaemia were similar across both treatment groups (7.4 events/patient year with exenatide and 6.3 with insulin glargine).

A higher number of participants discontinued the study with exenatide (N=54) compared with insulin glargine (N=25), for N=27 in the exenatide group the withdrawal was due to AEs. **Level 1+**

The second exenatide and insulin glargine study considered the treatments in respect to patient reported health outcome measures, N=549.[165] Both treatment groups showed baseline to endpoint improvements on several of the health outcome measures; these were not significant between the groups. Glycaemic control results were not reported. **Level 1+**

Exenatide vs biphasic insulin aspart

This study reported that HbA1c reduction in exenatide-treated patients (N=253) was non-inferior to that achieved with biphasic insulin aspart (N=248). In relation to body weight gain, the study showed a statistically significant difference favouring those receiving exenatide.[166]

Table 10.13 Exenatide vs biphasic insulin aspart

Nauck[166] N=501 T=52 weeks	Exenatide	Biphasic insulin aspart	Size effect
HbA_{1c}	–1.04	–0.89	NS
Fasting serum glucose	–1.8 mmol/l	–1.7 mmol/l	NS
Body weight	Exenatide-treated patients lost weight, while patients treated with biphasic insulin aspart gained weight Between group difference –5.4kg (95% CI –5.9 to –5.0 kg)		
AEs	The incidence of GI AEs was higher with exenatide than with aspart Nausea (33% incidence, 3.5% discontinuation) observed with exenatide Vomiting (15% incidence) The overall hypoglycaemia rates were similar across treatment groups at endpoint		

Exenatide + glitazone vs placebo + glitazone

This multicentre, double-blinded RCT compared the addition of exenatide to a glitazone with glitazone and placebo in a population of 233 suboptimally controlled people with Type 2 diabetes.[167]

Overall, the RCT showed that exenatide in combination with a glitazone improved glycaemic control in patients with Type 2 diabetes that is suboptimally controlled with a glitazone, either alone or in combination with metformin.

Table 10.14 Exenatide + glitazone vs placebo + glitazone

Zinman[167] N=233 T=16 weeks	Glitazone + placebo	Glitazone + exenatide	Size effect
HbA_{1c}	+0.09%	–0.89%	–0.98% (95% CI –1.21 to –0.74%, p<0.01)
Fasting serum glucose	+0.10 mmol/l	–1.59 mmol/l	–1.69 mmol/l (95% CI –2.22 to –1.17 mmol/l, p<0.001)
Body weight	–0.24 kg	–1.75 kg	–1.51 kg CI –2.15 to –0.88 kg, p<0.001)
Lipid profile	The study reported that no clinically significant changes occurred		
AEs	The most frequent AE was nausea, which was the reason for withdrawal of 9% and 1% of patients in the exenatide and placebo groups respectively The incidence of treatment-emergent oedema was similar in both groups (5.8% and 8% of patients in the exenatide and placebo groups respectively) The overall incidence of hypoglycaemia was also low and similar between groups (10.7% and 7.1% of patients in the exenatide and placebo groups respectively)		

8.4.4 Health economic evidence statements

The analysis by Ray et al. was based on a 26-week trial which found exenatide was associated with a 0.99% reduction in HbA1c compared to 1.07% with glargine. Exenatide was found to improve BMI, SBP, TC and LDL-C compared to glargine. No cost for exenatide in the UK was available as it had not been licensed at the time of publication so various proportions of the US price were tested from 20% to 100%. Exenatide was found to have a cost per QALY of £22,420 compared to glargine. The results were most sensitive to variation in the disutility values applied for weight change and nausea. The cost per QALY increased to £39,763 when disutility values for set levels of BMI were used rather than changes in weight.[169]

The health economic analysis of exenatide as a third-line agent in Type 2 diabetes is described in appendix C available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247. In the base-case analysis (see table 23) exenatide is shown to have an ICER of £280,495. Recognising the difficulties of factoring in the potential benefits of weight loss with exenatide, various sensitivity analyses were performed, but the ICER remained consistently high and in only one case became cost-effective, (£29,865 per QALY gained when exenatide patients were started with an initial BMI of 27 kg/m^2 compared to a 33 kg/m^2 for all other treatments and a utility gain of 0.064 due to 3% weight loss on exenatide, no nausea, compared to weight gain for other treatments). In this model therefore, human insulin is a consistently more cost-effective option in any patient in whom it is an acceptable form of treatment.

8.5 Oral glucose control therapies (2): other oral agents and exenatide; from evidence to recommendations

8.5.1 Thiazolidinediones (glitazones)

This section updates both the previous NICE inherited guideline and the previous NICE TA guidance on the use of glitazones for the treatment of Type 2 diabetes. NICE TA guidance 63 (2003).[113]

Significant further evidence was available for pioglitazone and rosiglitazone; these studies fell into three groups.

- Comparison of glucose-lowering (and other metabolic) outcomes.
- Durability of blood glucose control.
- True health outcome studies including safety issues.

The glucose-lowering studies appeared to add little to what was already known about these drugs. The positive effects of pioglitazone on HDL-C and TGs were also noted, and were believed to have contributed to the results of the PROactive study. The effects of rosiglitazone on total and LDL-C were noted. They were difficult to interpret because of the drug effects on the changes to the nature of LDL-C particles. Other surrogate outcomes of therapy were noted to be broadly positive, including minor effects on BP.

From the PROactive study on pioglitazone (the only study with this drug with real health outcomes as a primary endpoint) appeared to be broadly positive despite statistical concerns and the selected population (secondary prevention study). However, the magnitude of the effect size on CV outcomes appeared no better than for the active treatment policy group of the UKPDS study, principally sulfonylurea therapy, the results of which were also noted to be not entirely conclusive when considered in isolation.

There are concerns over fluid retention and hospitalisation for cardiac failure with both thiazolidinediones. Recent safety data has identified a clinically significant risk of distal fracture in women using these drugs. For rosiglitazone the meta-analysis of investigator reported MI from two major studies (one not in people with diabetes) and the manufacturer's trials database raised real concerns at the time of conclusion of the draft of the current guideline. These were only partly assuaged by the report of unchanged CV death compared to sulfonylureas/ metformin in the RECORD interim analysis. The GDG therefore undertook a review of further meta-analyses published since that time up to December 2007, together with EMEA, FDA, and MHRA pronouncements, also up to December 2007. Although there was no definitive evidence of excess myocardial ischaemia from rosiglitazone, the GDG felt that there was certainly a 'signal' of increased risk of non-fatal MI for rosiglitazone. The regulators' position seemed to be of confirmation of benefit: safety ratio, and continuing to allow marketing of rosiglitazone even though an alternative was available, albeit with warnings and restrictions. The GDG was also given to understand that pricing of these drugs would become similar. On balance, despite reservations over rosiglitazone, it was not felt to be possible to unequivocally recommend a preference for pioglitazone in all circumstances, but rather to allow the choice of agent to rest with the person with diabetes and their advisor, taking account of the then current regulatory advice (which may yet change).

However, the issues over fractures and fluid retention/cardiac failure and the costs of these drugs led the GDG to conclude that thiazolidinediones could not generally replace sulfonylureas as second-line therapy, except where sulfonylureas were contraindicated by particular risk of hypoglycaemia.

The health economic modelling appeared to identify that these drugs, and in particular the then more highly priced rosiglitazone, were not cost-effective compared to human insulin therapy. However, the GDG were concerned that quality of life aspects of insulin therapy,

including fear of hypoglycaemia, and the education and support costs of modern intensity of dose titration, were not adequately captured by the model. Furthermore, people of higher body weight and more insulin insensitive phenotype, as identified clinically by features of the metabolic syndrome (usually abdominal adiposity), respond better than average to thiazolidinediones, but often have barriers to insulin therapy related to weight gain, and respond less well to insulin. Accordingly they were content to allow the choice of either thiazolidinedione taking into account cost and the safety issues raised above where insulin injection therapy is likely to be poorly tolerated. This was noted to be in line with the thiazolidinedione NICE TA (guidance 63, 2003) the current guideline updates. As the initiation threshold for insulin is suggested as an HbA1c ≥7.5 %, it followed this should be adopted for thiazolidinediones too.

The evidence of durability of effect on blood glucose control of thiazolidinediones was noted. This was not part of the economic modelling. The GDG noted that there would be some cost offset and possible quality of life gain from any delay to initiation of insulin therapy, and perhaps from decreased requirement for uptitration of insulin doses over the years. This added to the uncertainty of the findings in regard of the cost-effectiveness of thiazolidinediones compared to insulin.

As thiazolidinediones worked in combination with metformin, fixed-dose combination products would be suitable for use where there were no cost implications or where improved drug adherence issues increase cost effectiveness. The GDG was not presented with specific evidence on this latter point.

8.5.2 Exenatide

Exenatide is a relatively new therapy, it is expensive, and has licensing restrictions within the glucose-lowering therapy pathway. The GDG did not consider it therefore for general use, but sought to determine those people in whom its use might be cost-effective as a third-line therapy.

There was little evidence comparing exenatide with other third-line therapies. Exenatide successfully lowered HbA1c, though the extent of this was not impressive compared to other therapies even allowing for the rather better baseline values of modern studies. Significant weight loss compared to all other therapies was clearly found, though the extent of this was not large, and required continued therapy to be maintained. Nausea appeared to be a significant problem, and it was unclear if this was related to (causative of) the weight loss to any extent.

The studies comparing exenatide to insulin did not achieve the HbA1c reduction with insulin expected from other studies, suggesting, together with the low doses used, that dose titration of the insulin comparator was inadequate. This was taken as suggesting that insulin might still be preferred for glucose lowering, even after considerations of hypoglycaemia, injection anxieties, and weight gain with insulin had been addressed.

Exenatide therapy is expensive, and the health economic modelling suggested it was not cost- effective for an unselected population as compared to commencing human insulin therapy. However, the GDG did not consider comparison with an unselected population to be applicable to some reasonably common clinical situations. They noted that all other third-line options were dominated by human insulin therapy in the economic model and that for obesity issues the costs of other aspects of obesity management (e.g. orlistat and bariatric surgery) had not been included. It was noted that previous NICE TAs had approved agents that were dominated in this economic model, including the glitazones (as second-line therapy when metformin and a sulfonylurea cannot be taken in combination) and insulin glargine. The GDG was uncertain that these agents (including exenatide) would be found to be not cost-effective if the model fully reflected the negative quality of life issues of insulin, including fear of

hypoglycaemia, and the costs of support and patient education for modern intensity of insulin dose titration.

Furthermore, the more obese require much higher insulin doses, such that insulin costs alone can easily exceed those of exenatide (depending on the mix of insulin types chosen for comparator) though the benefit from insulin could be expected to be higher than in the trials (for reasons of dose titration given above). In these circumstances a confident judgment of costs and benefits to be gained from HbA1c and weight change, and side effects, could not be made. However the GDG's judgment was that costs of insulin and exenatide by the end of the first year would be equivalent on average for people with a starting BMI (before these medications) of approximately >33 kg/m^2, while in this obese group the small metabolic advantage to insulin on HbA1c would easily be outweighed by the metabolic advantage of 4kg weight loss on exenatide. In this restricted circumstance, and particularly at higher BMI's, the cost-effectiveness of exenatide would then be at least as good as that of insulin.

The GDG noted an issue over the definition of obesity as it affects different ethnic groups, a problem also identified in the NICE guideline on obesity management,[12] although with no specific recommendations as to how to allow for it. Accordingly the GDG could only recommend that clinicians took ethnic group issues into account when judging the BMI above which exenatide might be indicated.

The GDG strongly felt that there was a role for third-line agents since this would allow delay of starting insulin therapy, and it was recognised that some individuals were very reluctant to switch to insulin. In circumstances where it was clinically desirable not to commence insulin, it was noted that the third-line agents were cost-effective compared to no action (continued poor blood glucose control). If human insulin was dropped from the economic model, exenatide would still be dominated by thiazolidinedione. However, it was not clear that the model adequately incorporated the divergence in body weight trend with these two types of medication, and thiazolidinediones have contraindications and safety issues of their own. Nevertheless the GDG concluded again that exenatide could only be recommended in a limited role.

As an expensive injectable the GDG therefore concluded the therapeutic positioning of exenatide should be after use of the conventional oral glucose-lowering drugs, in those people with significant body weight issues affecting health and quality of life, and should be considered only as an alternative where newer medications such as a thiazolidinedione were to be commenced, or insulin started therapy. The GDG reached a consensus on the thresholds of these criteria for this guideline in the absence of evidence to guide them.

Exenatide will be updated by NICE as part of a rapid update to this guideline which will also encompass other glucose-lowering therapies such as the gliptins.

ORAL GLUCOSE CONTROL THERAPIES (2): OTHER ORAL AGENTS AND EXENATIDE; RECOMMENDATIONS

For oral agent combination therapy with insulin please refer to chapter 11.

Thiazolidinediones (glitazones)[n]

R40 If glucose concentrations are not adequately controlled (to HbA1c <7.5 % or other higher level agreed with the individual), consider, after discussion with the person, adding a thiazolidinedione to:

- the combination of metformin and a sulfonylurea where insulin would otherwise be considered but is likely to be unacceptable or of reduced effectiveness because of:

n A short clinical guideline 'Newer agents for blood glucose control in Type 2 diabetes' is in development and is expected to be published in February 2009.

  - employment, social or recreational issues related to putative hypoglycaemia
  - barriers arising from injection therapy or other personal issues such as adverse experience of insulin in others
  - those likely to need higher insulin doses or with barriers to insulin arising from particular concerns over weight gain (namely those with obesity or abdominal adiposity)
- a sulfonylurea if metformin is not tolerated
- metformin as an alternative to a sulfonylurea where the person's job or other issues make the risk of hypoglycaemia with sulfonylureas particularly significant.

R41 Warn a person prescribed a thiazolidinedione about the possibility of significant oedema and advise on the action to take if it develops.

R42 Do not commence or continue thiazolidinedione in people who have evidence of heart failure, or who are at higher risk of fracture.

R43 When selecting a thiazolidinedione for initiation and continuation of therapy, take into account up-to-date advice from the relevant regulatory bodies (the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency), cost and safety issues (note that only pioglitazone can be used in combination with insulin therapy, see recommendation 49).[o]

Gliptins: GLP-1 enhancers

No recommendations are made on the use of gliptins as these drugs are not covered in this guideline.

Exenatide: GLP-1 mimetics

R44 Exenatide is not recommended for routine use in Type 2 diabetes.*

R45 Consider exenatide as an option only if all the following apply for the individual:

- a body mass index over 35.0 kg/m^2 in those of European descent, with appropriate adjustment in tailoring this advice for other ethnic groups
- specific problems of a psychological, biochemical or physical nature arising from high body weight
- inadequate blood glucose control (HbA1c ≥7.5 %) with conventional oral agents after a trial of metformin and sulfonylurea
- other high-cost medication, such as a thiazolidinedione or insulin injection therapy, would otherwise be started.

R46 Continue exenatide therapy only if a beneficial metabolic response (at least 1.0 % HbA1c reduction in 6 months and a weight loss of at least 5% at 1 year) occurs and is maintained.

o The summary of product characteristic for rosiglitazone was last updated in March 2008 – further updates regarding rosiglitazone and pioglitazone may occur in the lifetime of this guideline.

9 Glucose control: insulin therapy

9.1 Oral agent combination therapy with insulin

9.1.1 Clinical introduction

People with Type 2 diabetes with inadequate blood glucose control on oral agents have the pathogenetic problems which caused their diabetes, and still have significantly preserved islet B-cell function. There remains the possibility that medication designed to enhance insulin secretion, reduce insulin insensitivity, or otherwise improve blood glucose control might be useful in combination with insulin therapy, in improving blood glucose control, reducing insulin dose requirement, or mitigating side effects of insulin therapy.

The clinical question is which oral agents, singly or in combination, should be continued when starting insulin therapy.

9.1.2 Methodological introduction

Studies were identified which compared insulin in combination with oral hypoglycaemic agents (OHAs) with insulin monotherapy in insulin naive Type 2 diabetic patients. A Cochrane review$_{170}$ was identified which included 20 RCTs in a search performed in March 2004. Ten additional RCTs were identified, five of which were excluded due to methodological limitations.[171–175]

Of the remaining five RCTs the treatment comparisons were:

- insulin and metformin vs insulin and placebo (most patients in each group on pre-mixed twice daily insulin regimens)[176]
- neutral protamine hagedorn (NPH) insulin (bedtime) and sulfonylurea and metformin vs NPH insulin 30/70 (twice daily)[177]
- insulin glargine (once daily) and glimepiride and metformin vs NPH insulin 30/70 (twice daily)[178]
- biphasic insulin aspart 30/70 (twice daily) and pioglitazone vs biphasic insulin aspart 30/70 (twice daily)[147]
- NPH insulin (bedtime) and glimepiride vs NPH insulin (twice daily) vs NPH insulin 30/70 (twice daily)[179]
- biphasic insulin vs biphasic insulin and metformin vs glibenclamide and metformin (although only the biphasic insulin vs biphasic insulin and metformin comparison will be considered here).[64]

It should be noted that the number of different drug combinations and comparisons, dosing and titration regimens limit direct comparison between the studies. Furthermore, all of the studies with the exception of one[176] were open-label.

Of the five trials presented above, it can be noted that only two included a biphasic insulin arm with metformin or a sulfonylurea.[64,176] Further details of the five trials in the Cochrane review, which included biphasic insulin regimens in combination with OHAs (all published between 1987 and 1998, prior to this update), are given where this data was available in the Cochrane review at the request of the GDG. These trials compared:

- mixed insulin (25% regular, 75% protamine insulin) plus glibenclamide vs mixed insulin (25% regular, 75% protamine insulin) and placebo (N=140, Cochrane methodological quality score 2/7) (Bachman 1988)

- mixed insulin (intermediate acting NPH plus regular insulin) twice daily and glibenclamide vs mixed insulin (intermediate acting NPH plus regular insulin) twice daily and placebo (N=20, Cochrane methodological quality score 2/7) (Gutniak 1987)
- insulin (combination of short and intermediate acting insulin) once or twice daily plus glibenclamide vs insulin alone (combination of short and intermediate acting insulin) once or twice daily (N=27, Cochrane methodological quality score 2/7) (Ravnik-Oblak 1995)
- mixed insulin (70% NPH, 30% soluble) at suppertime plus glibenclamide vs mixed insulin (70% NPH, 30% soluble) and placebo (N=21, Cochrane methodology score 7/7) (Riddle 1992)
- mixed insulin (70% NPH, 30% regular human insulin) at suppertime plus glimepiride vs mixed insulin (70% NPH, 30% regular human insulin) and placebo (N=145, Cochrane methodology score 6/7) (Riddle 1998).

It is notable that some of these studies had small sample sizes and/or low methodological quality scores.

9.1.3 Health economic methodological introduction

Only one economic evaluation was identified.[180] The analysis was conducted over a short time period (4 months) and intermediate outcomes were reported. For economic analysis to inform resource allocation it is important to consider the impact on final health outcomes such as mortality and morbidity.181 The incremental costs and benefits of using insulin glargine compared to conventional insulin treatment were not reported.

An economic model was constructed based upon the UKPDS outcomes model to inform the GDG with regard to choice of glitazones or exenatide as third-line therapy in comparison to other third-line options. This is presented in appendix C available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

9.1.4 Evidence statements

Glycaemic control

Overall the data seems to suggest that patients receiving a combination treatment with insulin (NPH or pre-mixes) and metformin or a sulfonylurea showed significantly lower HbA1c levels when compared to those treated with insulin monotherapy. FPG values were not consistently assessed by most of the studies.

Table 11.1 HbA_{1c}

Comparison	Study	Change in HbA_{1c} %
NPH insulin + OHAs (SU or SU + metformin) vs insulin monotherapy (two or more daily injections)	Cochrane review[170] 1++	NS
NPH insulin (once daily) + SU vs NPH insulin (once daily)	Cochrane review[170] 1++	Significantly lower HbA_{1c} in the combination arm. Difference 0.3% (95% CI 0.0 to 0.6, p=0.03)
NPH or mixed insulin (once daily) + OHAs vs insulin (twice daily)	Cochrane review[170] 1++	Significantly lower HbA_{1c} levels in the insulin monotherapy arm (mean difference 0.4% (95% CI 0.1 to 0.8, p=0.03))
NPH insulin (bedtime) + SU vs NPH insulin (twice daily) vs NPH insulin 30 (twice daily)	1 study[179] 1+	Significantly lower HbA_{1c} levels in the combination arm (p<0.001)
Insulin (pre-mix twice daily) + metformin vs insulin (pre-mix twice daily)	1 study[176] 1++	Significantly lower HbA_{1c} levels in the combination arm (adjusted difference 0.5% 95% CI 0.1 to 0.9, p=0.02)
Insulin aspart (twice daily) + metformin vs insulin aspart (twice daily)	1 study[64] 1+	Significantly lower HbA_{1c} levels in the combination arm (mean treatment difference 0.39±0.15% (p=0.007))
Insulin glargine (once daily) + OHA (SU or metformin) vs NPH insulin 30/70 (twice daily)	1 study[178] 1+	Significantly lower HbA_{1c} levels in the combination arm (–1.64 vs –1.31%, p=0.0003)
Insulin aspart 30/70 (twice daily) + pioglitazone vs biphasic insulin aspart 30/70 (twice daily)	1 study[147] 1+	Significantly lower HbA_{1c} levels in the combination arm (mean difference –0.60% SD 0.22%, p=0.008)

SD, standard deviation; SU, sulfonylurea

Insulin dose

A Cochrane review[170] reported that insulin–OHA combination therapy was associated with a significantly lower insulin dose compared to insulin monotherapy. An RCT[176] reported the same trend for the combination of insulin and metformin.

Well-being and quality of life

The few studies that objectively assessed well-being, quality of life or treatment satisfaction did not report significant differences between insulin–OHA combination and insulin monotherapy. However, there was a trend towards higher levels of satisfaction for patients in the combination group (especially those receiving metformin).

Hypoglycaemia

Non-significant differences in the incidence of hypoglycaemic events between insulin–OHA and insulin monotherapy were reported across most of the studies identified. However, a higher number of hypoglycaemic events were observed in patients receiving monotherapy with biphasic insulin regimens (e.g. NPH 30/70).

Table 11.2 Hypoglycaemic events

Comparison	Incidence	Statistical significance
Insulin and metformin vs insulin and placebo (most patients in each group on pre-mixed twice daily insulin regimens)[176]	Insulin and metformin 82% with at least one episode vs insulin and placebo 66% Severe hypoglycaemia metformin (13%) vs placebo (1%)	RR=1.24, 95% CI 1.02 to 1.52, p=0.027 RR=9.48, 95%CI 1.24 to 72.2, p=0.009
NPH insulin (bedtime) and sulfonylurea and metformin vs NPH insulin 30/70 (twice daily)[177]	Insulin–OHA group mean number of hypoglycaemic events 2.7 vs insulin monotherapy 4.3	p=0.02
Insulin glargine (once daily) and glimepiride and metformin vs NPH insulin 30/70 (twice daily)[178]	Glargine plus OHA mean number of confirmed AEs 4.07 vs insulin 9.87 (all hypoglycaemic events) Glargine plus OHA 2.62 vs insulin 5.73 (symptomatic events) Glargine plus OHA 0.51 vs insulin 1.04 (nocturnal events)	p<0.0001 p<0.0009 p<0.0449
Biphasic insulin aspart 30/70 (twice daily) and pioglitazone vs biphasic insulin aspart 30/70 (twice daily)[147]	Minor hypoglycaemic episodes % of patients: BIAsp 30, 15% vs BIAsp 30+POI 12% Number of episodes: BIAsp 30, 47 and BIAsp 30+PIO, 15 Symptoms only % of patients: BIAsp 30, 40% vs BIAsp 30+PIO 34% Number of episodes: BIAsp 30, 171 and BIAsp 30+PIO, 115 Incidence (per patient-week for all episodes) BIAsp 30=0.132 vs BIAsp 30+PIO=0.083	Not reported
NPH insulin (bedtime) and glimepiride vs NPH insulin (twice daily) vs NPH insulin 30/70 (twice daily)[179]	Number of patients with at least one hypoglycaemic event: NPH insulin (bedtime) and glimepiride, 61.6% NPH insulin (twice daily), 71.6% NPH insulin 30/70 (twice daily), 72.4%	Not reported
Biphasic insulin aspart 30 (twice daily) and metformin vs biphasic insulin aspart 30 (twice daily)[64]	No major hypoglycaemic episodes during the trial, minor hypoglycaemic episodes were similar amongst treatment groups	NS

Weight gain

It was observed across most of the studies that treatment with insulin and other OHA (especially metformin) was associated with significantly less weight gain when compared with insulin monotherapy.

Only one study[147] comparing the combination of BIAsp 30 plus pioglitazone with BIAsp monotherapy showed a greater weight gain in patients treated with the combination therapy.

Other adverse events

Overall, no significant differences in frequency or severity of AEs were found for patients receiving insulin alone or combination therapy regimens. However, one study[147] found that more patients experienced product-related AEs in the biphasic aspart 30/70 plus pioglitazone group (28%) compared with patients receiving biphasic insulin aspart 30/70 monotherapy (20%). The combination group was also associated with a higher proportion of patients experiencing peripheral edema (6%) compared with aspart monotherapy (0%).

9.1.5 From evidence to recommendation

The new evidence continued to support the view that metformin should be continued when starting insulin therapy. The evidence was stronger than previously for sulfonylureas, for acarbose if used, and also for the thiazolidinediones. For sulfonylureas the situation was further complicated by much of the newer data coming from use with basal insulin regimens, while there was more uncertainty and concern over use with biphasic insulin (pre-mix) regimens due to risks of hypoglycaemia and the risk this might worsen achieved blood glucose control. Positive advice was tempered by concerns that the combination might cause excessive weight gain, and it was not possible to conclude whether this was clinically significant or otherwise a concern to the individual with Type 2 diabetes.

The cost and cost-effectiveness issues of continuing thiazolidinediones were considered at the time of review of the health economic modelling, although this issue was not specifically addressed by the modelling. Being high cost, it was unclear that the thiazolidinediones could give cost-effective health gains when continued at the time of starting insulin. However, it was noted that some people (often markedly obese) get a combination of reductions of insulin doses from high levels together with markedly improved blood glucose control when thiazolidinediones were added to insulin therapy.

RECOMMENDATIONS

R47 When starting basal insulin therapy:

- continue with metformin and the sulfonylurea (and acarbose, if used)
- review the use of the sulfonylurea if hypoglycaemia occurs.
-

R48 When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):

- continue with metformin
- continue the sulfonylurea initially, but review and discontinue if hypoglycaemia occurs.

R49 Consider combining pioglitazone with insulin therapy for:

- a person who has previously had a marked glucose lowering response to thiazolidinedione therapy
- a person on high-dose insulin therapy whose blood glucose is inadequately controlled. Warn the person to discontinue pioglitazone if clinically significant fluid retention develops.

9.2 Insulin therapy

9.2.1 Clinical introduction

Blood glucose control deteriorates inexorably in most people with Type 2 diabetes over a period of years, due to a waning of insulin production.[55] In these circumstances oral glucose-lowering therapies can no longer maintain blood glucose control to targets and insulin

replacement therapy becomes inevitable. Insulin deficiency is however only relative, not absolute, as there is still considerable endogenous insulin secretion occurring in response to the insulin insensitivity that is also usual in people with Type 2 diabetes. This means that the insulin regimens used in Type 1 diabetes (a condition of absolute insulin deficiency) may not be those needed in people with Type 2 diabetes.

The clinical question is which of the various pharmaceutical types of insulin, and in what combinations, are optimal for the management of Type 2 diabetes, both when initiating insulin and as insulin deficiency further progresses over the years.

9.2.2 Methodological introduction

Biphasic insulin preparations vs NPH

A limited number of clinical studies were identified which compare pre-mixes with NPH insulin.

There were three relevant RCTs. One study[182] compared biphasic insulin aspart 30/70 and NPH insulin in a population of 403 patients with a follow-up of 16 weeks. The other study[183] compared the combination of insulin aspart 30/70 and metformin with the combination of NPH insulin and metformin in a population of 140 patients with a follow-up of 12 weeks. The third study, a cross-over trial, compared a preprandial and basal regimen with insulin lispro and NPH, with a basal only regimen with twice daily NPH in 30 patients spending 12 weeks in each arm before cross-over.[184]

Differing populations, dosing and titration regimens may limit direct comparison between studies.

Biphasic human insulin preparations vs biphasic analogue preparations

A limited number of clinical studies were identified which compare biphasic analogue preparations with biphasic human insulin preparations.

One Cochrane review and meta-analysis was identified on this question.[185] This review was excluded as 88% of the included studies were judged to be of limited methodological quality. Eight studies in Type 2 diabetics had been identified and six studies in Type 1 and Type 2 diabetics. Of the studies included in the meta-analyses on HbA1c and hypoglycaemic episodes outcomes, only one study published post-2001 was included in each analysis.

Two RCTs were identified comparing once daily biphasic insulin analog formulation (insulin aspart containing 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine) with human pre-mixed insulin (30% regular, 70% NPH insulin).[186,187]

The study by Boehm[187] was an extension RCT of Boehm[186] comparing the long-term efficacy of these two formulations. An additional RCT compared three times daily biphasic insulin analog formulation (insulin aspart containing 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine) with once daily human pre-mixed insulin (30% regular, 70% NPH insulin).[188] One RCT compared a three times daily biphasic insulin analog formulation (50% insulin lispro and 50% neutral protamine lispro suspension) with once daily human pre-mixed insulin (30% regular insulin and 70% NPH).[189]

One RCT compared patients on metformin plus either once daily biphasic insulin analog formulation (insulin aspart containing 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine), NPH insulin or human pre-mixed insulin (30% regular, 70% NPH insulin).183 Another RCT compared a biphasic insulin analogue (insulin aspart containing 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine) with a daily basal-bolus regimen with insulin aspart before meals and evening human isophane insulin

(NPH).190 All studies were on patients with Type 2 diabetes except for one that included patients with Type 1 and Type 2 diabetes.[186]

Three open-label, single dose RCTs with methodological limitations were not considered further.

Differing populations, dosing and titration regimens may limit direct comparison between studies.

Multiple analogue insulin injection regimens compared to basal insulin or biphasic insulin regimens

A limited number of clinical studies were identified in this specific area.

A cohort study relevant to the question[191] conducted in India compared a multiple analogue insulin regimen with a pre-mix regimen in a cohort of 145 participants with a follow-up of 12 weeks.

The cohort study had the following limitations.

- Although described as a prospective study, it seems to be a retrospective collection of patients' data.
- It did not have a placebo-controlled arm.

Only one RCT was found that partially addressed the question.[192] This RCT did not directly compare multiple analogue insulin injection regimens with basal insulin or biphasic insulin regimens. The study was primarily designed to compare two different initiation treatment algorithms with insulin glargine (physician visit-base titration vs patient self-titration) in people with Type 2 diabetes suboptimally controlled on their previous antidiabetic treatment. A separate abstract reported the results for a subgroup of study participants who changed from once daily pre-mix insulin to once daily insulin glargine alone or with prandial insulin and/or oral antidiabetics (OADs). This reported baseline and endpoints values for HbA1c along with incidence of hypoglycaemia among seven groups of patients receiving different basal-bolus regimes with or without OADs.

This subgroup analysis should be interpreted with caution because:

- there was no subgroup treatment protocol to ensure consistent management
- there was only a historical control arm to demonstrate greater clinical efficacy of a multiple insulin regimen over a biphasic insulin regimen.

Long-acting insulin analogues (insulin glargine compared to NPH insulin, biphasic insulins or multiple daily injections)

A NICE technology appraisal (TA)[193] previously reviewed the evidence available until the end of 2001 and made recommendations on the use of insulin glargine in Type 2 diabetes. This guideline updates this appraisal and the GDG considered whether the appraisal recommendations should change in the light of new evidence.

Two meta-analyses [194,195] and 14 further RCTs [178,196–208] were identified which compared a regimen containing insulin glargine with another insulin containing regimen in those with Type 2 diabetes. One RCT compared morning and evening administration of insulin glargine.[209] One RCT compared insulin glargine with an optimised oral diabetic agent treatment arm.[210]

A recent meta-analysis by Horvath[195] compared the long-acting insulin analogues (insulin glargine and insulin determir) with NPH insulin. Only the results of the insulin glargine and NPH comparison are considered here. In this meta-analysis six RCTs were included in the

glargine and NPH comparison.[196,199,211–214] A further RCT by Yokohama was mentioned in the study but not included in the meta-analysis.[208]

An older meta-analysis by Rosenstock[194] which contained some of the same studies as the Horvath analysis combined four RCTs [211–214] which compared insulin glargine once daily with NPH insulin once or twice daily (in three studies NPH insulin was administered once daily,[211–213] and in the other study it was administered once or twice daily).[214] Four further RCTs compared once daily insulin glargine with once daily NPH insulin.[196,199,200,206] One RCT was excluded for methodological reasons.[208]

Eight RCTs compared insulin glargine with biphasic insulins.[178,198,201–205,207] In two studies [201,202] an insulin lispro mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro) administered twice daily was compared with bedtime insulin glargine. Two further studies compared intensive mixed preprandial regimens with insulin lispro before each meal compared to once daily insulin glargine.[203,205] Another study[178] compared insulin glargine once daily with human pre-mixed insulin (30% regular, 70% NPH insulin) twice daily, however these groups were not directly comparable as metformin and glimepiride were given with the insulin glargine and not with the pre-mixed insulin. Three studies [198,204,207] compared a once daily biphasic insulin analog formulation (insulin aspart containing 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine) with once daily insulin glargine, although in one of these studies[204] glimepiride was added to the glargine arm and metformin to the biphasic arm.

The study that compared morning and evening administration of insulin glargine included glimepiride in both arms.[209]

The review commissioned by NICE,[197,215] on which previous appraisal recommendations were based, noted that in studies where insulin glargine is demonstrated to be superior in controlling nocturnal hypoglycaemia, this may only be apparent when compared with once daily NPH and not twice daily NPH. It is thus notable that no new studies were identified which compared insulin glargine with NPH insulin administered twice daily.

The range of definitions of hypoglycaemia used and differing populations may limit direct comparison between studies.

9.2.3 Meta-analyses

Meta-analyses were conducted (using the Cochrane Collaboration's RevMan software) to investigate the choice of third-line therapies where more than one study was available for a comparison. Interventions considered were:

- human insulin – NPH or a pre-mix of unmodified NPH 30/70
- biphasic analogues (either lispro or aspart) – twice daily
- insulin glargine – once daily
- glitazones (pioglitazone and rosiglitazone)
- exenatide.

Because of the high acquisition costs of these third-line therapies, the pooled point estimates and CI of efficacy were used in a health economic model comparing these treatment options (see below. Full results are shown in appendix C available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247). The economic model was an adaptation of the UKPDS risk calculations, and in order to supply the risk factors in UKPDS, the following outcomes were sought:

- HbA1c
- systolic blood pressure (SBP)
- total high-density lipoprotein cholesterol (HDL-C)

- smoking status.

Of these, the only outcome where more than one study could be pooled was HbA1c. Change in weight or BMI was not one of the risk factors in UKPDS, and so was addressed in the economic model by sensitivity analyses (see appendix C for more detail available at www.rcplondon.ac.uk/ pubs/brochure.aspx?e=247).

Hypoglycaemia was not an outcome variable which could be varied in the UKPDS-based analysis. Accordingly a sensitivity analysis was performed by improving quality of life in insulins in evidence with less hypoglycaemia (see appendix C for more detail available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247).

The following studies were pooled:

- biphasic analogue vs human insulin: six studies, total N=1,001[182,183,186–189]
- glargine vs human insulin: two studies, total N=591[196,199]
- biphasic analogue vs glargine: three studies, total N=435.[198,201,202]

None of the comparisons had significant heterogeneity but the two studies comparing glargine to human insulin [196,199] had notably different baseline demographics and so a random effects analysis was used in this instance.

The comparison of biphasic analogues with human insulin showed no significant difference. The comparison of glargine with human insulin showed no significant difference.

The comparison of biphasic analogue with glargine had a pooled weighted mean difference of 0.43% HbA1c (95% CI 0.40 to 0.46) in favour of biphasic analogues. This analysis was dominated by one large trial1[98] but all three trials showed significant differences in the same direction of effect, which supports the validity of the pooled result.

9.2.4 Health economic methodological introduction

Two studies were found that compared the cost-effectiveness of glargine insulin with other forms of insulin.[193,216] Both studies were based on meta-analysis and used the UKPDS outcomes model to predict events and costs. However, they did not take in to account the impact on quality of life of AEs such as weight gain and vomiting.

For this guideline, an economic model was constructed based upon the UKPDS outcomes model to inform the GDG with regard to the cost-effectiveness of various third-line therapy options. This is presented in appendix C available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247

9.2.5 Evidence statements

Insulin glargine was not included in the Type 2 diabetes guideline 2002 under review. However, it was the subject of a NICE TA at that time, and the current review is an update of that.

9.2.5.1 Biphasic insulin preparations vs NPH

HbA1c

The two studies [182,183] found that HbA1c levels decreased linearly and statistically significantly in both treatment groups (biphasic insulin aspart 30/70 and NPH insulin) compared to baseline values. There was not a significant statistical difference between the two interventions. **Level 1+**

The third study found a significantly greater reduction in HbA1c in the lispro and NPH arm than in the twice daily NPH arm (p<0.01).[184] **Level 1+**

Fasting blood glucose/fasting plasma glucose

In patients receiving either biphasic insulin aspart 30/70 or NPH insulin, studies [182,183] showed similar reductions from baseline in FBG/FPG values. There was however no statistically significant difference between the two interventions. **Level 1+**

Postprandial blood/plasma glucose

One study[182] reported that the mean prandial glucose increment over the three main meals was significantly lower in the aspart 30/70 group than in the NPH group, (0.69 mmol/l lower; p<0.0001, between groups.) **Level 1+**

The other study[183] found no significant differences between the groups regarding the mean values for the 8-point self-monitoring of blood glucose (SMBG) profile at week twelve. The study reported that SMBG values for before breakfast and before lunch values tended to be lower for the NPH insulin group, while after dinner and 10 pm, values tended to be higher for the NPH insulin group as compared to the biphasic insulin aspart. **Level 1+**

In the insulin lispro vs NPH comparison, the postprandial glucose excursion was significantly lower in the lispro arm (p<0.001).[184] **Level 1+**

9.2.5.2 Body weight

Two studies [183,184] found non-significant differences in terms of body weight gain between the biphasic insulins and NPH. **Level 1+**

9.2.5.3 Adverse events

Both studies comparing insulin aspart with NPH [182,183] concluded that the number and type of AEs were similar for each of the treatment groups with non-significant differences between them. **Level 1+**

One study[182] found that in terms of incidence of hypoglycaemia, the RR was not statistically significantly different between treatments (RR=1.21 (95% CI 0.77 to 1.90), p=0.40). The other study reported that there was no significant difference between regimens for either overall or nocturnal hypoglycaemia.[184] **Level 1+**

The other study[183] found that nocturnal hypoglycaemia (midnight–6 am) was less frequently reported for patients receiving biphasic insulin aspart (seven patients) as compared to patients in the NPH insulin group (11 patients). No statistical analysis was reported. **Level 1+**

9.2.5.4 Lipid profile

One study[184] reported changes in lipid measures between groups and found a significantly lower fasting low-density lipoprotein cholesterol (LDL-C) and LDL-C/HDL-C ratio in the biphasic insulin (lispro) and NPH arm compared with twice daily NPH (p=0.035). After a standard meal both LDL-C (p=0.012) and HDL-C (p=0.004) were significantly higher in the biphasic insulin (lispro) and NPH arm compared with twice daily NPH arm. **Level 1+**

Table 11.3 Biphasic human insulin preparations vs biphasic analogue preparations

	RCT[188] Three times daily biphasic insulin aspart vs once daily human pre-mixed insulin N=177 Duration: 24 weeks	RCT[186] Twice daily biphasic insulin aspart vs once daily human pre-mixed insulin N=294 Duration: 12 weeks *Type 1 and 2 diabetes	RCT[187] Twice daily biphasic insulin aspart vs once daily human pre-mixed insulin N=125 Duration: 24 months	RCT[183] Metformin plus: once daily biphasic insulin aspart or NPH insulin or human pre-mixed insulin N=140 Duration: 12 weeks	RCT[189] Three times daily biphasic insulin aspart vs once daily human pre-mixed insulin N=40 Duration: 12 weeks	RCT[190] Three times daily biphasic insulin aspart vs a basal-bolus regiment using insulin aspart before meals and NPH at bedtime N=394 Duration: 16 weeks
Mean HbA_{1C} at endpoint	NS	NS	NS	NS	7.6±1.1 vs 8.1±1.4%; p=0.021, mean change from baseline (favouring biphasic insulin aspart)	Mean difference in HbA_{1C} at end: –0.05 (upper limit of 95% CI 0.14% (which is below the non-inferiority criterion of 0.4%) non-inferiority demonstrated)

continued

Table 11.3 Biphasic human insulin preparations vs biphasic analogue preparations – *continued*

	RCT[188] Three times daily biphasic insulin aspart vs once daily human pre-mixed insulin N=177 Duration: 24 weeks	RCT[186] Twice daily biphasic insulin aspart vs once daily human pre-mixed insulin N=294 Duration: 12 weeks *Type 1 and 2 diabetes	RCT[187] Twice daily biphasic insulin aspart vs once daily human pre-mixed insulin N=125 Duration: 24 months	RCT[183] Metformin plus: once daily biphasic insulin aspart or NPH insulin or human pre-mixed insulin N=140 Duration: 12 weeks	RCT[189] Three times daily biphasic insulin aspart vs once daily human pre-mixed insulin N=40 Duration: 12 weeks	RCT[190] Three times daily biphasic insulin aspart vs a basal-bolus regiment using insulin aspart before meals and NPH at bedtime N=394 Duration: 16 weeks
FPG	–	NS	–	NS	Pre-breakfast: 177.7±9.6 vs 147.4±6.3 mg/dl, p<0.001 (favouring human pre-mixed insulin)	–
PPG	Lunch (156 vs 176 mg/dl, p=0.0289), Before dinner (142 vs 166 mg/dl, p=0.0069) After dinner (154 vs 182 mg/dl, p=0.0022) Mean blood glucose range: 104 vs 123 mg/dl; p=0.0111 blood glucose increment (over all three meals) 25 vs 37 mg/dl; p=0.02111 (all favouring biphasic insulin aspart)	After breakfast (10.40 (0.37) vs 11.40 (0.36); p<0.05) Before lunch (6.64 (0.28) vs 7.57 (0.27); p<0.02) After dinner (9.22 (0.33) vs 10.20 (0.32); p<0.02) Bedtime (8.22 (0.31) vs 9.10 (0.30); p<0.05) blood glucose increment (over all three meals) 1.66 (0.22) vs 2.34 (0.19 mmol/l; p<0.02) (all favouring biphasic insulin aspart)	–	–	After lunch (155.6±5.8 vs 192.2±8.5 mg/dl; p<0.001) After dinner (166.3±7.2 vs 198.2±10.0 mg/dl; p<0.001) (flavouring biphasic insulin aspart)	No statistically significant difference between the treatments found in 8-point PG profiles, mean values of PG, average prandial PG increment profiles
Body weight	–	NS	NS	NS	–	NS
Hypoglycaemia						
Major	NS	NS	2nd year N=0 (0%) vs N=6 (10%; p=0.04) (favouring biphasic insulin aspart)	NS	NS	NS
Minor	NS	NS	NS	NS	NS	NS
Nocturnal	NS	NS (major and minor)	–	NS	–	NS
AEs	NS	NS	NS	NS	NS	NS

PPG, postprandial glucose

HbA1c

Overall, on endpoint means HbA1c levels biphasic analogue preparations were comparable to human pre-mixed insulin,[183,186,187,188] as well as to a basal-bolus regimen of insulin aspart and NPH.[190] **Level 1+**

One RCT found three times daily biphasic insulin lispro (50/50) gave a significantly greater reduction from baseline in mean HbA1c values compared with once daily pre-mixed human insulin 30/70.[189] **Level 1+**

Fasting blood glucose

Two RCTs found no significant differences among the treatment groups on FBG.[186,183] **Level 1+**

One RCT found that FBG was significantly increased in patients on three times daily biphasic analogue insulin compared with once daily human pre-mixed insulin.[189] **Level 1+**

Postprandial glucose

In terms of PPG, three RCTs reported significant treatment differences in favour of biphasic insulin aspart.[188,186,189] **Level 1+**

Bodyweight

No studies reported any significant differences between treatment groups.[186,187,183,190] **Level 1+**

Adverse events

Studies reported similar AEs profiles for biphasic analogue insulin and biphasic human insulin.[188,186,187,183,189,190] **Level 1+**

Hypoglycaemia

Overall, few major hypoglycaemic episodes were associated with either biphasic analogue or human insulin.[188,186,183,189,190] **Level 1+**

A longer-term efficacy study found that during the second year of treatment significantly fewer patients in the once daily biphasic analogue insulin than the human pre-mixed insulin group experienced a major episode.[187] **Level 1++**

No study reported any significant differences between treatments on minor or nocturnal hypoglycaemic episodes.[188,186,183,190] **Level 1+**

9.2.5.5 Multiple analogue insulin injection regimens compared to basal insulin or biphasic insulin regimens

HbA1c

For HbA1c levels the cohort study reported that both multiple insulin regimen and pre-mix insulin regimen lowered HbA1c levels significantly compared to baseline values. Pre-mix insulin analogue fared better than the basal-bolus analogue therapy in lowering HbA1c (1.58% vs 1.16% respectively, $p<0.05$). Also 41% more patients in the pre-mix group could achieve target HbA1c of <7% at the end of 12 weeks (45.61% vs 32.26%). **Level 2+**

FPG/PPPG

Both regimes lowered FPG and postprandial plasma glucose (PPPG) levels significantly as compared to baseline. No statistical comparison was performed between groups. **Level 2+**

Body weight

The body weight did not change significantly in either group at the end of the study. **Level 2+**

Hypoglycaemia events

The percentage of patients experiencing minor hypoglycaemia was significantly lower in the pre-mix group than in the basal-bolus group at 12 weeks (16.7% vs 58.06%, $p<0.05$). **Level 2+**

Throughout the study period of 12 weeks, there were no major hypoglycaemic episodes reported in both the treatment groups. **Level 2+**

Subgroup analysis

The analysis of the sub-population previously receiving pre-mix insulin suggests that optimisation of basal insulin therapy with once daily insulin glargine is safe (according to the low incidence of severe hypoglycaemic events) and results in significant improvements in glycaemia control.

The same analysis indicates that once daily insulin glargine in combination with prandial therapies (prandial insulin and/or OADs) offers additional glycaemic benefits.

Long-acting insulin analogues (insulin glargine compared to NPH insulin, biphasic insulins or multiple daily injections)

NB. Glargine and its comparators are often used in these studies in combination with OAD medications. For simplicity, references to these drugs are not included in the evidence statements unless they differ between the two groups.

Table 11.4 Insulin glargine vs NPH insulin

	Meta-analysis[195] Bedtime insulin glargine vs NPH once or twice daily N=3,151 Duration: 6–12 months	Meta-analysis[194] Bedtime insulin glargine vs NPH once or twice daily N=2,304 Duration: 24–28 weeks	RCT[196] Bedtime insulin glargine vs bedtime NPH N=110 Duration: 36 weeks	RCT[200] Insulin glargine once daily vs once daily NPH N=204 Duration: 4 weeks	RCT[199] Bedtime insulin glargine vs bedtime NPH N=481 Duration: 24 weeks	RCT[206] Bedtime insulin glargine vs bedtime NPH N=443 Duration: 24 weeks
Proportion achieving 7% HbA_{1c} target	–	NS	–	–	NS (7.5% target)	NS (7.5% target)
Mean HbA_{1c} at endpoint	WMD of change of HbA_{1c} from baseline to study endpoint: NS	NS	NS	NS	NS	Change in mean HbA_{1c} at endpoint greater in glargine group (–0.99% vs –0.77%, p=0.003)
FPG	–	8±0.1 vs 9±0.0 mmol/l (p=0.02) at endpoint	5.75±0.02 vs 5.96±0.03 mmol/l (p<0.001) (mean values in last 12 weeks of the study)	NS	NS (FBG)	NS
Insulin dose	–	NS	NS	NS	–	NS
Body weight	–	–	NS	NS	–	NS
Hypoglycaemia: overall rates	Symptomatic and overall hypoglycaemia RR 0.84 (0.75, 0.95) p=0.005 in favour of glargine	11% risk reduction with insulin glargine in documented symptomatic hypoglycaemia (p=0.0006). 46% risk reduction with insulin glargine in documented severe hypoglycaemia (p=0.04)	4.1±0.8 vs 9.0±2.3 episodes/patient year (p<0.05) of symptomatic but not confirmed hypoglycaemia during the first 12 weeks. NS thereafter	NS	27% risk reduction with insulin glargine in documented symptomatic hypoglycaemia (p=0.042)	Number of hypoglycaemic episodes lower in glargine group (682 vs 1019; p<0.004)
Nocturnal	Symptomatic nocturnal hypoglycaemia RR 0.66 (0.55, 0.80) p<0.0001 in favour of glargine	26% risk reduction in nocturnal hypoglycaemia (p<0.0001). 58% risk reduction in severe nocturnal hypoglycaemia (p<0.02)	–	7.3% vs 19.1%; (p=0.0123) of patients experienced symptomatic nocturnal hypoglycaemia	22% risk reduction with insulin glargine compared to NPH insulin (p<0.001) and this was 19% for confirmed nocturnal events (p<0.01)	Number of hypoglycaemic episodes lower in glargine group (221 vs 620; p<0.001)
Daytime	–	NS	–	NS	–	–
AEs	NS (no meta-analysis)	NS	NS	NS	NS	NS

Table 11.5 Insulin glargine vs biphasic insulins

	RCT[201] Bedtime insulin glargine vs twice daily insulin lispro mix 75/25 N=105 Duration: 32 weeks	RCT[202] Bedtime insulin glargine vs twice daily insulin lispro mix 75/25 N=97 Duration: 32 weeks	RCT[198] Bedtime insulin glargine vs a twice daily biphasic insulin analogue 70/30 N=233 Duration: 28 weeks	RCT[207] Bedtime insulin glargine vs a twice daily biphasic insulin analogue 70/30 N=157 Duration: 28 weeks	RCT[205] Bedtime insulin glargine vs insulin lispro thrice daily vs insulin lispro mid mixture (50% lispro/50% NPL) thrice daily N=159 Duration: 24 weeks	RCT cross over[203] Bedtime insulin glargine vs insulin lispro 50/50 at breakfast and lunch and lispro 25/75 in evening N=60 Duration: 8 months	RCT[178] Morning insulin glargine plus glimepiride and metformin vs twice daily human remixed insulin 70/30 N=371 Duration: 24 weeks	RCT[204] Insulin glargine once daily plus glimepiride vs biphasic insulin analogue 70/30 twice daily plus metformin N=255 Duration: 26 weeks
Decrease in HbA_{1c} from baseline	–0.9%±0.9 vs –3.1%±1.0% p=0.003	–0.42%±0.92% vs –1.0%±0.85% p<0.001	–2.36%±0.11% vs –2.79%±0.11% p<0.01	–2.46±1.6% vs –2.89±1.6% p=0.035	–0.3±1.1% vs –1.1±1.1% (p=0.001) vs –1.2±1.1% p<0.001	–1.76±0.11% vs –1.98±0.11 p=0.0083	–1.64 vs –1.31%, p=0.0003	Mean difference in HbA_{1c} from baseline: –0.5 (–0.8, –0.2) p=0.0002 (corrected for baseline)
Mean HbA_{1c} at endpoint	7.8%±1.1% vs 7.4%±1.1% p=0.002	8.14%±1.03% vs 7.54%±0.87% p<0.001	7.41±1.24% vs 6.91±1.17 p<0.01	7.4±1.3% vs 7.0±1.3% p=0.035	–	7.34±0.11% vs 7.08±0.11% p=0.003	–	7.9±1.3% vs 7.5±1.1% p=0.01
Proportion achieving 7% HbA_{1c} target	18% vs 42% p=0.002	12% vs 30% p=0.002	40% vs 66%, p<0.001 (HbA_{1c} <7.0%)	41% vs 65% p=0.03	24.5% vs 40.4% vs 59.3% (p not given)	31% vs 44% NS	NS	NS
Mean FBG at endpoint	123.9 mg/dl±34.9 vs 139.3±36.6 mg/dl p<0.001	7.39±1.96 vs 7.9±1.92 mmol/l p=0.007	–	Mean reduction in FPG NS	–2.6±2.4 mmol/l vs –0.9±2.2 mmol/l (p<0.001 vs + 0.9±1.8 mmol/l (p<0.001)	NS	–0.9 mmol/l (95%CI –1.3 to –0.6) adjusted mean between treatment difference in favour of glargine	NS
Insulin dose	0.57±0.37 U/kg vs 0.62±0.37 U/kg p<0.001	0.36±0.18 U/kg vs 0.42±0.20 U/kg p<0.001	0.55±0.27 U/kg vs 0.82±0.40 U/kg p<0.05	0.57±0.30 IU/kg vs 0.91±0.40 IU/kg p not given	0.43±0.22 IU/(kg day) vs 0.50±0.23 IU/(kg day) vs 0.59±0.30 IU/(kg day) p<0.005	0.276±0.207 IU/kg vs 0.353±0.256 IU/kg p=0.0107	28.2 IU vs 64.5 IU	0.39 IU/kg vs 0.40 IU/kg p=0.65

Mean change in body weight	1.6±4.0 kg vs 2.3±4.0 kg p=0.006	0.06±2.49 kg vs 0.82±2.56 kg p=0.001	3.5±4.5 kg. vs 5.4±4.8 kg p<0.01	3.0±4.3 kg vs 5.6±4.6 kg p=0.0004	0.7±3.8 kg vs 2.3±4.3 kg vs 1.8±3.4 kg (p not given) BMI increase significantly greater in lispro vs glargine	NS	NS	–
Hypoglycaemia: overall rates	0.39±1.24 vs 0.68±1.38 episodes/patient per 30 days p=0.041	NS	0.7±2.0 vs 3.4±6.6 episodes per patient year p<0.05	Proportion of participants reporting at least one hypoglycaemic event: 42% vs 68% p=0.0013	1.0 per 100 patient days vs 1.4 per 100 patient days vs 1.5 per 100 patient days (p not given)	2.57±3.22 vs 3.98±4.74 episodes/patient/ 30 days p=0.0013	4.07 vs 9.87 mean number of confirmed hypoglycaemic events; p<0.0001	Proportion of patients experiencing minor hypoglycaemic episodes: 9% vs 20.3% p=0.0124
Nocturnal	NS	0.34±0.85 vs 0.14±0.49 episodes/patient/ 30 days p=0.002	–	Proportion reporting nocturnal hypoglycaemia: 10% vs 25% p=0.021	–	NS	0.51 vs 1.04 mean number of confirmed nocturnal hypoglycaemic events per patient years p<0.0449	–
Daytime	–	0.10±0.51 vs 0.46±1.28 vs episodes/patient/ 30 days p=0.003)	–	–	–	–	–	–
AEs	NS	NS	NS	NS	NS	–	NS	NS

IU, A/Q; WMD, weighted mean differences

None of the studies [194–196,199,200,206] reported differences between the insulin glargine and NPH groups in terms of proportion of patients achieving target HbA1c, insulin dose, body weight, daytime hypoglycaemia or AEs. One study found a significantly greater reduction in the mean HbA1c at endpoint in the insulin glargine arm.[206] Five studies [194–196,199,206] found significant risk reductions in overall risk of hypoglycaemia with insulin glargine compared to NPH insulin (one only in the first 12 weeks)1[96] while the shorter study found no difference.[200] Five studies [194,195,199,200,206] reported significant risk reductions in terms of nocturnal hypoglycaemia with insulin glargine compared to NPH insulin. Additionally, FPG values were significantly lower at endpoint in the glargine groups in two studies[196,214] but showed no significant difference in the shorter study.[200] **Level 1+**

Seven studies [198,201–205,207] reported better HbA1c outcomes with the insulin mixes compared to insulin glargine. The other study found significantly higher reductions in HbA1c with insulin glargine from baseline, however insulin glargine was combined with OAD drugs which were not received by the insulin mix group.[178] With respect to decreases in FBG from baseline results, they were less consistent. Statistically significant decreases in FBG were reported in insulin glargine groups compared to the insulin mix groups in four studies,[178,201,202,205] although three studies did not find a significant difference.[203,204,207] Insulin doses were higher in the insulin mix groups in all studies.[178,198,201–205,207] In five studies the insulin mix groups had significantly increased body weight from baseline compared with insulin glargine.[198,201,202,205,207] Two studies found no significant difference in body weight change between the groups [178,203] and the remaining study [204] reported a greater weight increase in the insulin glargine and glimepiride group than in the biphasic insulin analogue and metformin group although they did not report if this was statistically significant. In terms of hypoglycaemia, one study found no significant difference [202] in overall hypoglycaemia rates, while the remaining studies [178,198,201,203–205,207] found overall hypoglycaemia rates were better with insulin glargine than insulin mixes. For nocturnal hypoglycaemia, two studies reported no significant difference between the groups,[201,203] another found higher rates in the glargine group [202] and two others found significantly reduced rates in that group compared to the insulin mix group.[178,207] Only one study reported daytime hypoglycaemia rates and these were found to be significantly higher in the insulin mix group.[202] No significant differences between the groups were reported in terms of AEs.[178,198,201,202,204,205,207] **Level 1+**

Morning vs evening administration of insulin glargine

Standl et al.[209] compared insulin glargine delivered at different times of the day to determine the impact on glycaemic control and rates of hypoglycaemia. It was found that morning and evening administration of glargine was equivalent with respect to the incidence of nocturnal hypoglycaemia. Similar improvements in HbA1c, FBG and the proportion of patients achieving an HbA1c of less than 7% was demonstrated in the two arms of the study, without any difference in the incidence of AEs. **Level 1+**

Insulin glargine vs oral therapy

Gerstein et al.[210] compared the addition of insulin glargine to current treatment with the intensified oral glucose-lowering therapy. HbA1c outcomes were reported to be significantly better in the glargine group even after adjusting for baseline HbA1c and oral therapy. FPG was also significantly lower and lipid parameters were significantly improved in the glargine group. There was no significant difference in hypoglycaemia, and the glargine group had a significantly greater weight increase. **Level 1+**

There was no significant difference in hypoglycaemia, and the glargine group had a significantly greater weight increase. **Level 1+**

9.2.16 Health economic evidence statements

In the long-acting insulin TA[193] there was an estimated cost-effectiveness ratio of £33,000 compared to NPH insulin, using the price of a vial of glargine. Using cartridges or pens gave higher cost-effectiveness ratios, £41,000 and £43,000 respectively. The results were most sensitive to the assumption on utility gained from reducing fear of hypoglycaemia. If it was assumed that there was no utility gain from this then the cost-effectiveness ratio rose to approximately £10 million per QALY.

The second study[216] found a cost-effectiveness ratio of £13,000 per QALY gained compared to NPH insulin. But it did not take into account the disutility associated with the side effects of insulin glargine and no comparison was made with other third-line therapies.

The base-case results of the analysis of third-line therapy conducted for this guideline (see appendix C available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247) found that human insulin was as effective but less expensive than biphasic insulin, and more effective and less expensive than insulin glargine.

9.2.17 From evidence to recommendations

Pre-mix insulin

There was limited evidence for comparisons of pre-mix insulin with NPH insulin in people with diabetes. Because of the use of unselected populations of people with Type 2 diabetes taking little account of factors such as degree of insulin deficiency, high or low mealtime insulin requirement, diurnal patterns of blood glucose control, and sensitivity to hypoglycaemia, the studies did not help inform clinical decision making. These insulins, compared to basal insulins, target postprandial blood glucose control. The issue of whether postprandial blood glucose control was of any specific importance, rather than being important because glucose levels are highest at that time, is not being addressed in this guideline. There was confidence that no health outcome studies on the issue had been published. The GDG felt that it was inappropriate to make strong recommendations promoting pre-mix insulin over NPH or the opposite, except to observe that as insulin deficiency progressed mealtime insulin therapy would be more likely to be indicated.

There was limited evidence on the comparisons between insulin analogue pre-mixes and human insulin pre-mixes. There was definite evidence statistically of some reduction in postprandial blood glucose control in the period after injection when using an analogue rather than human insulin, as was to be expected from other data with rapid-acting insulin analogues. Equally there was some data on the reduction of hypoglycaemia, consistent with other analogue data. These effects were clinically quite small and therefore of questionable cost-effectiveness, a view supported by the health economic modelling.

Unfortunately all comparative trials had been performed using different recommendations of timing of insulin injection before meals for human and analogue insulins (in line with licences). The advantage of injecting immediately before meals (usually twice a day) in daily life to people with diabetes was felt to be a significant quality of life issue justifying the use of the analogues. Studies asking whether human insulin pre-mixes could be given immediately before meals without deterioration of blood glucose control (hyperglycaemia early and hypoglycaemia late) compared to analogues had not been performed.

Basal insulins including long-acting insulin analogues

The previous guidance for use of insulin glargine endorsed its use in people with Type 2 diabetes where the injections were given by a carer, where hypoglycaemia was a problem when using NPH insulin, and where insulin administration would otherwise require twice daily insulin injections. The studies performed since were a useful contribution not only to the

understanding of insulin glargine, but more so, to the optimal use of insulin in people with Type 2 diabetes, in particular for people starting insulin therapy.

Very little useful information was found to assist in advising on the optimal insulin regimen once progression of islet B-cell failure had progressed further, for example in people 3–5 years or more after starting insulin therapy. The observational study from India was open to bias in patient and provider selection, and the subgroup analysis from A Trial comparing Lantus® Algorithms to achieve Normal blood glucose Targets in patients with Uncontrolled blood Sugar (AT.LANTUS) was similarly open to bias and in small numbers of people. The preferred view was that as islet B-cell deficiency progressed people tended to a state of insulin deficiency closer to those with Type 1 diabetes, suggesting that prior NICE guidelines advice for that group of patients could be applied.

The strongest of the new evidence for insulin starters appeared to relate to comparisons with NPH insulin, and of these the data on comparison with once daily (bedtime) human NPH insulin was the most novel. It was noted that these treat-to-target studies have the problem, given their limited duration, of driving control in the compared groups towards the same levels, and indeed pre-breakfast glucose levels and HbA1c were similar for insulin glargine and NPH, at similar insulin doses. The differences in nocturnal hypoglycaemia were convincing, if small

in absolute terms. Despite post hoc analyses of the relationship between HbA1c and nocturnal hypoglycaemia showing convincing advantage of insulin glargine over NPH insulin, it was impossible to determine what the balance of advantage between the two measures would be in real clinical practice, where differences in hypoglycaemia tend to drive differences in insulin dosage and thus overall blood glucose control (which would be to the advantage of the long- acting analogue).

Although not the subject themselves of a randomised comparison, the approaches used in the treat-to-target studies of active dose titration in the context of appropriate education, self-monitoring and support were an important means of obtaining optimal blood glucose control whatever insulin was employed.

An issue relates to the choice of insulin preparation for starting insulin in people with Type 2 diabetes. As noted above, and provided that insulin was started reasonably early in the disease process before HbA1c had deteriorated too far, there was little justification for the use of more intensive mealtime plus basal insulin regimens in this situation. The studies comparing insulin glargine with pre-mix insulin regimens gave mixed results, with improved HbA1c apparently resulting from an ability to titrate twice daily insulin dosage faster (in total) than once daily injections, but at a cost of increased hypoglycaemia and weight gain. These results and the absence of longer term data on performance of the two regimens, together with complexities such as the possibility of using three injections of pre-mix, or of adding mealtime insulin to basal glargine, meant that the GDG was unable to identify overall advantage to one approach or the other.

The previous NICE guidance in relation to a single daily injection of insulin glargine not having to be given at any precise time was noted to be useful for those whose injections are given by others.

The GDG found the health economic modelling problematic in the area of insulin therapy. Major problems seem to relate to the difficulties of including fear of hypoglycaemia and its effect on everyday lifestyle, restrictions on lifestyle with insulin injections, and the present day educational costs associated with intensive insulin dose adjustment to achieve good target control. While some attempts had been made to incorporate some of these in sensitivity analyses, it was not possible to be sure of their validity, though the face value results all suggested that human insulin regimens were the only cost-effective approach.

RECOMMENDATIONS

R50 When other measures no longer achieve adequate blood glucose control to HbA1c <7.5% or other higher level agreed with the individual, discuss the benefits and risks of insulin therapy. Start insulin therapy if the person agrees.

R51 When starting insulin therapy, use a structured programme employing active insulin dose titration that encompasses:

- structured education
- continuing telephone support
- frequent self-monitoring
- dose titration to target
- dietary understanding
- management of hypoglycaemia
- management of acute changes in plasma glucose control
- support from an appropriately trained and experienced healthcare professional.

R52 Insulin therapy should be initiated from a choice of a number of insulin types and regimens.

- Preferably begin with human NPH insulin, taken at bedtime or twice daily according to need.
- Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories:
  - those who require assistance from a carer or healthcare professional to administer their insulin injections
  - those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes
  - those who would otherwise need once daily basal insulin injections in combination with oral glucose-lowering medications.
- Consider twice-daily biphasic human insulin (pre-mix) regimens in particular where HbA1c is elevated above 9.0 %. A once-daily regimen may be an option when initiating this therapy.
- Consider pre-mixed preparations of insulin analogues rather than pre-mixed human insulin preparations when:
  - immediate injection before a meal is preferred, or
  - hypoglycaemia is a problem, or
  - there are marked postprandial blood glucose excursions.

R53 Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycaemia.

R54 Monitor a person using a basal insulin regimen (NPH or a long-acting insulin analogue (insulin glargine) for the need for mealtime insulin (or a pre-mixed insulin preparation)). If blood glucose control remains inadequate (not to agreed target levels without problematic hypoglycaemia), move to a more intensive, mealtime plus basal insulin regimen based on the option of human or analogue insulins.

R55 Monitor a person using pre-mixed insulin once or twice daily for the need for a further preprandial injection or for an eventual change to a mealtime plus basal insulin regimen, based on human or analogue insulins, if blood glucose control remains inadequate.

9.3 Insulin detemir

The GDG considered including sitagliptin and insulin detemir in this guideline; however, they were advised by NICE not to do so. NICE is undertaking a rapid update of recommendations in this guideline on second- and third-line drugs for managing blood glucose, which will cover these drugs. The updated guideline will be published early in 2009. For more information see www.nice.org.uk and search for 'Type 2 diabetes newer agents'.

9.4 Insulin delivery devices (CG66)

Insulin pumps are not considered here; they have been the subject of a recent NICE TA, and are not widely used in people with Type 2 diabetes.[217]

9.4.1 Clinical introduction

Insulin was previously normally delivered from syringes, necessitating accurate measuring of insulin doses drawn up from insulin vials under suitably hygienic conditions. Modern pen-injector devices obviate most of the problems of measuring up doses while avoiding most of the hygiene problems, and offer a convenient and safe means of carrying around injection equipment. However, several models of injector are available, including some designed for those with visual and physical impairments.

The clinical question addressed here was whether any particular pen-injector had an evidence- based advantage over any other, including groups of people with difficulty using such devices.

9.4.2 Methodological introduction

Six crossover RCTs were identified which compared insulin pens or other delivery systems with conventional syringes.[219–224] One study was excluded for methodological reasons.[224] Two crossover RCTs were also identified which compared different types of insulin pens.[220,225]

This area was not covered in detail by the previous guideline, and studies were only searched for from 1995 onwards to prevent the inclusion of obsolete devices.

None of these studies were of a particularly high methodological quality with few reporting any details of randomisation, concealment or a power analysis. Few studies took into account the insulin delivery method that patients had used previously. Most studies assessed patient preference by use of their own specifically developed for purpose questionnaires; it was notable that some of these contained ‘leading’ questions.

9.4.3 Health economic methodological introduction

No health economic papers were identified for this question.

9.4.4 Evidence statements: syringes vs other insulin delivery systems

One study found pre-lunch blood glucose values were lower during pen treatment ($p<0.01$) but no other significant differences were found between pens and syringes for blood glucose profiles or in terms of HbA1c.[219] Three other studies found no differences between syringes and other delivery devices in terms of glycaemic control.[221–223] **Level 1+**

Two studies noted no significant difference in the incidence of hypoglycaemic episodes between pens and syringe treatments.[219,221] In other studies no AEs were considered by the investigator to be related to study treatment[223] or the safety profiles for pen and the vial/syringe appeared similar.[222] **Level 1+**

Operational use

In 1 study patients starting insulin using a pen found the insulin injections easy (63%) or very easy (33%) at the end of 12 weeks, whilst those who commenced insulin with conventional syringes found it more difficult with only 24% finding it very easy by the end of 12 weeks and 51% finding it easy (p=0.0005).[221] **Level 1+**

Other studies (which did not report significance) found that the operations needed for insulin administration with a pen compared to a syringe were faster (88%)[219] and that the pen device was found easier to use overall compared to the syringe (74% vs 21% respectively).[222] **Level 1+**

In a study of patients with motor dysfunction and/or visual problems, an insulin injection device with a large easy-to-read dial, large push button for injection and audible clicks for each unit injected, was found to be easier to use compared to a vial and syringe by 82% of patients with the practical aspects of the injection device (dosing and injecting) rated as very easy or easy by 86%.[223] **Level 1+**

A study of visually impaired patients found that 80% were able to set and dispense 3 insulin doses after written instructions when using the insulin injection device with easy-to-read dial, large button for injection and audible clicks for units injected. This was significantly more than those using a syringe (27%, p<0.001) or a pen device (61%, p<0.001).[220] **Level 1+**

Pre-selection of dose

A study comparing a pen with a conventional syringe and vial found that setting and drawing up the dose of insulin was significantly easier for patients using the pen (p=0.0490).[221] **Level 1+**

Other studies (which did not report significance) reported that 86% of participants found that pre-selection of insulin dose with a pen was easier than insulin withdrawal from a vial with a conventional syringe[219] and that 85% of patients reported that they found it easier to read the insulin dose scale with the pen than the vial/syringe (10% found reading the insulin dose scale easier using the vial/syringe).[222] **Level 1+**

Pain

A study found that injection pain was significantly lower with a pen than with syringes and vials (p=0.0018). Patients commencing on syringes reported a significantly lower level of injection pain after the switch to using the pen (p=0.0003).[221] Another study reported participants found insulin injections with the pen, compared to the conventional syringe, were 55% less painful, although 43% did not notice any difference.[219] **Level 1+**

Preference for a device

In the study of patients with motor dysfunction and/or visual problems, the insulin injection device with the easy-to-read dial, large button for injection and audible clicks for units injected, was significantly preferred to the vial and syringe (82% vs 10%, p<0.001).[223] **Level 1+**

In all studies comparing pens with conventional syringes more patients stated a preference for the pens over the conventional syringe and vial.[219–222] **Level 1+**

Insulin delivery devices vs other insulin delivery devices

NovoPen® 3 vs HumaPen Ergo® vs Humalog Pen® vs InnoLet® vs FlexPen®

Auditory confirmation of dose setting was heard by 100% of study participants for NovoPen® 3, 98% for FlexPen®, 90% for InnoLet®, 75% for HumaPen Ergo® and 63% for the Humalog Pen®. This was significantly different between the NovoPen® 3 and the Humalog Pen® ($p<0.001$), the HumaPen Ergo® ($p<0.001$), and InnoLet® ($p<0.01$), and the FlexPen® and the Humalog Pen® ($p<0.001$), and HumaPen Ergo® ($p<0.01$).[225] **Level 1+**

For tactile feedback, (the proportion of patients physically sensing they had dialled a correct dose) this was 100% for the FlexPen®, 92% for the NovoPen® 3, 81% InnoLet®, 67% HumaPen Ergo® and 50% for the Humalog Pen®. Significantly more patients reported that they had dialled the correct dose for the FlexPen® compared with the Humalog Pen® ($p<0.001$), HumaPen Ergo® ($p<0.001$) and InnoLet® ($p<0.01$). Significant differences were also noted between the NovoPen® 3 and Humalog Pen® ($p<0.001$) and the HumaPen Ergo® ($p<0.01$).[225] **Level 1+**

Patients reported most confidence in setting the correct dose when rating the NovoPen® 3 and FlexPen®. Scores for the NovoPen® 3 were significantly higher than those for the InnoLet® ($p<0.001$), HumaPen Ergo® ($p<0.001$) and Humalog Pen® ($p<0.001$), whereas the FlexPen® scored significantly higher than the Humalog Pen® ($p<0.01$).[225] **Level 1+**

InnoLet® vs Humulin Pen®

In a group of visually impaired patients, the InnoLet® insulin device (easy-to-read dial, large button for injection and audible clicks for units injected) was found to be significantly more effective than the Humulin Pen® in terms of visual accuracy when reading the dose scale (92% vs 45%, $p<0.001$). Additionally, significantly more patients using InnoLet® were able to intuitively set and dispense a 20U insulin dose (84% vs 41%, $p<0.001$) and InnoLet® was significantly preferred to the Humulin Pen® (87% vs 13%, $p<0.001$).[220]

There was no strong published evidence that insulin pen injectors were a preferred option for insulin injection, but in clinical practice this was not questionable. The studies comparing devices did not compare all devices, were inevitably unblinded, and were manufacturer sponsored in single centres for the most part. The issue of bias was real. It was considered that some devices performed better than others, but also that this was generally known to regular prescribers. Prescribers should be fully familiar with the devices they were recommending; this would be difficult for all the devices available.

One injection device, the InnoLet®, was not a pen injector, but was aimed more at people with physical disabilities in manipulating injection systems. The studies were consistent with clinical experience in suggesting that this device was successful in enabling self-injection in some people who could not otherwise do it easily or reliably.

Please refer to the Diabetes UK guidance for the issue of disposal of devices/sharps.

R56 Offer education to a person who requires insulin about using an injection device (usually a pen injector and cartridge or a disposable pen) that they and/or their carer find easy to use.

R57 Appropriate local arrangements should be in place for the disposal of sharps.

R58 If a person with type 2 diabetes has a manual or visual disability and needs insulin, offer a device or adaptation that:

- takes into account his or her individual needs
- he or she can use successfully.

1

10 Cardiovascular risk estimation

10.1 Clinical introduction

Nearly all people with Type 2 diabetes are at high cardiovascular (CV) risk – high enough to justify statin therapy without further assessment.[273] Others are at more extreme risk.[273] Other therapies in addition to cholesterol-modifying drugs used to ameliorate CV risk include blood glucose lowering, blood pressure (BP) lowering, and anti-platelet therapies (see recommendations in these areas), together with lifestyle measures. Logically the intensity with which these therapies are used should be determined in part by the level of risk. To a limited extent this can be assessed clinically by summation of presence of risk factors (high waist circumference, low-density lipoprotein cholesterol (LDL-C) level, HbA1c, BP, smoking, family history of premature vascular disease, ethnic group, abnormal serum high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG)) or the presence of particular risk factors (microalbuminuria, previous CV event). However, many of these variables are continuous distributions so it makes sense to ask whether tools are available that make full use of the data which could be made available from their measurement. As diabetes itself is a risk factor, any such approach would have to be diabetes specific.

The clinical questions addressed were whether any risk calculator (risk engine) or risk chart, specifically designed for people with diabetes, gave valid and useful assessments of CV risk in people with diabetes, and in what circumstances they might be used.

10.2 Methodological introduction

A total of five studies were identified as relevant to the question.[274–278] It should be noted that studies reporting internal validations of their models (i.e. a first level of validation in which the model is required to reproduce the data originally used in its calibration) were excluded.

The five studies included compared the prognostic value of several methods of risk prediction (either computerised tools or chart/table-based tools). These tools aim at identifying high-risk patients and determine whether a patient will receive a therapy that modifies cardiovascular disease/coronary heart disease (CVD/CHD) morbidity and mortality.

One observational study[277] assessed differences between absolute CHD risks calculated by the Joint British Societies' (JBS) risk calculator chart and UKPDS risk engine. The study had a median follow-up of 4.2 years and compared the two methods on a cohort of diabetic populations from guideline 26 NHS-general practices.

One study[275] assessed differences between absolute CHD risks calculated by the Framingham study risk equation and UKPDS risk engine. The study compared the two methods by using clinical records from UK diabetic patients.

One study[276] compared the prognostic value of four methods to predict CVD and CHD risk (JBS risk calculator, the CardioRisk Manager, the Prospective Cardiovascular Münster (PROCAM) calculation and the UKPDS risk engine) using data from a UK clinical-based population database of diabetic patients.

One study[278] assessed the prognostic value of three risk calculators for CVD and CHD (Framingham study risk equation, Systematic Coronary Risk Evaluation (SCORE) project risk score and Diabetes Epidemiology Collaborative Analysis of Diagnostic criteria in Europe (DECODE) risk equation) using UKPDS data.

One study[274] reported 74 validation exercises involving 18 clinical trials for the Archimedes diabetes model. (No studies were found comparing the Archimedes diabetes model with other risk calculators.)

It should be noted that the likelihood of variation in terms of risk prediction is greatest between the tools in the format of either a chart or a table. This is because patient characteristics are either dichotomised or approximated resulting in broad categories of risk. The computer-based tools have similar patient characteristics as inputs and should therefore give similar answers. However, important differences exist in the number and type of equations used and assumptions made about missing patient data.[p]

10.1.27 Methods of risk prediction analysed

Framingham based risk assessments

The Framingham CV risk function, which is widely employed to estimate CVD and CHD risk, is a survival model based on the Weibull distribution and derived from the risk profiles of 5,573 CHD-free members of the Framingham cohort, aged 30–74 years and followed for 12 years, 6% of whom had diabetes (N=337). The JBS charts and the CardioRisk Manager program make use of modified versions of the Framingham model.

JBS risk calculator chart utilises eight risk factors (age, sex, systolic or diastolic BP, smoking status, presence or absence of diabetes mellitus, left ventricular hypertrophy (LVH) and total and HDL-

C) to calculate absolute CHD risk in those patients aged between 30 and 74 years.

The CardioRisk manager program (computer-based) calculates and displays an individual's absolute and relative 10-year risks of CHD, stroke, or various other endpoints of CVD and can be used to estimate the expected benefit of modifying risk factors. The model uses the full Framingham risk score (rather than an approximation of it). The eleven variables included are: age, sex, systolic or diastolic BP, smoking status, presence or absence of diabetes mellitus and LVH and total and HDL-C, atrial fibrillation, history of CVD, antihypertensive therapy.

The UKPDS risk engine

The UKPDS risk engine (computer-based) for determining CHD risk is based on data from 4,540 participants in the UKPDS study and includes diabetes specific covariates. The UKPDS risk engine model utilises nine risk factors, these are: age at diagnosis, duration of diabetes, sex, ethnicity, smoking status, SBP, HbA1c, total and HDL-C to calculate CHD risk.

The differences between the JBS risk calculator and the UKPDS risk engine are that the UKPDS model recognises glycaemic control as a continuous risk factor, rather than a dichotomous variable such as absence or presence of diabetes. Furthermore, age is replaced by two diabetes specific variables; age at diagnosis and duration of diabetes. Ethnicity is also included as a risk factor in the UKPDS equation but not in the Framingham equation.

The UKPDS modified risk engine (stroke)

There is a modified UKPDS engine used to calculate the risk of a first stroke. The equation is based on data from 4,549 patients enrolled in the UKPDS. Variables included in the final model were duration of diabetes, age, sex, smoking, systolic blood pressure (SBP), total cholesterol (TC) to HDL ratio and presence of atrial fibrillation. Not included in the model were BMI, HbA1c, ethnicity, and ex-smoking status.

p Charts and tables are easy to use and an estimate of risk can be obtained without knowledge of all the patients' characteristics. The advantage of the computer-based tools is the ability to allow fine graduations instead of broad categories of risk. The disadvantage is that patient characteristics either have to be available or be measured by the clinician.

PROCAM score system

It constitutes a relatively simple point-scoring scheme for calculating the risk of CHD (fatal or non-fatal MI or acute coronary death). These scores were derived from a Cox proportional hazards model calculated from 10 years of follow-up of the cohort of middle-aged men in the PROCAM study. The model is based on 325 acute coronary events occurring within 10 years of follow-up among 5,389 men, 35 to 65 years of age at recruitment into the PROCAM study. The model uses eight independent risk variables (ranked in order of importance): age, low-density lipoprotein (LDL), HDL-C, SBP, family history of premature MI, diabetes, smoking, and TGs.

SCORE risk charts

The SCORE risk charts were intended for risk stratification in the primary prevention of CVD and CHD. The equation is based on a pooled dataset from 12 European cohort studies, mainly carried out in general population settings (N=205,178). Ten-year risk of fatal CVD was calculated using a Weibull model in which age was used as a measure of exposure time to risk rather than as a risk factor. Variables included were TC and TC/high-density lipoprotein (HDL) ratio. However, due to non-uniformity*[q] in the ascertainment of diabetes, the SCORE study did not include a dichotomous diabetes variable into the risk function and neither produce a separate risk score system for people with diabetes.

DECODE risk score

The model used the large European DECODE cohort (25,413 patients from 14 European studies) to develop risk scores for CVD mortality over 5 year and 10-year follow-up periods. The risk factors used by the model were: age, fasting and 2-h glucose (including cases of known diabetes), fasting glucose alone (including cases of known diabetes), cholesterol, smoking status, systolic BP and BMI. The model developed a score for absolute risk (AR) based on country-specific CVD death rates for 1995. An important limitation of the model is that the lack of knowledge of whether the participants included in the DECODE cohort already had CVD at baseline.

The Archimedes model

It is a mathematical model that attempts to replicate the pathophysiology of diabetes with a high level of biological and clinical detail. The model includes the pertinent organ systems, more than 50 continuously interacting biological variables, and the major symptoms, tests, treatments, and outcomes. The several equations on which this model is built can simulate a variety of clinical trials and reproduce their results with good accuracy.

The Archimedes model is written at a fairly deep level of biology. It is continuous in time, and it preserves the continuous nature and simultaneous interactions of biological variables.*[r] Structurally, it is written with differential equations and is programmed in an object-oriented language called Smalltalk.

10.1.3 Health economic methodological introduction

No health economic papers were identified.

q Data on diabetes had not been collected uniformly in SCORE study cohorts. In a majority of the cohorts the diagnosis of diabetes was based only on a self-report (sometimes with corroborative evidence from a family doctor) and in some study cohorts information on diabetes was not available.

r For example, in the Archimedes model the equations are not calculating the risk of an outcome such as a MI, but are rather modelling the occlusion of specific coronary arteries in specific locations. The model also includes FPG as a continuous variable, and they incorporate not only the degree of elevation in FPG but also the duration of time that the FPG has been elevated to different degrees.

10.1.4 Evidence Statements

10.1.4.1 UKPDS risk engine vs Framingham quation

One observational study was identified assessing the prognostic value of these two methods in a cohort of patients newly diagnosed with Type 2 diabetes.277 In addition the sensitivity and specificity of both models at a 15%, 10-year CHD risk threshold (NICE guidelines) was compared with that of the ADA lipid threshold (LDL □2.6 mmol/l or TG □4.5 mmol/l). **Level 2++**

Overall

At the level of the entire cohort, the number of events predicted by the Framingham equation underestimated both true CVD and CHD events by 33% and 32% respectively, as opposed to the statistically non-significant 13% of CHD events in the case of the UKPDS risk engine. (See tables 13.1–13.3.)

Gender/ hypertension treatment

The Framingham results suggested a tendency towards a greater degree of underestimation of CHD events in men than women (41% vs 26%) and for pre-treated rather than untreated BP (42 vs 31%). (See tables 13.1–13.3.)

Risk stratification

When using both risk calculation methods similar proportions were assigned, 10-year scores less than 15% (Framingham 27.3% and UKPDS 25.7%). However, the UKPDS risk engine assigned a 10-year score over 30% to 187 (43.7%) of the study participants as compared with only 88 (20.5%) when derived from Framingham.

Table 13.1 Proportion of actual and predicted CVD events using the Framingham equations

	N	Actual events	Predicted	Ratio P/A	Discrimination	Calibration
All cohort members	428	98	66	0.67	0.673	32.8 (p<0.001)
Males	241	63	41	0.65	0.669	*
Females	187	35	25	0.71	0.678	*
Pre-treated BP	136	40	24	0.60	0.634	*
Untreated BP	292	58	42	0.66	0.690	*

Table 13.2 Proportion of actual and predicted CHD events using the Framingham equations

	N	Actual events	Predicted	Ratio P/A	Discrimination	Calibration
All cohort members	428	60	41	0.68	0.657	19.8 (p=0.011)
Males	241	41	24	0.59	0.726	*
Females	187	19	14	0.74	0.697	*
Pre-treated BP	136	24	14	0.58	0.666	*
Untreated BP	292	36	25	0.69	0.663	*

Table 13.3 Proportion of actual and predicted CHD events using the UKPDS risk engine

	N	Actual events	Predicted	Ratio P/A	Discrimination	Calibration
All cohort members	428	60	52	0.87	0.670	17.1 (p=0.029)
Males	241	41	37	0.90	0.673	*
Females	187	19	16	0.84	0.618	*
Pre-treated BP	136	24	19	0.79	0.696	*
Untreated BP	292	36	33	0.92	0.648	*

10.1.4.2 Framingham and UKPDS risk engine vs ADA lipid threshold

The 15%, 10-year CHD risk threshold with both the Framingham and UKPDS risk engines had similar sensitivity for primary CVD as the lipid level threshold 85.7 and 89.8% vs 93.9% (p=0.21 and 0.34) and both had greater specificity 33.0 and 30.3% vs 12.1% (p<0.001 and p<0.001).

10.1.413 UKPDS risk engine vs JBS risk chart

One study[275] compared the prognostic value between these two risk calculators by using data from NHS clinical databases. **Level 3**

Overall

Overall, the UKPDS risk engine was found to calculate a significantly higher mean 10-year risk (UKPDS vs JBS, 21.5 vs 18.3%, p<0.0001) with the mean difference of 3.2% (95% CI 2.7–3.8). However, both methods identified approximately 65% of patients with Type 2 diabetes who would require primary prevention intervention and therefore have comparable accuracy in identifying these high-risk patients.

Gender differences

A bias towards men to have a much higher CHD risk with the UKPDS risk engine was reported. The mean difference in risk score between men and woman was approximately 8.4% with the UKPDS risk engine in comparison with 1.7% with the JBS calculator. For men, the UKPDS risk engine calculated CHD risk approximately 6% higher than the JBS calculator.

Risk stratification

Both methods identified similar proportions of patients with CHD risk of at least 15% over 10 years. However, the main differential feature found between the two methods was the tendency of the UKPDS risk engine to identify significantly more patients in the high-risk category (>30%) in comparison with JBS (p<0.001). (See table 13.4.)

Table 13.4 CHD 10-year risk stratification (UKPDS risk engine vs JBS risk chart)

	<15%	15–30%	>30%
UKPDS	34.4%	43.0%	22.6%
JBS	34.4%	58.3%	7.3%

10.1.424 JBS risk calculator, the CardioRisk Manager, the PROCAM calculation and the UKPDS risk engine

One study[276] assessed the prognostic value across four risk calculators. Analysis was conducted by accessing medical records from a cohort of diabetic patients who had attended a NHS clinic for a period of 10 years. **Level 3**

Overall, the study showed that all tests (except PROCAM) demonstrated acceptable discrimination with respect to CHD/CVD, however all underestimated the risk of future events.

Table 13.5 Discrimintation of the four methods of risk prediction		
Discrimination C-index (95% CI)		
	CVD	**CHD**
JBS	0.80 (0.75–0.85)	0.77 (0.74–0.80)
CRM	0.76 (0.72–0.79)	0.73 (0.70–0.77)
PROCAM	0.67 (0.62–0.73)	0.65 (0.59–0.71)
UKPDS	0.74 (0.70–0.78)	0.76 (0.72–0.80)
CRM, Cardio Risk Manager		

10.1.425 Framingham study risk equation, SCORE project risk score and DECODE risk equation

One study[278] evaluated these three risk equations in patients with Type 2 diabetes using UKPDS data. **Level 3**

The 10-year fatal CVD event rate

The 10-year fatal CVD event rate (95% CI) observed in UKPDS was 7.4% (6.5–8.3). Framingham underestimated this by 32% with an AR of 5.0%, SCORE overestimated risk by 18% (AR 8.7%) whereas DECODE (AR 6.6%) yielded an acceptable estimate.

For males, only SCORE provided a reasonable estimate. In females, only Framingham performed well.

For Caucasians (N=3,207), the 7.9% (6.7–9.0) observed event rate was underestimated by 34% using Framingham (AR 5.2%), overestimated by 19% using SCORE (AR 9.4%), and estimated appropriately by DECODE (AR 7.1%).

The 10-year fatal CHD event rate

The 10-year fatal CHD event rate (95% CI) observed in UKPDS was 6.3% (5.5–7.1). Framingham underestimated this (AR 4.3%) while SCORE provided a reasonable estimate (AR 5.7%). Both equations provided reliable estimates for females but not males. For Caucasians, the observed rate of 7.2% (6.3–8.1) was underestimated by both Framingham (4.6%) and SCORE (6.2%).

Table 13.6 Discrimination of the three methods of risk prediction (aROC analysis)	
Discrimination C-index (95% CI)	
	CVD mortality
Framingham	0.76
SCORE	0.77
DECODE	0.67
aROC, areas under the receiver operating characteristics	

10.1.4.16 External validation of the Archimedes diabetes model

A study[274] reported results from a total of 74 validation exercises which were conducted involving different treatments and outcomes in 18 clinical trials (10 of which were not used to build the model).[s] **Level 3**

For 71 of the 74 exercises there were no statistically significant differences between the results calculated by the model and the results observed in the trial. Overall, the correlation coefficient for all 74 exercises is r=0.99.

If the outcomes in the control group and the absolute differences between the control and treated groups are compared for model and trial, the correlation coefficient is r=0.99. Focusing specifically on the absolute differences in the outcomes, which determines the number needed to treat, the correlation coefficient is r=0.97. For the 10 trials that were not used to build the model, the correlation coefficient is also r=0.99.

10.1.5 From evidence to recommendations

The UKPDS risk engine and to a lesser extent the older JBS-2 charts had some evidence of validity in people with Type 2 diabetes, at least once over the age of 40 years. However, in their latest revision JBS-2 charts for people with Type 2 diabetes are not available. Other estimations based on the Framingham population were not reliable, and the reasons for this were understood. No system included all the desirable variables, with the exception of Archimedes, but this was not intended as a clinical tool.

It was noted that a wide range of epidemiological studies suggested that people with diabetes were over twice as likely as the background population (age and sex matched) to develop CVD, and that many had confounding factors (such as use of antihypertensive or glucose-lowering medications) which prevented use of calculators. Studies such as the UK validation analysis reported above were clearly not consistent epidemiologically with UK populations at diagnosis, and furthermore excluded people already on therapy, and are therefore not reliable as a means of estimating the size of the population justifying therapy except for comparing tools. The group concluded that the normal approach, once age was considered, of managing nearly all people with Type 2 diabetes as having risk >20%/10-years was appropriate, particularly as outcome from MI is known to be worse for those with diabetes, and preventative therapy therefore more cost effective.

Particular concerns were also expressed by the GDG over people with microalbuminuria, those with more extreme family histories of CVD, and those with previous and recurrent CV events. This and the age problem meant that it was recognised that any risk estimation had a limited role. However, the GDG were also concerned that some people with Type 2 diabetes do not have the classical phenotype of the disease with abdominal adiposity (or obesity) and low HDL-C. It was concerned that such people should be recognised at diagnosis and managed more conservatively.

10.1.6 Recommendations

14. Consider a person to be at high premature cardiovascular risk for his or her age unless he or she:

14.1. is not overweight, tailoring this with an assessment of body weight associated risk according to ethnic group[t]

s Ten of the trials (DPP, HPS, MICROHOPE, LIPID, HHS, SHEP, LRC-CPPT, MRC, VA-HIT, and WOSCOPS) were not used at all to build the physiology model; they provided external or independent validations of the model. The remaining eight trials (UKPDS, HOPE, CARE, Lewis, IRMA-2, DCCT, IDNT, and 4-S) provided internal or dependent validations.

t Please see the NICE Obesity guideline (CG43), www.nice.org.uk/guidance/index.jsp?action=byID&o=11000

14.2. is normotensive (<140/80 mmHg in the absence of antihypertensive therapy)

14.3. does not have microalbuminuria

14.4. does not smoke

14.5. does not have a high-risk lipid profile

14.6. has no history of cardiovascular disease, and

14.7. has no family history of cardiovascular disease.

15. If the person is considered not to be at high cardiovascular risk, estimate cardiovascular risk annually using the UK Prospective Diabetes Study (UKPDS) risk engine.[279]

16. Consider using cardiovascular risk estimates from the UKPDS risk engine for educational purposes when discussing cardiovascular complications with the individual.[279]

17. Perform full lipid profile (including high-density lipoprotein cholesterol and triglyceride estimations) when assessing cardiovascular risk annually, and before starting lipid-modifying therapy.

11 Management of blood lipid levels

11.1 Overall clinical introduction

Nearly all people with Type 2 diabetes are at high cardiovascular (CV) risk. Epidemiologically that excess risk is independently associated with their hyperglycaemia together with high blood pressure (BP) and dyslipidaemia, the last typically the low high-density lipoprotein cholesterol (HDL-C) and raised triglyceride (TG) levels found as components of the metabolic syndrome.[280] Studies have suggested that people with Type 2 diabetes without declared cardiovascular disease (CVD) are at as high a risk of a CVD event as someone without diabetes with declared CVD.[273] While this is disputed by other studies, it still leaves individuals with Type 2 diabetes as nearly always in the high CVD risk category, and accordingly it has been usual to manage them actively as if for secondary rather than primary prevention of CVD. Nevertheless, in a few people with Type 2 diabetes the clinical phenotype is not that associated with high CV risk, albeit these people being generally remarkable for not being overweight nor having features of the metabolic syndrome, and being insulin sensitive. More importantly people with Type 2 diabetes who have declared CVD are at much higher risk (>1.5–2.6) of further events or CV death as people with CVD without diabetes.[273] Such extreme risk would appear to justify more intensive management than usually offered to someone who has, for example, had a heart attack.

The management of CV risk through glucose lowering, BP lowering, and anti-platelet therapy is dealt with elsewhere in this guideline. This chapter deals with lipid-lowering therapy; dietary modification also being dealt with in a separate chapter. Paradoxically, although low-density lipoprotein cholesterol (LDL-C) levels are not particularly raised in people with Type 2 diabetes compared to the background population, the opportunity to lower risk through lipid management is currently greatest through drugs which lower LDL-C, principally the statins. Nevertheless, a variety of other lipid modifying drugs are available and will be considered in turn.

11.2 Targets and intervention levels

11.2.1 Clinical introduction

The principal aspects of the blood lipid profile recognised as risk factors for CVD include LDL-C, HDL-C, and TGs. As the means of management of these is widely available (lifestyle and drugs) it might seem logical to treat them as safe targets. Unfortunately there is no ‘safe’ level, nor a level at which they do not contribute to vascular risk, a situation analogous with blood glucose control and BP control. This leads to the question of the level of blood lipids that should be acceptable without intensive therapy in people with diabetes, or whether instead it is risk and not lipid levels that should be managed.

The clinical question is to what levels if any should LDL-C, HDL-C and serum TG be managed in clinical practice.

11.2.2 Methodological introduction

There were three studies which were specifically relevant to target levels for lipid levels and two meta-analysis studies.

The Cholesterol Treatment Trialists’ (CTT) Collaborators completed a prospective meta-analysis in 14 randomised trials of statins, published in 2005.[281] This analysis included data from 90,056 (N=45,054 allocated a statin, N=45,002 controls) participants with diabetes. The studies included were published over 10 years from 1994–2004.

A meta-analysis was completed which considered pharmacological lipid-lowering therapy in Type 2 diabetes. This analysis included 14 studies (total N=17,749), six primary prevention studies (N=11,025) and eight secondary prevention studies (N=6,724). The studies included were published from 1987–2003.[282]

11.2.3 Health economic methodological introduction

No health economic papers were identified.

The health economic analysis performed for statin therapy (appendix D, available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247) addressed the question of target levels in part. This is considered further in the section on statin therapy.

11.2.4 Evidence statements

11.2.4.1 Outcomes

CTT collaborators

The CTT collaborators meta-analysis identified that there is an approximately linear relationship between the absolute risk reductions in LDL-C found in the 14 studies and the proportional reductions in the incidence of coronary and other major vascular events.[281]

The proportional reductions in major vascular event rates per mmol/l LDL-C reduction were very similar in all subgroups examined (i.e. including the diabetic subgroup), including not just individuals presenting with LDL-C below 2.6 mmol/l (100 mg/dl). **Level 1++**

Table 14.1 Risk reductions in LDL-C

	Percentage proportional reduction per mmol/l LDL-C reduction
Overall death rate	12% reduction in all-cause mortality; RR 0.88 (0.84 to 0.91, p<0.0001)
CHD death	19% reduction in CHD death; 14/1,000 fewer deaths among those with pre-existing CHD and 4/1,000 among those without pre-existing CHD
Major coronary events	23% reduction in the incidence of first major coronary events; RR 0.77 (p<0.001) Diabetic subgroup, without pre-existing vascular disease; RR 0.74 (0.62 to 0.88, p<0.001)
Coronary revascularisation	24% reduction in the incidence of first coronary revascularisation (proportional reductions in coronary artery grafting and angioplasty were similar); RR 0.76 (0.73 to 0.80, p<0.0001)
Stroke	17% reduction in the incidence of first stroke; RR 0.83 (0.78 to 0.88, p<0.0001)
Major vascular events	21% reduction in the incidence of major vascular events; RR 0.79 (0.77 to 0.81, p<0.0001) Diabetic subgroup, without pre-existing vascular disease; RR 0.75 (0.66 to 0.86)

CHD, coronary heart disease

Meta-analysis – lipid lowering therapy

The lipid-lowering therapy meta-analysis showed that the RR reductions were similar for both primary and secondary prevention.[282] However, the average absolute risk reduction was more than twice as high for those with coronary artery disease (secondary prevention) than for those without it (primary prevention).

Primary prevention trials – fixed effects analysis due to level of heterogeneity (p=0.18). The pooled RR for CV events with lipid-lowering therapy was 0.78 (0.67 to 0.89), with number needed to be treated (NNT) for benefit of 34.5 (for 4.3 years).

Secondary prevention analysis – random effects analysis as there was substantial between study heterogeneity (p=0.03). The pooled RR for CV events with lipid-lowering therapy was similar to that for primary prevention 0.76 (0.59 to 0.93), with NNT for benefit for of 13.8 (for 4.9 years).

The authors concluded that target cholesterol levels and the effectiveness of dose titration (or the use of multiple agents) have not been rigorously examined. Most studies compared a lipid- lowering drug with placebo but did not evaluate the effect of reaching specific cholesterol levels. **Level 1++**

11.2.5 From evidence to recommendations

The GDG reviewed the evidence, and their clinical experience of trying to manage the complexities of CV risk in clinical practice. They recognised the primacy of trying to control risk cost effectively against treating-to-target, but also noted the practical utility of measurements in assessing response to therapies and providing motivation to people with diabetes. Ultimately the issue of cost effectiveness could only be resolved in the context of the interventions being used to modify the lipid profile, and the evidence in this area was therefore subsumed into the recommendations on the use of CV risk estimation, statins and fibrates.

11.3 Statins and ezetimibe

11.3.1 Clinical introduction

Cholesterol lowering remained difficult, and indeed controversial, until the late 1980s when statins became available. Subsequently these drugs became the mainstay of lipid-lowering therapy, supported eventually by CV outcome studies. As discussed above, people with Type 2 diabetes are at high CV risk, and most of their morbidity and increased mortality comes from coronary, cerebral, and peripheral arterial disease. In earlier NICE technology appraisals (TAs) and the prior Type 2 diabetes guideline, statins were recommended for all people with extant CVD or at high risk thereof, states which include most people with Type 2 diabetes.[283]

Clinical questions which arise include whether more potent and more expensive statins should ever be used (and if so when), the use of statins in younger people with Type 2 diabetes, whether any people should not be routinely given statins, and the use of alternatives such as fibrates (addressed in the following fibrate section) and ezetimibe addressed by a 2007 NICE TA.[284]

11.3.2 Methodological introduction

The issues around statins initiation therapy for the prevention of CV events have been covered in a recently published NICE TA, 'Statins for the prevention of cardiovascular events',[283] which included RCTs conducted in people with Type 2 diabetes.

In addition, an ezetimibe TA[284] was in development at the time of this review (ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia). According to the scope, this TA is looking at the following clinical scenarios/comparisons.

- Patients (including Type 2 diabetes population) whose condition is not adequately controlled with a statin alone.
  - Ezetimibe + statin vs statins monotherapy.
  - Ezetimibe + statin vs statins + other lipid-lowering agent.
- Patients (including Type 2 diabetes population) in whom a statin is considered inappropriate, or is not tolerated.

- Ezetimibe monotherapy vs placebo.
- Ezetimibe vs other lipid-lowering agent.

- On these grounds, this review has excluded:
  - all the studies that were included by the NICE TA 94 on statins
  - any study that should be picked out by the ezetimibe TA.

Studies comparing statins with fibrates, (head-to-head comparisons or combination therapy) since these are being analysed by the fibrate question. The purpose of this review is not to repeat the statins or ezetimibe TAs, but to provide supplementary information about dose escalation, sequencing of statins, and use of alternative agents (fibrates and nicotinic acid).

Seven RCTs were identified which reviewed the effectiveness and safety of statins.[285–291] One study was excluded due to major methodological limitations.[285]

Among the remaining six studies, three RCTs were conducted specifically on patients with Type 2 diabetes, (see table 14.2).

Table 14.2 Study interventions

Study	N=	T=	Interventions
Shepard J (2006)[291]	1,501	4.9 years	Atorvastatin (10 vs 80 mg)
Miller M (2004)[287]	151	6 weeks	Simvastatin (40 vs 80 mg vs placebo)
Berne C (2005)[288]	465	16 weeks	Rosuvastatin (10 mg vs atorvastatin 10 mg)

The other three studies were post hoc analyses of large trials:[u] Collaborative Atorvastatin Diabetes Study (CARDS) (atorvastatin 10 mg vs placebo),[289] Anglo-Scandinavian Cardiac Outcomes Trial: Lipid lowering arm (ASCOT-LLA) (atorvastatin 10 mg vs placebo),[290] and Diabetes Atorvastatin Lipid Intervention (DALI) (atorvastatin 10 vs 80 mg).[286]

It should be noted that differing dosing and titration regimens, follow-up periods and the differing populations included, may limit direct comparison between studies.

11.3.13 Health economic methodological introduction

No health economic papers were identified.

A health economic evaluation was developed by a health economist for the lipid modification group which looked at different doses of statins. This was presented to the GDG for this guideline as it was thought to be useful evidence.

The model was later further developed to consider specifically aspects of titration target and titration strategy in people with diabetes, and is described in appendix D.

In summary this considered two uptitration levels (total or LDL-C: 5.0/3.0 and 4.0/2.0 mmol/l) for people already started on simvastatin 40 mg/day, and either a one-step uptitration to 80 mg/day, or two-step to atorvastatin 80 mg/day.

u These large trials were included in the statins NICE TA.

11.3.4 Evidence statements

11.3.4.1 Cardiovascular outcomes

Studies conducted on Type 2 diabetes population

One RCT[291] found that over the 5 years of double-blind treatment, the incidence of a major CV event[v] was significantly lower in patients receiving atorvastatin 80 mg than in those receiving atorvastatin 10 mg. This represented a 25% reduction in the risk of major CV events in favour of the high-dose group (p>0.026). This trend was observed across all quintiles of patient age and duration of diabetes and in patients with HbA1c ≤7% and A1C >7%. **Level 1++**

The same RCT[291] reported significant differences between the groups, in favour of atorvastatin 80 mg, for the secondary outcomes of time to cerebrovascular event (p<0.037) and time to CV event (p<0.044). **Level 1++**

Post hoc sub-analysis

A post hoc analysis of the ASCOT-LLA study[290] found a significantly lower incidence of CV events in the subpopulation of people with Type 2 diabetes treated with atorvastatin –10 mg when compared with those receiving placebo. (Hazard ratio 0.77, 95% CI 0.61 to 0.98, p<0.036.) **Level 1+**

A post hoc analysis of the DALI trial[286] showed that both standard and aggressive therapy with atorvastatin (10–80 mg) did not reverse endothelial dysfunction (as measure by the surrogate marker of flow mediated vasodilatation). **Level 1+**

A post hoc analysis of the CARDS trial[289] analysed the time between initiation of atorvastatin 10 mg and the appearance of significant differences in the incidence of CV events when compared to placebo. The study demonstrated that by 1 year of follow-up the estimate of the treatment effect of atorvastatin 10 mg on the primary endpoint of major CV events was already at its final values of 37% reduction, and by 18 months the CI did not include unity. **Level 1++**

11.3.4.2 Lipid levels

Studies conducted on the Type 2 diabetes population

An RCT[291] reported that end-of-treatment LDL-C levels increased by 3% to a mean of 98.6 mg/dl (2.5 mmol/l) in patients who continued atorvastatin 10 mg, while a further reduction of 19% to a mean of 77.0 mg/dl (2.0 mmol/l) was observed in those assigned to atorvastatin 80 mg (p <0.0001). **Level 1++**

The same study[291] reported significant differences between the groups, in favour of atorvastatin 80 mg, for total cholesterol (TC) levels and TG. **Level 1++**

One RCT[287] reported that simvastatin 80 mg treatment resulted in significantly lower low-density lipoprotein (LDL) levels compared with simvastatin 40 mg (p<0.001). **Level 1+**

The same study[287] showed that after a 6-week treatment, approximately 87% of patients treated with simvastatin 80 mg, and 82% of patients treated with simvastatin 40 mg, had LDL values that met or exceeded the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) treatment goal of <100 mg/dl (2.6 mmol/l), compared with only 14.3 of patients treated with placebo. No statistical significance was reported. **Level 1+**

v Death from CHD, non-fatal, non-procedure related MI, resuscitated cardiac arrest, or fatal or non-fatal stroke.

An RCT[288] comparing treatment with rosuvastatin 10 mg vs atorvastatin 10 mg, reported that at the end of the study rosuvastatin-treated patients had significantly lower LDL levels compared with the atorvastatin group ($p<0.0001$). The study also reported that at 16 weeks, significantly more patients achieved their LDL goal with rosuvastatin compared with atorvastatin (94% vs 88%, $p<0.05$). **Level 1+**

Post hoc sub-analysis

The ASCOT-LLA post hoc study[290] found that among diabetic participants in the atorvastatin group, TC and LDL levels at year one of follow-up were lower than in the placebo group by ~1.3 and 1.2 mmol/l respectively. By the end of the study, these differences were 0.9 and 0.9 mmol/l respectively. However, no statistical analysis was performed. **Level 1+**

In relation to lipid levels, the DALI post hoc analysis found that after 30 weeks, patients receiving atorvastatin 80 mg had significantly lower LDL levels than those treated with only 10 mg of atorvastatin ($p<0.01$).

11.3.4.3 Safety issues

Studies conducted on Type 2 diabetes population

An RCT[291] found no significant differences between the treatment groups (atorvastatin 10 mg and 80 mg) in the rate of treatment related adverse events (AEs), including myalgia, or persistent elevations in liver enzymes. No incidents of rhabdomyolysis were reported in either treatment group. **Level 1++**

One RCT[287] comparing different doses of simvastatin (simvastatin 40 and 80 mg) concluded that no drug related serious clinical AEs were observed in the treatment groups. However, the study reported that two patients on simvastatin 80 mg treatment had an Alanine Transaminase (ALT) and Asparte Transaminase (AST) level >3 times the upper limit of normal; one of these patients was discontinued because of these elevations (the liver function tests returned to normal after discontinuation of the therapy). **Level 1+**

An RCT[288] comparing treatment with rosuvastatin 10 mg vs atorvastatin 10 mg, reported that both treatments were well tolerated, with overall incidences of AEs being similar between the groups. According to the study ten patients discontinued because of AEs, three in the rosuvastatin group and seven in the atorvastatin group. There were no cases of myopathy. **Level 1+**

Post hoc sub-analysis

The model developed for this guideline suggested that one-step titration from simvastatin 40 mg to 80 mg daily was very cost-effective in those with no previous CV event or extant CVD where TC still exceeded 4.0 mmol/l or LDL-C exceeded 2.0 mmol/l.

For those with already diagnosed CVD (or developing CVD) two-step titration (firstly to 80 mg simvastatin and then if indicated to atorvastatin 80 mg daily) was found to be cost-effective in those with already diagnosed CVD and whose TC still exceeded 4.0 mmol/l or LDL-C exceeded 2.0 mmol/l.

11.3.5 From evidence to recommendations

The GDG were cognisant of the previous NICE statin appraisal, the prior Type 2 diabetes guidelines, the ezetimibe appraisal, the deliberations of the NICE guidelines group on management of CVD, and the health economic analysis. The evidence of effectiveness and safety of generic statins, and in particular simvastatin seemed clear, and at current prices probably cost- saving in the population with Type 2 diabetes over the age of 40 years

(irrespective of experience of CVD). There may be individuals in this group at lower CV risk (discussed in section 13), but these people would be uncommon and easily identified by the absence of CV risk factors (see 13.1.6). In others statin therapy should usually be with generic simvastatin at standard dosage (40 mg) in line with the prior TA[283] and the Heart Protection Study.

The group recognised that some people below the age of 40 years were also at high risk (10 year risk >20%, or 20 year risk >40%). It was considered that they would have to be identified by conventional risk factors; presence of features of the metabolic syndrome, strong family history, ethnic group, and evidence of microvascular damage such as nephropathy. Such people would then be treated with a statin, particularly as their 10-year risk horizon came to include 40 years of age or greater. However, the contraindication of the use of statins in pregnancy was felt to be great enough to deserve special mention, for any woman of childbearing potential.

The health economic analysis suggested titration to simvastatin 80 mg was highly cost-effective in those whose lipid levels were not controlled to target levels of 4.0/2.0 mmol/l (T-/LDL-C) irrespective of presence or absence of diagnosed CVD.

In those with CVD the health economic analysis suggested that uptitration from simvastatin 80 mg to a more efficacious statin (modelled as atorvastatin 80 mg daily) was cost-effective if the titration targets were not met on the simvastatin.

The GDG noted the stronger evidence base for atorvastatin than other higher efficacy statins. In regard of the use of ezetimibe (addition to simvastatin), they noted that guidance was provided by the NICE ezetimibe TA.

Unfortunately there is no easy way of calculating CV risk in people already under preventative management (which would be likely to include recent lifestyle change, aspirin, renin-angiotensin blockers and perhaps other drugs, as well as statins themselves). The alternative approach of using lipid levels was less attractive, but had the advantage of being pragmatic, and allowing monitoring of response.

11.4 Fibrates

11.4.1 Clinical introduction

Fibrates have a long and controversial history as lipid-lowering agents, beginning with clofibrate over 30 years ago and being implicated in the problems which led to withdrawal of cerivastatin in the 1990s. However, bezafibrate, fenofibrate and ciprofibrate have shown considerable staying power in the market. Statins have, however, eclipsed fibrates as primary cholesterol-lowering agents, so the issues surrounding fibrates relate to specific lipid abnormalities. In clinical practice these mostly concern hypertriglyceridaemia, itself strongly associated with low HDL-C levels, this problem being particularly common in people with Type 2 diabetes (more so than raised LDL-C levels).

The clinical question then relates to whether and when a fibrate should be initiated before statin therapy, and the circumstances under which a fibrate should be added to, or substituted for, statin therapy.

11.4.2 Methodological introduction

There were eleven studies identified which included fibrates and involved participants with Type 2 diabetes. Nine studies were reviewed, two studies comparing fenofibrate and placebo were excluded,[292,293] as the Effects of long-term fenofibrate therapy on cardiovascular events in 9,795 people with Type 2 diabetes mellitus (FIELD) study,[294] which had N=9,795 participants across 63 centres, was included.

One study considered fluvastatin and fenofibrate with fenofibrate monotherapy.[295]

There were three studies which considered fenofibrate in comparison with statin monotherapy and the combination of fenofibrate and a statin; atorvastatin,[296] rosuvastatin,[297] and simvastatin.[298]

The remaining four studies included gemfibrozil in comparison with placebo,[299] in comparison with statin monotherapy; simvastatin[300] and statin monotherapy and the combination of gemfibrozil and a statin; pravastatin,[301] and atorvastatin.[302]

11.4.3 Health economic methodological introduction

Two evaluations were identified one conducted in the UK and in one the US. In both studies no clinical evidence was found for fenofibrate and so it was assumed to be equally effective as gemfibrozil. Both studies used a 5-year time horizon. The US study was excluded as it was not generalisable to the UK setting.

11.4.4 Evidence statements

11.4.4.1 Ouctomes – fenofibrate

Fenofibrate vs placebo

The double-blind, multicentre FIELD study with N=9,795 participants compared fenofibrate 200 mg/day with a placebo in a Type 2 diabetes population, over a 5-year duration.[294]

11.4.4.2 Lipids

At 4 months, 1 year, 2 years and at completion of the study there were significant decreases in TC, LDL-C and TG levels and increases in HDL-C levels with fenofibrate compared with placebo.

Table 14.3 Fenofibrate outcomes

	TC	LDL-C	HDL-C	TG
Absolute (mmol/l) and RR (%) differences between the treatment groups, p<0.05 for all time points				
4 months	–0.58 (–11.4%)	–0.39 (–12.0%)	0.05 (5.1%)	–0.56 (–28.6%)
1 year	–0.58 (–11.6%)	–0.38 (–11.9%)	0.05 (4.5%)	–0.58 (–30.2%)
2 years	–0.56 (–11.1%)	–0.36 (–11.7%)	0.04 (3.5%)	–0.52 (–27.4%)
Study close	–0.33 (–6.9%)	–0.17 (–5.8%)	0.01 (1.2%)	–0.41 (–21.9%)

For study participants who started other lipid-lowering therapy during the study (total N=2,720, N=944 placebo group and N=1,776 fenofibrate group) they showed smaller changes in lipid levels, but the significance between the groups remained p<0.05 at 2 years. At study close the changes remained significant for TC and TGs between the groups; however, the changes in LDL-C and HDL-C were NS.

11.4.4.3 Adverse events

There were small percentages (0.5 with placebo and 0.8% with fenofibrate) of possible serious adverse drug reactions. Four participants had rhabdomyolysis which fully resolved

(N=3 with fenofibrate and N=1 with placebo). Rates of new cancer diagnosis were similar between groups.

GI events were the most frequently reported event, these were noted with N=975 (20%) of the fenofibrate and N=927 (19%) of the placebo group. **Level 1++**

Fenofibrate vs simvastatin

This single centre, double-blind study compared fenofibrate 160 mg/day with simvastatin 20 mg/day and both monotherapies with the combination of fenofibrate and simvastatin, with N=300 participants.[298]

Fenofibrate was found to have significantly greater reductions in TC and for LDL-C than simvastatin and than the combination of the drugs, differences between simvastatin and the combined group were NS.

The fenofibrate and combined groups had significantly higher decreases in TGs than simvastatin (NS between fenofibrate and combined treatments).

11.4.4.4 Adverse events

There were no serious drug related AEs. **Level 1++**

Fenofibrate vs atorvastatin

This study compared fenofibrate 200 mg/day and atorvastatin 20 mg/day monotherapies compared with the combination of fenofibrate and atorvastatin, with N=120 participants.[296]

11.4.4.5 Treatment goals

The treatment goals for LDL-C (2.4 mmol/l), TGs (2.6 mmol/l) and HDL-C (1.2 mmol/l) were reached in significantly more (reached by 97.5%, 100% and 60% respectively, $p<0.05$) participants for the combination of fenofibrate and atorvastatin than the monotherapies. The fenofibrate group compared with the atorvastatin group reached the treatment goals in a significantly higher percentage for HDL-C (30% vs 17.5%) and TGs (92.5% vs 75%), while the reverse was true for LDL-C with 80% of the atorvatstatin reaching the treatment goal compared with 5% of the fenofibrate group.

11.4.4.6 Lipids

The combination treatment reduced the TC, TGs and LDL-C significantly more than the atorvastatin or the fenofibrate as monotherapies. This combination also significantly increased HDL-C compared with atorvastatin monotherapy but not compared with fenofibrate.

11.4.4.7 Adverse events

There were no significant AEs reported in this study. **Level 1+**

Fenofibrate vs fluvastatin

This double-blind study over 12 months compared the combination of extended-release fluvastatin 80 mg and fenofibrate 200 mg and the monotherapy of fenofibrate 20 mg, N=48 participants.[295]

At 6 months the combination showed a significantly higher reduction in LDL-C compared with fenofibrate monotherapy. For the 12-month point significantly there were greater reductions

in LDL-C and TG levels and increases in HDL-C with the combination group compared with the monotherapy.

11.4.4.38 Adverse events

No serious AEs were reported, N=3 discontinued in the study due to myalgia. **Level 1++**

Fenofibrate vs rosuvastatin

This multicentre study incorporated both a double-blind, fixed-dose phase and an open-label titrating dose phase, N=216.[297]

Fixed dose: the 6-week fixed-dose phase had placebo, rosuvastatin 5 mg and rosuvastatin 10 mg groups.

There were significant decreases for both rosuvastatin 5 mg and 10 mg groups compared with increases with placebo in TC (–36.6%, –31.4% vs 1.1%, p<0.001) and TGs (–24.5%, –29.5% vs 4.7%, p<0.001) and compared with decreases in LDL-C levels with placebo (–40.7%, –45.8% vs –0.6%, p<0.001). At week 6, 77.4% of those in the rosuvastatin 10 mg group had reached the LDL-C goal of <100 mg/dl, compared with 8.3% of those receiving placebo.

11.4.4.39 Titrating dose

This 18-week phase used sequential dose increases at 6-week intervals provided the LDL-C level remained >50 mg/dl (>1.3 mmol/l).

The groups were:

- placebo in fixed dose – rosuvastatin 10 mg (with possible increases to 20 and 40 mg)
- placebo in fixed dose – fenofibrate 67 mg once daily (with possible increases to BD and TID fenofibrate)
- rosuvastatin 5 mg in fixed dose – rosuvastatin 5 mg and fenofibrate 67 mg once daily (with possible increases to BD and TID fenofibrate)
- rosuvastatin 10 mg in fixed dose – rosuvastatin 10 mg and fenofibrate 67 mg once daily (with possible increases to BD and TID fenofibrate).

By the final stage of the dose-titration phase a smaller proportion of those on the groups which received rosuvastatin 10 mg required dose titration than in the other two groups.

11.4.4.40 Lipids

There was a significant decrease in LDL-C with placebo/rosuvastatin compared with a slight increase with placebo/fenofibrate. This reduction in LDL-C was also significantly greater than that found with rosuvastatin 5 mg/fenofibrate, but was NS compared with rosuvastatin 10 mg/fenofibrate.

The reductions in TG levels between the groups which had placebo in the fixed-dose phase were NS. The decrease in TG levels with rosuvastatin 10 mg/fenofibrate were significantly greater than those with placebo/rosuvastatin.

For each group those who reached the goal of LDL-C <100 mg/dl at the end of both the fixed- dose and the titrating-dose phase were; rosuvastatin 40 mg (86.0%, N=50), rosuvastatin 10 mg and fenofibrate 67 mg TID (75.5%, N=53), rosuvastatin 5 mg and fenofibrate 67 mg TID (75.0%, N=60), and fenofibrate 67 mg TID (4.1%, N=49).

11.4.4.11 Adverse events

The most frequently reported AEs in a small number of participants were GI related, myalgia and increases in ALT and creatine kinase (CK) levels. **Level 1+**

Table 14.4 Fenofibrate comparison studies

		TC	LDL-C	HDL-C	TG
Muhlestein JB (2006)[298]	Fenofibrate	–1.2% (p<0.0001 vs simvastatin and combination)	–5.6% (p<0.0001 vs simvastatin and combination)	NS vs comparisons	–38.2% (NS vs combination)
	Simvastatin	–26.2% (NS vs combination)	–34.1% (NS vs combination)	NS	–24.8% (p<0.0001 vs fenofibrate and combination)
	Combination	–27.1%	–29.1%	NS	–49.4%
Athyros VG (2002)[296]	Fenofibrate	253±17 to 213±14 (–16)	163±15 to 140±15 (–15)	NS with combination	281±24 to 167±15 (–41)
	Atorvastatin	252±17 to 174±10 (–31)	161±15 to 97±7 (–31)	34.6±3.2 to 37.7±4.5 (9)	278±24 to 195±22 (–30)
	Combination	255±19 to 159±7 (–37) (p<0.05 vs fenofibrate and atorvastatin)	163±16 to 89±6 (–46) (p<0.05 vs fenofibrate and atorvastatin)	35±3.5 to 43±4.3 (22) (p<0.05 vs atorvastatin)	278±23 to 139±12 (–50) (p<0.05 vs fenofibrate and atorvastatin)
Derosa G (2004)[295]	Fluvastatin/ fenofibrate	NS vs fenofibrate	–35% (p<0.05)	34% (p<0.05)	–35% (p<0.05)
	Fenofibrate	NS	–25%	14%	–17%
Durrington PN (2004)[297]	Placebo/ fenofibrate		0.7% (p<0.001 vs placebo/rosuvastatin)	NS between groups	NS vs placebo/rosuvastatin
	Placebo/ rosuvastatin		–46.7%	NS	–30.3%
	Rosuvastatin 5 mg/ fenofibrate		–34.1% (p<0.001 vs placebo/rosuvastatin)	NS	–47.1% (p=0.001 vs placebo/rosuvastatin)
	Rosuvastatin 10 mg/ fenofibrate		–42.4%	NS	NS vs placebo/rosuvastatin

11.4.4.12 Outcomes – gemfibrozil

Gemfibrozil vs placebo

This study compared gemfibrozil 1,200 mg and a matched placebo in the Veterans Affairs High Density Lipoprotein Intervention Trial (VA-HIT) and included a subgroup diabetic, N=627.[299]

This study considered major CV events and identified in the diabetes group a significant reduction in the risk of major CV events of 32%, of CHD death 41%, and of stroke 40%, compared with placebo.

The lipid level analysis was not analysed by diabetic subgroup. **Level 1+**

Gemfibrozil vs simvastatin

This study compared gemfibrozil 1,200 mg compared with simvastatin 20 mg, N=70.[300]

This study did not complete comparisons between the groups, both treatments significantly decreased TC and TG levels, and increased HDL-C compared with the baseline. There were significant decreases in LDL-C with simvastatin compared with baseline but not with gemfibrozil.

There were small numbers of incidents of GI events with gemfibrozil and generalised weakness and muscle pain with simvastatin. **Level 1+**

Gemfibrozil vs pravastatin

This double-blind, multicentre study with N=268 participants compared gemfibrozil 1,200 mg and pravastatin matched placebo with pravastatin 40 mg and gemfibrozil matched placebo.[301]

Lipids

There were significantly greater reductions in TC and LDL-C with pravastatin than with gemfibrozil. Conversely there was a significantly greater reduction in TG levels with gemfibrozil than with pravastatin p<0.001. Changes in HDL-C were NS between the groups.

Adverse events

The AEs reported were considered not severe and the most frequent were GI related (N=28 gemfibrozil and N=24 pravastatin). **Level 1++**

Gemfibrozil vs atorvastatin

This open-label, crossover study compared gemfibrozil and atorvastatin and a combination of both drugs, in a titrating dose study, N=44.[302]

Lipids

The atorvastatin and combination groups had significantly greater reductions in LDL-C than the gemfibrozil group (reductions NS for atorvastatin vs combination). For TG levels the gemfibrozil and combination groups had significantly greater reductions than the atorvastatin group (reductions NS for gemfibrozil vs combination). There were NS differences between the monotherapies and the combination treatment for HDL-C levels.

Adverse events

GI related (abdominal discomfort, constipation, loose stools, nausea) were reported by N=6 (atorvastatin), N=11 (gemfibrozil) and N=8 (combination). **Level 1+**

Table 14.5 Gemfibrozil comparison studies

		TC	LDL-C	HDL-C	TG
Schweitzer M (2002)[301]	Gemfibrozil	–0.42±0.77	–0.22±0.76	NS	–0.77±1.01, (p<0.001 vs pravastatin)
	Pravastatin	–1.35±0.67, (p<0.001 vs gemfibrozil)	–1.3±0.59, (p<0.001 vs gemfibrozil)	NS	–0.27±0.82
Wagner AM (2003)[302]	Gemfibrozil		147±2.7 to 142±2.7	NS	167±9.7 to 113±9.7
	Atorvastatin		152±2.7 to 99±2.7 (p<0.0001 vs gemfibrozil)	NS	162±9.7 to 143±9.7 (0.01 vs gemfibrozil)
	Combination		148±2.7 to 106±2. 7 (p<0.0001 vs gemfibrozil)	NS	190±10.6 to 117±10.6 (p<0.05 vs atorvastatin)

11.4.5 Health economic evidence statements

Feher et al.[303] was a very simple analysis although it was unclear how the costs in the treated groups were calculated. Only costs of the drugs and a cost per CHD event were included. The costs used are now out of date and assuming the same risk reduction for statins and fenofibrate would result in statins being cost saving.

11.4.6 From evidence to recommendations

While the evidence was not as strong as for the statins, there was convincing evidence of the effectiveness of fibrates in CV protection in people with Type 2 diabetes. Some of the trials (e.g. FIELD) in which this evidence was found included people with TG levels down to the upper end of the normal range (~1.8 mmol/l). However, while the price of fibrates was considerably above that of generic statins, the more effective fibrates as judged by TG lowering were about half the price of proprietary statins when both are used at standard doses.

Hypertriglyceridaemia is a complex condition with both a genetic basis and often being secondary to other medical conditions, including poor blood glucose control. The GDG recognised it was not writing a guideline on management of hypertriglyceridaemia in people with Type 2 diabetes, but because of the interaction with blood glucose control and other medical conditions often associated with Type 2 diabetes (including renal impairment and liver disease), it could not avoid some general guidance in the area.

In drawing up the recommendations the GDG was also cognisant of the need to be aware of:

- the likely combination with statin therapy (given its recommendations on statins) and the higher rate of side effects of combined usage
- the more immediate risks of pancreatitis with higher levels of TGs
- the difficulty of assessing LDL-C levels when TG levels were above 4.5 mmol/l. A useful pragmatic compromise was felt to be to base recommendations around cut-off levels of 2.3 and 4.5 mmol/l.

There is evidence of differences between fibrates: gemfibrozil had greater interactions with other drugs commonly used in diabetes care; bezafibrate was cheaper and less effective in TG lowering and with a poorer CV evidence base than fenofibrate; and ciprofibrate was more poorly investigated. Therefore recommendations were based around fenofibrate, though with a role for bezafibrate where CV risk was less pronounced, and ciprofibrate as an alternative.

Further information on fibrate statin combinations might become available when the ACCORD trial reports.[35]

11.5 Nicotinic acid and derivatives

11.5.1 Clinical introduction

Abnormalities of blood lipid profiles, including serum HDL-C and TGs, are recognised CV risk factors, and are particularly likely to be abnormal in people with Type 2 diabetes. Nicotinic acid preparations are one approach to improving lipid profiles. Nicotinic acid administration is associated with side effects due to vasodilatation, and derivatives (acipimox) and modified-release preparations have been made available to try and reduce the problem. The clinical question is then what role nicotinic acid derivatives might have in the management of Type 2 diabetes.

11.5.2 Methodological introduction

There were four studies identified in this area. Two of the studies were multicentre, double-blind RCTs, one of which considered immediate-release nicotinic acid against placebo, N=125;[304] the other study compared different doses of an extended-release nicotinic acid with placebo, N=148.[305]

There were also two single centre studies identified, one crossover, non-blinded study which considered nicotinic acid compared with no therapy, N=13.[306] There was only one study which considered nicotinic acid with any other drug and this was, nicotinic acid compared with pravastatin, N=44.[307]

It should be noted that two of these studies used samples which were combinations of diabetic and non-diabetic participants, one study represented the outcomes entirely separately[304] and therefore the N=543 non-diabetic participants are not reported here, solely the N=125 diabetic participants. The other study gave combined results for the drug efficacy results but separate results for the glycaemic effects, with a total sample of N=44 but a Type 2 diabetic sample of N=11, therefore the results are reported pooled with the other participants for the efficacy section.[307]

11.5.3 Health economic methodological introduction

Two papers were identified. Armstrong et al.[308] was given a negative rating because the time horizon was very short and would not capture all the benefits of treatment.

Olson et al.[309] was excluded as it was not a diabetic population and did not present results according to risk.

An additional paper was suggested in the consultation comments, Roze et al.[310] The base-case analysis excluded people with diabetes, but a sensitivity analysis was conducted for a diabetic population. All patients received the same statin treatment with additional prolonged-release nicotinic acid compared to no additional treatment. This paper was excluded as this was not considered a suitable comparison for people with diabetes who have failed on statin monotherapy.[310]

11.5.14 Evidence statements

Nicotinic acid vs placebo/ no therapy

Table 14.6 Lipid profiles (shaded areas not measured or reported in that study)

	Nicotinic acid 3,000 mg/d vs placebo[304]	Nicotinic acid ER 1,000 mg/d and 1,500 mg/d vs placebo[305]	Nicotinic acid 1,500 mg/d vs no therapy (crossover)[306]
HDL	HDL increased by 29% vs 0% with placebo, p<0.001	1,000 mg increases in HDL of +19% vs placebo, p<0.05 1,500 mg increases of +24% vs placebo, p<0.05	Significant increase compared with placebo, p=0.0001
LDL	LDL decreased by 8% compared with 1% for placebo; p<0.001	1,000 mg NS 1,500 mg LDL decreases compared with placebo at weeks 12 and 16 (p<0.05)	NS
VLDL			Significant decrease compared with placebo, p=0.0009
TC		Statistical analysis not reported	Significant decrease compared with placebo, p=0.0001
TC/HDL ratio		1,000 mg decrease in TC/HDL ratio –12%(2.8%), p<0.01 1,500 mg decrease in TC/HDL ratio –22%(2.7%), p<0.01	Significant decrease compared with placebo, p=0.0001
TGs	TGs decreased by 23% compared with 7% with placebo, p<0.001	1,000 mg NS 1,500 mg reductions in TG of –13% to –28% vs placebo, p<0.05	Significant decrease compared with placebo, p=0.0006

Overall nicotinic acid was found to show reduction in LDL, TGs and the TC/HDL ratio and increases in HDL, compared with placebo in all three studies with more significant changes for doses of 1,500 mg/day and greater. **Level 1+**

Table 14.7 Glycaemic effects

	Nicotinic acid 3,000 mg/d vs placebo[304]	Nicotinic acid ER 1,000 mg/d and 1,500 mg/d vs placebo[305]	Nicotinic acid 1,500 mg/d vs no therapy (crossover)[306]
HbA_{1c}	Nicotinic acid – no change Placebo HbA_{1c} decreased by 0.3% compared with nicotinic acid, p=0.04	1,000 mg – NS 1,500 mg – HbA_{1c} increased of 0.29%, p=0.48 compared with placebo	HbA_{1c} increased compared with placebo, p=0.002
Fasting glucose	Nicotinic acid showed an increase in average levels; 8.1 mg/dl vs a decrease of 8.7 mg/dl with placebo, p=0.04		NS
24-hour plasma glucose profile			Increased compared with placebo, p=0.047
24-hour urinary glucose			Increased compared with placebo, p=0.016

Nicotinic acid showed some glycaemic effects compared with placebo, one study identified that HbA1c remained stable with nicotinic acid but had a significant decrease with placebo, this study included a downtitration of nicotinic acid if HbA1c exceeded 10%, this occurred in N=10 of the nicotinic acid group and N=8 of the placebo group.[304]

Two studies identified an increase in HbA1c with doses of 1,500 mg/d, compared with placebo for both immediate-release and extended-release formulations.[305,306] **Level 1+**

Adverse events

Increases in uric acid were identified in two of the studies, for one this was from 339 to 386 µmol/l and was significant compared with placebo, p<0.001.[304] The second study noted that N=2 participants had very high uric acid levels of 684 and 761 µmol/l.[306] The third (extended-release) study found no significant differences in uric acid levels.[305]

Flushing was considered a minor complaint in one study, numbers not reported.[306] Two thirds of those taking the extended-release nicotinic acid formulation reported flushing at some point during the trial, approximately 10% of those taking placebo reported it.[305] **Level 1+**

Nicotinic acid vs pravastatin

One study considered nicotinic acid 1,500 mg/day compared with pravastatin 40 mg/day, followed by a combination therapy phase of nicotinic acid 1,000 mg/day with pravastatin 20 mg/day. This study included both diabetic and non-diabetic participants (N=11, Type 2 diabetes).[307] This study considered the results for lipid profiles for the combined diabetic and non-diabetic participants. The glycaemic effect results were considered separately for diabetic and non-diabetic participants.

Lipid profiles

Nicotinic acid was not found to be more effective than pravastatin as the later showed significant reductions in LDL and TC levels compared with nicotinic acid. Combination therapy showed significant decreases in LDL, TC and TG levels compared with nicotinic acid and significant increases in HDL and decreases in TG levels compared with pravastatin. **Level 1+**

Table 14.8 Lipid profiles

	Nicotinic acid 3,000 mg/d vs pravastatin 40 mg/d	Nicotinic acid 1,000 mg/d with pravastatin 20 mg/d vs nicotinic acid 3,000 mg/d	Nicotinic acid 1,500 mg/d with pravastatin 20 mg/d vs pravastatin 40 mg/d
HDL	NS	NS	Increased with combination compared with pravastatin (35.6±4.1 vs 16.4±5.8, p<0.001)
LDL	Pravastatin showed reductions in LDL compared with nicotinic acid (–32.1±3.0 vs –16.9±3.3, p<0.01)	Decreased with combination compared with nicotinic acid (–35.7±3.3 vs –16.9±3.3, p<0.01)	NS
TC	Pravastatin showed reductions in TC compared with nicotinic acid (–24.9±2.0 vs –9.8±2.9, p<0.001)	Decreased with combination compared with nicotinic acid (–23.8±2.9 vs –9.8±2.9, p<0.001)	NS
TG	NS	Decreased with combination compared with nicotinic acid (–39.4±6.7 vs –31.8±6.8, p=0.03)	Decreased with combination compared with pravastatin (–39.3±5.4 vs –28.0±5.1, p=0.01)
Lipoprotein-(a)	NS	NS	NS

Glycaemic effects

Diabetic participants: nicotinic acid monotherapy showed an increase in HbA1c by approximately 8% (p=0.03), pravastatin showed no change in HbA1c level and the increase seen with combination therapy was non-significant. Nicotinic acid monotherapy increased FPG by approximately 26% (p=0.02), there were no changes with pravastatin or combination therapy.

Non-diabetic participants: nicotinic acid monotherapy showed an increase in HbA1c by approximately 4% (p=0.02), combination therapy showed an increase of approximately 6% (p<0.01), pravastatin showed no change. None of the treatments showed changes in FPG. Level 1+

Adverse events

All of the participants in the nicotinic acid group complained of flushing, this generally lasted from 10 to 15 minutes and was ameliorated with aspirin. Nine participants (21%) withdrew from this study with significant flushing or nausea with nicotinic acid, one participant withdrew with nausea from the pravastatin group. **Level 1+**

11.5.5 From evidence to recommendations

This group of drugs was not considered in the previous guideline (2002).[414] The limited number of studies presented suggested that nicotinic acid can have some advantageous effect on serum HDL-C and lipids, but also that it has some negative effects on blood glucose control. In the absence of outcome trials in people with Type 2 diabetes, and given also the problems of using the current preparations (notably flushing despite prophylactic aspirin, dose titration and use of modified-release preparations), no general recommendation could be given for use of nicotinic acid. The group were aware of some possible special indications in people with extreme hypertriglyceridaemia, but felt this to be outside the remit of the current guideline.

11.6 Omega 3 fish oils

11.6.1 Clinical introduction

The concept of beneficial and harmful dietary fats has come to the fore in recent years. Some evidence does exist for the use of omega 3 fish oils in certain circumstances such as post-MI. The clinical question then was what role these oils might have in the management of people with Type 2 diabetes.

11.6.2 Methodological introduction

There were seven studies identified for participants with Type 2 diabetes. A Cochrane systematic review, for which the last search had been completed in September 2000,[311] included studies that were 2–24 weeks in duration.

A second systematic review and meta-analysis[312] investigated the haematological and thrombogenic effects of omega 3 fatty acids and did not report on glycaemic and lipid control outcomes. Included studies were of 4–24 weeks duration.

There were five RCTs identified. Four of the studies compared; fish oil, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and placebo,[313] fish oil (one group taking EPA and one taking DHA) compared with olive oil[314] and fish oil (EPA and DHA) compared with corn oil,[315,316] all of these studies used capsules of the oils. Two of the studies were conducted in the same centre using a virtually identical patient group and research method.[315,316]

The final study compared the effects of a daily fish meal and light or moderate exercise, with no fish and light or moderate exercise.[317] These studies were of 6–8 weeks duration.

It should be noted that a systematic review including studies conducted in the general population (search performed up to February 2002) was also identified.[318] This review concluded that there was no evidence of a clear benefit of omega 3 fats on health.

Participants in these studies were often requested to follow dietary guidelines and their compliance with these may have affected the findings.

11.6.3 Health economic methodological introduction

No health economic papers were identified.

11.6.4 Evidence statements

Table 14.9 Study comparisons

	Cochrane review[311]	Jain S (2002)[313]	Petersen M (2002)[316]	Pederson H (2003)[315]	Woodman RJ (2002)[314]
Type and dose of omega 3	Any type of dietary supplement with omega 3 fatty acids included	Maxigard capsule (180 mg EPA acid and 120 mg DHA acid) BD	4 g/capsules of fish oil/day containing 2.6 g EPA and DHA/day	4 g/capsules of fish oil/day containing 2.6 g EPA and DHA – equivalent to a daily intake of 50–60g of fatty fish	4 g EPA or 4 g DHA once a day with evening meal
TGs	14 studies: decrease compared with placebo: –0.56 mmol/l (–0.71 to –0.40), p<0.00001	Decrease compared with placebo: (p<0.001) Baseline TGs mg %: Maxigard: 209.6±59.1 Placebo: 189.6±52.0	Decrease compared with corn oil: (–0.54±0.13) to (–0.04±0.17), p=0.025 Baseline TGs: Fish oil: 2.35±0.27 Corn oil: 2.76±0.46	Decrease compared with corn oil: (–0.53±0.11) to (–0.08±0.16), p=0.025. Baseline TGs: Fish oil: 2.3±0.3 Corn oil: 2.6±0.5	Decrease compared with olive oil: 19% (p=0.022) EPA and 15% (p=0.022) DHA Baseline TGs: EPA: 1.3±0.7 DHA: 1.6±0.6 Olive oil: 1.7±0.6
TC	NS	Decrease compared with placebo: (p=0.05)	NS	NS	
LDL-C	11 studies: increase compared with placebo: 0.24mmol/l (0.005 to 0.43), p=0.01	Decrease compared with placebo: (p=0.014)	NS		
HDL-C	NS	Decrease compared with placebo: (p<0.001)	NS	Increase compared with corn oil: (0.07±0.01 vs. –0.01±0.01) p=0.045	NS
HDL-C subgroups			HDL2a decreased compared with corn oil: (p=0.07). HDL2b increased compared with corn oil: (p=0.012)		Increase in HDL2 compared with olive oil: 16% (p=0.026) EPA and 22% (p=0.05) DHA. Increase in HDL3: 11% (p=0.026) EPA and NS with DHA
HbA_{1c}	NS	Decrease compared with placebo: (p=0.009)	NS	NS	NS
FBG	NS	Decrease compared with placebo: (p=0.004)	NS	NS	Increased compared with olive oil; EPA (p=0.002) and DHA (p=0.002)
Weight	NS			NS	
BP		Decrease compared with placebo: systolic (p=0.0003), diastolic (p=0.0003)	NS		NS

Cochrane review and RCTs

The table above details the evidence from the RCTs comparing omega 3 and placebo, or corn oil or fish oil.

All studies (Cochrane review and the five RCTs) found that treatment with omega 3 significantly reduced TGs compared to placebo. **Level 1+**

The only other area where the Cochrane review identified significant changes was in LDL-C where omega 3 were associated with a significant increase compared with placebo. **Level 1++**

Subgroup analysis – Cochrane review

A subgroup analysis was undertaken with the hypertriglyceridaemic participants, doses of fish oil and trial duration.

Hypertriglyceridaemic participants (control TGs >4 mmol/l)

An increased reduction in TGs was identified in trials (N=3) with only hypertriglyceridaemic participants; –1.45 mmol/l (–2.89 to –0.01, p=0.05), compared with studies with non-hypertriglyceridaemic participants (N=11) –0.40 mmol/l (–0.61 to –0.19, p=0.0002).

Increases in LDL-C levels were significant in the hypertriglyceridaemic groups (N=2 trials),

0.6 mmol/l (0.16 to 1.04, p=0.008), but they were NS in the non-hypertriglyceridaemic groups (N=9 trials).

Dose of fish oil

Trials with high doses of fish oil (>2 g EPA, N=4) showed a significant increase in LDL-C

0.51 mmol/l (0.18 to 0.84, p=0.003), this was NS for lower doses (<2 g EPA, N=7).

Levels of TGs in the high-dose groups decreased by 1.11 mmol/l (–2.21 to –0.10, p=0.03), but in the low-dose group this was less at 0.54 mmol/l (–0.69 to –0.38, p<0.00001).

Trial duration

In trials of longer than 2 months LDL-C levels increased by 0.33 mmol/l (0.00 to 0.65, p=0.05), the increases were NS in trials shorter than 2 months.

TG levels were reduced by 0.81 mmol/l (–1.21 to –0.41, p=0.00008) in the longer trials and by less than 0.36 (–0.58 to –0.13, p=0.002) in the shorter ones. **Level 1++**

11.6.2.1 Daily fish meal and exercise comparison study

Triglycerides

The study which included fish meals found that compared with the control (no fish meals, light exercise) the inclusion of a daily fish meal significantly reduced TGs, –0.9±1.3 mmol/l, p=0.0001, with fish/moderate exercise reducing by 1.21±0.3 mmol/l and fish/light exercise by 1.22±0.3 mmol/l p=0.0001. The addition of exercise without the fish also showed a significant decrease in TGs –0.7±0.3 mmol/l, p=0.03, compared with the control.[317]

HDL-C (subgroups)

The study which included fish meals found that high-density lipoprotein 2 cholesterol (HDL2-C) was significantly increased, 0.06 mmol/l, p=0.01 and high-density lipoprotein 3 cholesterol (HDL3-C) significantly reduced by the inclusion of fish compared with the low-fat control group, –0.05 mmol/l, p=0.01.[317] **Level 1+**

Cardiovascular effects

A meta-analysis found that participants who took omega 3 fatty acids had a significant reduction in diastolic BP of 1.79 mmHg (95% CI, –3.56, –0.02; p=0.05) and a non-significant reduction in systolic BP (p=0.32). There was also a non-significant reduction in heart rate (p=0.52).[312] **Level 1++**

Thrombogenic factors

The pooled analysis of the data of two studies, showed a significant increase in factor VII of 24.86% (95% CI, 7.17, 42.56; p=0.006).[312] **Level 1++**

11.6.5 From evidence to recommendations

From the evidence available fish oils as a homogeneous therapeutic concept is problematic, as the evidence included showed a variation in the fish oil dosage used. Clinical experience confirmed that large total doses of oils used to get an adequate dose of omega 3 fish oils in some preparations can cause adverse effects. From the evidence available omega 3 fish oil preparations could help lower TG levels, but overall showed minimal improvement in lipid profiles in people who had not had a MI. The GDG agreed there were financial consequences in prescribing omega 3 supplements when the evidence showed no clear benefit.

It was recognised that the recommendations made must be understood as only applying for omega 3 fish oil supplementation, and not to recommendations on sources of dietary fats.

11.6.6 Recommendations

R76 Review cardiovascular risk status annually by assessment of cardiovascular risk factors, including features of the metabolic syndrome and waist circumference, and change in personal or family cardiovascular history.

Statins and esetimibe

R77 Once a person has been started on cholesterol-lowering therapy, assess his or her lipid profile (together with other modifiable risk factors and any new diagnosis of cardiovascular disease) 1–3 months after starting treatment, and annually thereafter. In those not on cholesterol- lowering therapy, reassess cardiovascular risk annually, and consider initiating a statin (see recommendations 77 and 78).

Fibrates

R83 If there is a history of elevated serum triglycerides, perform a full fasting lipid profile (including high-density lipoprotein cholesterol and triglyceride estimations) when assessing cardiovascular risk annually.

R84 Assess possible secondary causes of high serum triglyceride levels, including poor blood glucose control (others include hypothyroidism, renal impairment and liver inflammation, particularly from alcohol). If a secondary cause is identified, manage according to need.

12 Antithrombotic therapy

12.1 Antiplatelet therapy

12.1.1 Clinical introduction

Antiplatelet therapy now has an established role in the management of people at high risk of cardiovascular (CV) events. People with Type 2 diabetes are known to have CV risk higher than matched populations after allowance for other CV risk factors, and in some studies as high as those without diabetes who have declared cardiovascular disease (CVD).[273] National guidelines and the previous NICE (inherited) Type 2 diabetes guideline recommend use of aspirin in people at high CV risk.[319,320] Other antiplatelet agents (clopidogrel and dipyridamole modified release (MR)) have been the subject of a NICE technology appraisal (TA) but without specific calculation for the higher CV event rate or the specific risk reduction in people with Type 2 diabetes.321 The increasing occurrence of Type 2 diabetes in younger people raises the additional question of the use of antiplatelet therapy in those who CV risk may be not be very high.

The guidelines are not concerned with the use of antiplatelet therapy after acute cardiological events or cardiac interventions, or after acute cerebrovascular events.

The clinical question then is whether antiplatelet medications should be used in people with Type 2 diabetes, or in which subgroups of such people, and if so which agents and in what doses.

12.1.2 Methodological introduction

Aspirin

There were only two studies which were reviewed that considered aspirin and CVD in people with Type 2 diabetes from 2001 onwards. There were a number of large trials completed which evaluated aspirin in populations which had a diabetic subgroup included. A review which included the Early Treatment of Diabetic Retinopathy Study 1992 (ETDRS), Thrombosis Prevention Trial 1998 (TPT), Hypertension Optimal Treatment trial 1998 (HOT), and Primary Prevention Project 2001 (PPP), the efficacy of low- and high-dose aspirin has been evaluated and reductions on CV endpoints in high-risk patients demonstrated. However, this review also noted that these trials had small numbers of participants with diabetes and that no head-to- head comparison of low- versus high-dose therapy has been conducted in diabetics.

The two studies reviewed comprised one RCT involving participants with Type 2 diabetic nephropathy and compared aspirin with dipyridamole, a combination of aspirin and dipyridamole with placebo. The authors stated that they believed this study to be the first clinical trial of aspirin in Type 2 diabetic nephropathy.[322]

The second study was an open-label RCT which compared aspirin with vitamin E with 4,495 participants of whom 1,031 were diabetic. This study had been planned with a 5-year follow-up but was terminated early (at 3.7 years) on the advice of the independent Data Safety and Monitoring Board (DSMB) when newly available evidence on the benefit of aspirin in primary prevention was available.[323]

There was also a multicentre RCT with a Type 2 diabetic sample (N=1,209),[324] however, this study compared aspirin with picotamide, which is unlicensed and therefore the study was excluded.

Clopidogrel vs aspirin

Six large RCTs were identified, all of which had long follow-up periods, allowing assessment of the long-term CV event risk.[325–330] The studies were conducted in the general population but included subgroup analysis of those with diabetes, none of the studies discriminated between those with Type 1 or with Type 2 diabetes.

One RCT, a post hoc sub-analysis from the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE)[w] study (N=3,866 with diabetes) compared aspirin monotherapy with clopidogrel monotherapy.[326]

Four RCTs compared the combination of aspirin plus clopidogrel with aspirin plus placebo.

- The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance study (CHARISMA)[328] with a median follow-up of 28 months compared the combination of clopidogrel 75 mg/day plus a low dose of aspirin with a low dose of aspirin alone, in those with either clinically evident CVD (secondary prevention) or multiple vascular risk factors (primary prevention) (N=6,556 for those with diabetes, 42% of the total sample).
- The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial[327] included those with unstable angina or non-Q wave MI within 24 hours of an acute event, mean follow-up of 9 months. The principal objectives of this study were to compare the early and long-term efficacy and safety of the use of clopidogrel vs placebo on top of standard therapy with aspirin. 12,562 patients were given clopidogrel 300 mg bolus and then 75 mg daily plus aspirin (75–325 mg daily) or placebo plus aspirin (N=2,840 for those with diabetes, 22.6% of the total sample). The patients were followed for a maximum of 12 months (mean 9 months).
- The PCI-CURE[330] which was a sub-analysis of 2,658 CURE study patients requiring percutaneous coronary intervention (PCI). Diabetic patients represented 18.9% (N=504) of the total sample.
- The Clopidogrel Reduction of Events During Extended Observation (CREDO)[329] trial evaluated the efficacy of continuing clopidogrel on top of standard therapy with aspirin for 1 year following PCI. Participants received either a clopidogrel loading dose (300 mg) or placebo 3–24 hours before intervention. Patients in both treatments arms then received clopidogrel 75 mg/day for 28 days. Between 4 weeks and 12 months, patients in the loading-dose group received prolonged clopidogrel therapy, and those in the control group received placebo. Both treatment groups received aspirin throughout the study. Diabetic patients represented 26.4% (N=560) of the total sample.

Only one RCT, Management of ATherothrombosis with Clopidogrel in High-risk patients with recent transient ischaemic stroke (MATCH), was identified comparing the combination of clopidogrel plus aspirin with clopidogrel plus placebo.[325] Patients with recent ischaemic stroke or transient ischaemic attack and at least one additional vascular risk factor were randomised to aspirin 75 mg plus clopidogrel 75 mg or clopidogrel 75 mg plus placebo for 18 months. (N=7,599 for those with diabetes, 68% of the sample.)

It should be noted that differing dosing and titration regimens and the differing populations included in the studies, such as patients with no clinical evidence of CVD,[328] to patients with recent ischaemic stroke[325] or patients undergoing a coronary surgery[330] may limit direct comparison between studies.

w CAPRIE was a large randomised trial of the efficacy of clopidogrel and acetylsalicylic acid (ASA) in reducing the risk of a composite endpoint of ischaemic stroke, MI, or vascular death in patients with recent ischaemic stroke, recent MI, or established peripheral arterial disease (PAD) (secondary prevention). The study reported a significant benefit of clopidogrel over aspirin in relation to the primary outcome (non-fatal MI, non-fatal stroke, or vascular death) with a RR reduction of 8.7% (95% CI 0.3 to 16.5, p=0.043) compared with ASA in this broad population with a history of atherothrombosis (112 patients would need to be treated with clopidogrel rather than aspirin over this time to prevent one vascular event).

12.1.13 Health economic methodological introduction

One study was identified looking at aspirin compared to standard care, but the main outcomes for the trial were blood pressure (BP) targets and results of the addition of aspirin were not given for the diabetes subgroup.[331]

In the HTA clopidogrel used in combination with aspirin compared to aspirin alone in the treatment of non-ST segment elevation acute coronary syndromes (ACS), diabetes was considered as one of the risk factors contributing to high risk.[332]

In the study by Weintraub et al.[333] clopidogrel was compared to aspirin in patients hospitalised within 24 hours of onset of symptoms indicative of ACS who did not have significant ST segment elevation. A subgroup analysis was performed for diabetics.[333]

In the studies by Ringborg et al.[334] and Cowper et al.[335] the cost-effectiveness of clopidogrel plus aspirin for 12 months was compared to only 1 month of therapy. In the Ringborg study diabetes was not found to be a significant risk factor and the results for the whole population are reported here.[334] In the Cowper study diabetes was considered a high-risk factor.[335]

12.1.14 Evidence statements

Aspirin and dipyridamole

This study found that there was a significant decrease in proteinuria with aspirin (–15.9%), with dipyridamole (–14.8%) and with the combination of aspirin and dipyridamole (–37.3%) compared with an increase in proteinuria found with placebo (1.9%), p=0.0007. Significant decreases were also identified in the urinary protein/creatinine ratio with the three treatment groups compared with the placebo.

There were no changes identified in BP, renal function tests and blood sugar. No adverse events (AEs) were noted during this study. **Level 1+**

Aspirin and vitamin E

This study was terminated early (3.7 years) and in the diabetic subgroup there were no significant changes identified with aspirin in incidence of major CV and cerebrovascular events. **Level 1+**

12.1.14.1 Clopidogrel vs aspirin

CAPRIE: Post hoc sub-analysis

This sub-analysis found a significantly lower incidence of CV events in diabetic patients receiving clopidogrel compared to those treated with aspirin. Furthermore, the incidence of rehospitalisation for any bleeding event was significantly lower with clopidogrel than with the aspirin group (see table 15.1). **Level 1+**

Table 15.1 CAPRIE: Post hoc sub-analy sis

CAPRIE (Diabetic subpopulation N=3,866)	Aspirin	Clopidogrel	Size effect
Primary endpoint stroke, MI, vascular death or rehospitalisation for ischaemia or bleeding	17.7%	15.6%	RRR 12.4% ARR 2.1% p=0.042 NNT 48
Incidence of rehospitalisation for any bleeding event	2.8%	1.8%	RRR 37% (95% CI 3.8–58.7) p=0.031
Subset of patients treated with insulin at baseline (N=1,134) Primary endpoint stroke, MI, vascular death or rehospitalisation for ischaemia or bleeding	21.5%	17.7%	RRR 16.7% ARR 3.8% p=0.106 NNT 26.3

ARR, absolute relative risk; NNT, number needed to treat; RRR, relative risk reduction

The authors acknowledged several limitations of this sub-analysis:

- compared with the original CAPRIE primary cluster endpoints this was a different endpoint ('softer' according to the authors)
- the study was not sufficiently powered to allow identification of specific individual endpoints
- the duration and severity of diabetes were unknown
- specific details regarding control of diabetes, such as glycosylated haemoglobin levels or glycaemic control were not collected. **Level 1+**

12.1.12 Aspirin + clopidogrel vs aspirin + placebo

CHARISMA study

The CHARISMA study did not find a significant benefit associated with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the incidence of the primary endpoint of MI, stroke, or death from CV causes in patients with clinically evident CVD or at high risk for such disease. **Level 1++**

The same study found a moderate, though significant, benefit associated with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the secondary composite endpoint of MI, stroke, or death from CV causes, or hospitalisation for unstable angina, transient ischemic attack or revascularisation (see table 15.2). **Level 1++**

The CHARISMA study found no significant differences in the rate of severe bleeding between the two groups. However, the combination of clopidogrel and aspirin was associated with a significantly higher rate of moderate bleeding in comparison with treatment with aspirin plus placebo (see table 15.2). **Level 1++**

Table 15.2 CHARISMA study

CHARISMA	Aspirin + clopidogrel	Aspirin + placebo	Size effect
Primary endpoint MI, stroke, or CV death	NS		
Secondary endpoint MI, stroke, CV death, or hospitalisation for unstable angina, TIA, or revascularisation	16.7%	17.9%	RR 0.92 95% CI 0.86 to 0.995 p=0.04
Severe bleeding	NS		
Moderate bleeding	2.1%	1.3%	RR 1.62 95% CI 1.27 to 2.08 p<0.001

TIA, transient ischaemic attack

Subgroup analysis

A subgroup analysis suggested that in the population of patients with clinically evident CVD (symptomatic) the combination of clopidogrel plus aspirin was significantly beneficial in comparison with placebo plus aspirin with respect to the primary efficacy endpoint. (Among the 12,153 symptomatic patients, there was a marginally significant reduction in the primary endpoint with aspiring plus clopidogrel. See table 15.3.) **Level 1++**

The analysis suggested that there was a risk associated with dual antiplatelet therapy in the asymptomatic group since among the 3,284 asymptomatic patients there was a 6.6% relative increase in the rate of primary events with clopidogrel plus aspirin, compared to 5.5% with placebo (see table 15.3). **Level 1++**

Furthermore, in the subgroup of asymptomatic patients, there was a significant increase in the rate of death from all causes among the patients assigned to clopidogrel plus aspirin as compared with those assigned to placebo plus aspirin, as well as a significant increase in the rate of death from CV causes among those assigned to the combination therapy (see table 15.3). **Level 1++**

The rates of severe bleeding were higher, but not significant, among both the asymptomatic and symptomatic patients receiving the combination therapy compared to those receiving aspirin plus placebo (see table 15.3). **Level 1++**

Among asymptomatic patients, there was no significant difference in the rates of moderate bleeding between the two groups. In contrast, the rates of moderate bleeding among symptomatic patients were significantly higher in those treated with aspirin plus clopidogrel than in patients receiving aspirin plus placebo (see table 15.3). **Level 1++**

Table 15.3 CHARISMA study: subgroup analysis

CHARISMA: Subgroup analysis		Aspirin + clopidogrel	Aspirin + placebo	Size effect
Patients with clinically evident CV disease (symptomatic) N=12,153	Primary endpoint MI, stroke, or CV death	6.9%	7.9%	RR 0.88 95% CI 0.77–0.998 p=0.046
	Severe bleeding	NS		
	Moderate bleeding	2.1%	1.3%	p<0.001
Patients with risk factors for CVD (asymptomatic) N=3,284	Primary endpoint MI, stroke, or CV death	6.6%	5.5%	p=0.20
	Death from all causes	5.4%	3.8%	p=0.04
	Death from CV causes	3.9%	2.2%	p=0.01
	Severe bleeding	NS		
	Moderate bleeding	NS		

CREDO study

The CREDO study found that at 12 months long-term clopidogrel and aspirin treatment significantly reduced the risk of death, MI or stroke in comparison with those treated with clopidogrel and aspirin for 4 weeks and then aspirin plus placebo for 11 months. RR reduction of 27%, 95% CI (3.9%–44.4%), p=0.02. Absolute reduction 3% (p=0.02). **Level 1++**

The study also showed that the clopidogrel pre-treatment loading dose did not significantly reduce the combined risk of death, MI, or urgent target vessel revascularisation at 28 days. **Level 1++**

There was no significant difference in the risk of major bleeding between the groups, though there was a higher risk of major bleeding identified for those treated with long-term clopidogrel and aspirin compared with those taking aspirin plus placebo. **Level 1++**

12.1.4.3 Clopidogrel + aspirin vs clopidogrel + placebo

MATCH study

The study found that combination treatment with aspirin plus clopidogrel did not significantly reduce the primary composite CV morbidity or mortality endpoint[x] compared with clopidogrel plus placebo. **Level 1++**

The secondary endpoint analysis (ischaemic stroke and/or vascular death, all-cause stroke, non- fatal events and rehospitalisation) showed no significant difference between the addition

x Primary composite endpoint: first occurrence of an event in the composite of ischaemic stroke, MI, vascular death (including haemorrhagic death of any origin), or rehospitalisation for an acute ischaemic event (including unstable angina pectoris, worsening of peripheral arterial disease requiring therapeutic intervention or urgent revascularisation, or TIA).

of aspirin to clopidogrel versus clopidogrel plus placebo, though rates were lower with aspirin than with placebo, added to clopidogrel**. Level 1++**

In terms of AEs, the study concluded that adding aspirin to clopidogrel resulted in significantly more bleeding complications than in the placebo and clopidogrel arm, doubling the number of events (see table 15.4). **Level 1++**

Table 15.4 MATCH

MATCH	Clopidogrel + aspirin	Clopidogrel + placebo	Size effect
Life-threatening bleedings*	2.6%	1.3%	RR 1.26 95% CI (0.64–1.88) p<0.0001
Major bleedings	2%	1%	RR 1.36 95% CI (0.86–1.86) p<0.0001
Minor bleedings	3%	1%	p<0.0001

* Life-threatening events were more frequent in the aspirin plus clopidogrel versus clopidogrel monotherapy, irrespective of whether they were GI (1.4 vs 0.6%) or intracranial (1.1 vs 0.7%)

There was no significant difference in overall mortality between the two treatment groups. The most common type of haemorrhagic complication was GI bleeding. **Level 1++**

Subgroup analysis

Post hoc analysis found no significant difference among the 5,197 diabetic patients included in the MATCH trial in terms of the incidence of primary endpoint. **Level 1++**

12.15 Health economic evidence statements

In the treatment of non-ST segment elevation ACS in high-risk patients the cost-effectiveness of clopidogrel used in combination with aspirin compared to aspirin alone £4,939 per QALY.[332]

A US study compared clopidogrel to aspirin in diabetic patients hospitalised within 24 hours of onset of symptoms indicative of ACS, the cost-effectiveness was $8,457–9,857 per life-year gained.[333] (In this analysis a cost-effectiveness ratio less than $50,000 was considered cost- effective.)

12.16 From evidence to recommendations

Little extra evidence of note on use of aspirin was available since the last review. However, there is now better understanding of the extent of the CV risk faced by people with Type 2 diabetes. The rather poor direct evidence for people with Type 2 diabetes led to difficulties in assessing the level of risk above which aspirin therapy should be advised. The GDG accepts that its view that all people at, or over, the age of 50 years should treated is somewhat arbitrary. Primary prevention below that age would be by assessment of higher CV risk (family history of premature vascular disease, abnormal lipid profile, marked abdominal adiposity). While the group were aware of some discussions over the dose of aspirin to be used in people with diabetes, they were not presented with any evidence that could lead to a variation from the usual national recommendations of 75 mg.

NICE guidance for dipyridamole MR related only to people with cerebrovascular events.

The evidence for the use of clopidogrel was noted to relate to acute and non-acute situations. The current guideline review was not concerned with acute vascular events or interventions. The CHARISMA and MATCH trials suggested that the combination of aspirin and clopidogrel carried a significant side-effect risk of a serious nature not balanced by secure health gain, and therefore could not be generally recommended. NICE guidance for secondary prevention of vascular events in people without diabetes was that clopidogrel should not be used instead of aspirin except where intolerance or hypersensitivity to the latter was present. The specific evidence for people with diabetes, mostly sub-analyses, did not suggest that advice should be varied for people with Type 2 diabetes.

12.10.7 Recommendations

18. **Offer low-dose aspirin, 75 mg daily, to a person who is 50 years old or over if blood pressure is below 145/90 mmHg.**

19. **Offer low-dose aspirin, 75 mg daily, to a person who is under 50 years old and has significant other cardiovascular risk factors (features of the metabolic syndrome, strong early family history of cardiovascular disease, smoking, hypertension, extant cardiovascular disease, microalbuminuria).**

20. **Clopidogrel should be used instead of aspirin only in those with clear aspirin intolerance (except in the context of acute cardiovascular events and procedures). Follow the recommendations in the NICE TA 'Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events'.**[321]

13 Kidney damage

13.1 Diabetes kidney disease management

13.1.1 Clinical introduction

Kidney disease in people with Type 2 diabetes is becoming an ever larger health burden.[336] This reflects a number of trends including the increasing prevalence of people with diabetes, the better cardiovascular (CV) survival with modern management, and the better management of progression of kidney damage itself. The trend to younger onset of Type 2 diabetes is also likely to see more kidney damage as these people are at lower CV risk, while in the elderly the condition is ever more complicated by comorbidities disease.

Primary prevention of kidney damage from diabetes centres around the prevention of microvascular (classical diabetic nephropathy) and arterial (and thus renovascular) damage discussed in other chapters of this guideline – the current section is concerned with detection and secondary prevention of kidney damage. For reasons of coherence some recommendations overlap with, or are reproduced from, other sections of the guideline.

The clinical questions addressed here include how often and by what means to detect and confirm the possibility of diabetic renal disease, and the means of monitoring its progression. In those with detected renal disease issues arise as to the means to reduce or stop such progression, and the point at which to engage specialist renal management.

13.1.2 Methodological introduction

Both methodologically and clinically this question attempts to cover a broad research area which encompasses different key issues relevant to the diagnosis and management of renal disease (e.g. monitoring of renal function (GFR, measurement of serum creatinine, renal ultrasound) and qualitative and quantitative measurements for albuminuria (screening tests).

A total of nine studies were identified as relevant to the question.[337–345]

Given the diversity of studies the evidence has been divided into the following categories:

- studies comparing the accuracy of different equations used to estimated GFR
- studies looking at qualitative methods to detect microalbuminuria
- studies comparing several quantitative methods to assess renal disease such as renal ultrasound, serum creatinine, estimated glomerular filtration rate (eGFR) and tests for albuminuria (i.e. UAER, urinary albumin concentration (UAC), albumin:creatinine ratio (ACR).

13.1.2.1 Equations estimating GFR in Type 2 diabetes population

General background

- Although GFR can be measured directly using inulin, the classic method for measuring inulin clearance requires an intravenous infusion and timed urine collections over a period of several hours. Therefore, GFR is costly and cumbersome. Several other alternative measures have been devised; however, predictive equations have proven simpler.
- In adults the equations used are the Modification of Diet in Renal Disease (MDRD) study and the Cockcroft-Gault (CG) equations.
- Both the CG and the MDRD equations were developed in predominantly non-diabetic individuals.

- The CG equation has the advantage of being more widely known, easier to remember and more extensively validated than the MDRD formula. However, the MDRD formula does not require knowledge of the patient's weight (making it far more suitable for automated laboratory reporting), and does not need correction for body surface (and therefore does not require knowledge of the patient's height).
- The MDRD study equation has not been validated in children (aged under 18 years), pregnant women, the elderly (aged over 70), racial or ethnic subgroups other than Caucasians and African-Americans, in individuals with normal kidney function who are at increased risk for CKD or in normal individuals.

Studies included

No RCTs were identified comparing the performance of different equations estimating GFR in a Type 2 diabetes population.

Two cross-sectional studies [344,345] were identified as looking at the performance of the estimating equations in patients with diabetes and CKD.

One study[344] compared the abbreviated MDRD equation with the CG in 249 CKD patients with diabetes. The study used data from the renal function laboratory at the Cleveland Clinic Foundation which performed approximately 9,000 measurements of GFR by 125 I-iothalamate renal clearance from 1982 to 2002 and maintained a database with demographic and laboratory variables.

The other study[345] compared the performance of three equations (CG, MDRD and a simplified CG).[y] Data for the study was taken from 200 adult diabetic patients with CKD attending a hospital in Pessac, France. GFR was evaluated by clearance of the radionuclide marker was measured after intravenous injection of 51Cr-EDTA.

Studies in which serum creatinine assays were not adjusted (calibrated) to mimic that of the MDRD study laboratory were excluded[z] (it should be noted that the same exclusion criteria has been adopted by the NICE CKD guideline – due to be published in September 2008). In addition, studies were excluded if gold standards test were not used as the reference test or if they had a small sample size (N<100).

13.1.2.2 Qualitative methods to assess microalbuminuria

General background

To be useful as screening tests, qualitative (or semiquantitative) tests must have high detection rates for microalbuminuria (not only increased albumin concentrations in urine). According to the US Laboratory Medicine Practice Guidelines the sensitivity of a clinically useful qualitative test should be higher than 95%.

Dipstick tests are subject to false positives because of patient dehydration, hematuria, exercise, infection, and extremely alkaline urine. Conversely, dipstick tests also are subject to false negatives as a result of excessive hydration and urine proteins other that albumin.

y To protect the CG from the influence of body weight it was replaced by its mean value (76 kg) to calculate a new formula: modified CG (MCG).

z The majority of the between laboratory difference is due to calibration differences. Bias between different creatinine assays produces predictable and significant differences in estimates of GFR. Currently, there is no universally accepted standardisation for creatinine assays. A potential solution is for laboratories to align their creatinine assay to that used by the MDRD laboratory. Isotope dilution mass spectrometry (IDMS) is another alternative.

Studies included

No RCTs were identified addressing this issue.

Three cross-sectional studies [339,340,343] were found evaluating the performance of a qualitative method (Micral-Test II) with other methods to assess microalbuminuria in Type 2 diabetes populations.

One study[339] compared the Micral-Test II with nephelometry in 166 patients with Type 2 diabetes and essential hypertension.

Another study[340] assesses the accuracy of the Micral-Test II, UAC, and ACR in a random urine specimen in 278 diabetic patients.

One study[343] compared the Micral-Test II with UAC by immunoturbidimetric.

Studies with a small sample (N<100) were excluded.

13.1.223 Studies comparing several quantitative methods to assess renal disease

General background

- The most commonly used measure of overall kidney function in clinical practice is serum creatinine concentration. Unfortunately, this measurement is affected by many factors other than the level of kidney function and varies markedly with age, gender and muscle mass. Moreover, as it was stated above, there is significant calibration issues associated with the measurement of serum creatinine that lead to inter-laboratory variation.
- Consequently, many guidelines, including the Kidney Disease Outcomes Quality Initiative (K/DOQI), British Renal Association and Kidney Disease Improving Global Outcomes (KDIGO) guidelines have recommended that serum creatinine concentration alone should not be used to assess the level of kidney function.
- UAC and ACR are alternative ways of estimating loss of glomerular permselectivity when using single urine samples instead of timed urine collections (i.e. UAER in a 24-hour sample).The amount of albumin lost in the urine will primarily depend on the degree of damage to the glomerular membrane, whereas UAC, in addition, will depend on the extent to which the urine has been concentrated in the tubular system.
- By dividing UAC by urinary creatinine concentrations (i.e. ACR), an attempt is made to correct for inter- and intraindividual differences in daily urine volume.

Studies included

No RCTs were identified addressing this issue.

Four cross-sectional studies [337,338,341,342] were found comparing different quantitative methods to assess renal disease.

One study[337] analysed the status of eGFR (by diethylene triamine pentaacetic acid (DTPA) renal scan) vis-à-vis other non-invasive modes of assessment of renal involvement (UAER, serum creatinine and ultrasound) in 100 diabetic patients.

One study[338] determined the diagnostic performance of albuminuria (ACR) and a serum creatinine >120 µmol to detect an eGFR <60 ml/min/1.73m^2 in a population of 4,303 diabetics.

Similarly, one study[342] examined the ability of ACR to detect clinically meaningful CKD (GFR

<60 ml/min 1.73 m2) compared with estimated GFR (by using the MDRD equation) in a population of 7,596 diabetics.

Another study[341] analysed the association between GFR (by DTPA renal scan) and UAER (timed urine collection) in 301 Type 2 diabetes patients. In particular, the study determined the prevalence and characteristics of patients with impaired renal function (GFR <60 ml/min 1.73 m2) and an AER within the normoalbuminuric range.

13.153 Health economic methodological introduction

No health economic papers were identified.

13.174 Evidence statements

13.1.481 Equations estimating GFR in Type 2 diabetes population

Bias

One study[344] reported that in the whole CKD group (diabetics and non-diabetics N=828), the MDRD equation was superior to the CG equation in terms of bias. The MDRD equation slightly underestimated the measured eGFR while the CG equation significantly overestimated the eGFR (–0.5 vs 3.5 ml/min per 1.73 m2 p<0.001). **Level 2+**

The study[344] showed that the MDRD equation was also significantly less biased than the CG in the diabetic subgroup (N=249) and in people with a measured GFR <30 ml/min per 1.73m2 (N=546) p<0.001 in each group. **Level 2+**

The study[344] concluded that the MDRD and CG equations were significantly more biased in people with GFR >60 ml/min per 1.73 m2 (N=117). The MDRD equation underestimated the measured eGFR, while the CG equation significantly overestimated the GFR (–3.5 vs 7.9 ml/min per 1.73 m2, p<0.001). The equations were also biased, but to a lesser extent in patients with GFR 30–60 ml/min per 1.73 m2. Level 2+

One study[345] revealed a bias for the MDRD and MCG – the differences between the predicted and the measured GFR were correlated with their means (MDRD: r=0.054, p<0.0001; MCG: r=0.27, p<0.001). There was no such bias for CG.

Test correlation

In terms of test correlation, the study[344] demonstrated that in the CKD population, both the MDRD (r=0.90) and CG equations (r=0.89) correlated highly with measured[125] I-iothalamate GFR. **Level 2+**

One study[345] showed that over the whole population the mean isotopic GFR was 56.5±34.9 ml/min/1.73 m^2, the mean CG 61.2±35.6 (p<0.01 vs isotopic), the mean MCG. 60.0±29.9 (p<0.05 vs isotopic) and the mean MDRD, 51.0±24.3 (p<0.001 vs isotopic). The MCG was better correlated with isotopic GFR than was the CG (CG: r=0.75, MCG: r=0.83; p<0.05 vs CG, MDRD: r=0.82; p=0.068 vs CG). **Level 2+**

Accuracy

In relation to accuracy, the study[344] showed that in the diabetic group, the MDRD equation was significantly more accurate (63%) than the CG equation (53%) p<0.05. **Level 2+**

One study[345] stated that the receiver operating characteristic (ROC) curves showed that the MDRD and the MCG had a better maximal accuracy for the diagnosis of moderate (N=119; area under curve (AUC): 0.866 for CG, 0.920 for MDRD, 0.921 for MCG; both 0.891 vs CG) and severe (N=52; AUC: 0.891 for CG, 0.930 for MDRD, 0.942 for MCG; both p<0.05 vs CG) renal failure. **Level 2+**

The same study[345] concluded that as the MCG was more accurate for high GFR, and the MDRD was more accurate for low GFR, the MCG could be used at low serum creatine values and the MDRD at high values.

13.1.442 Studies looking at qualitative methods to assess microalbuminuria

One study[339] comparing the Micral-Test II with nephelometry demonstrated that the dipstick had a sensitivity of 83% and a specificity of 96%. The correlation between nephelometry and Micral Test II results was 0.81 (p<0.0001). **Level 2+**

The same study[339] showed that when the ROC curve for the Micral-Test II as a diagnostic test for microalbuminuria was analysed, the calculated mean area under the ROC curve (±SEM) was 0.91±0.03 (CI 95% 0.85–0.96) and the corresponding best cut-off value was 30.5 mg/l. **Level 2+**

One study[343] comparing the Micral-Test II with UAER (in a 24-hour timed urine collection) reported a sensitivity 88% and a specificity 80%.

When performance was assessed by different concentrations readings the study found that Micral-Test II strips performed reasonably well at 0.50 and 100 mg/l with a high percentage of true negatives (93%, 0 mg/l), true positives (81%, 50 mg/l and 91%, 100 mg/l), low percentages of false negatives (7%, 0 mg/l) and false positives (19%, 50 mg/l and 9%, 100 mg/l). However, at 20 mg/l Micral strips did not perform well (51% false positive). **Level 2+**

One study[340] assessing the accuracy of the Micral-Test II, the UAC and the ACR in a random urine specimen found the following test correlations:

- UAER vs UAC: 0.76 p<0.0001
- UAER vs ACR: 0.74 p<0.0001
- ACR vs UAC: 0.86 p<0.0001

The study[340] also reported that age and 24-hour creatinuria presented a negative correlation (278 patients, r=–0.19, p=0.002). No correlation was observed between age and UAER (r=0.02, p=0.74), age and UAC (r=0.07, p=0.22) and age and UACR (r=0.11, p=0.08). **Level 2+**

The same study[340] showed that the specificity of UAC and UACR was similar when considering the 100% sensitivity cut-off points. The sensitivity and specificity of the Micral-Test II strip for a 20 mg/l cut-off point (as indicated by manufacturer) on fresh urine samples based on ROC curve analysis (N=130) were 90 and 46% respectively. **Level 2+**

In terms of accuracy, the study[340] stated that the comparison among the areas under the ROC curves for UAC, UACR and the Micral-Test II took into account the individual results, for each single patient (N=130), of the three screening methods being tested and of the reference test method (UAER).The study concluded that a similar area was observed under the UAC (0.934±0.032) and UACR (0.920±0.035) curves (p=0.626).

The area under the curve was smaller for the Micral-Test II (0.846±0.047) than for UAC (p=0.014). **Level 2+**

13.1.443 Studies comparing several quantitative methods to assess renal disease

Ultrasound – serum creatinine – albuminuria – GFR

One study[337] analysed the status of GFR (by DTPA renal scan) vis-à-vis other non-invasive modes of assessment of renal involvement (UAER, serum creatinine and ultrasound) in 100 Type 2 diabetes patients. Patients were divided into three subgroups depending on the

duration of initial detection of Type 2 diabetes. Group A constituted patients with less than 5 years duration, group B 5–15 years and group C more than 15 years duration.

Ultrasound

The study[337] reported that most of the patients in group A and B had a large kidney with preserved corticomedullary (CM) differentiation (83.9% and 80%); only group C had a significantly higher prevalence of large kidney with loss of CM differentiation (75.9%). **Level 2+**

Serum creatinine

The study[337] concluded that there was no difference between group A and B as far as the serum creatinine was concerned. High level of serum creatinine was only significantly associated with group C (44.8%). **Level 2+**

Albuminuria

The study[337] found that normoalbuminuria and microalbuminuria were significantly higher in group A (25.8% and 74.2%). Macroalbuminuria was higher in both group B and C (80% and 69%).

For UAER group A had a significantly lower level compared to both B and C ($p<0.01$), however, there was no significant difference between group B and C with respect to the amount of both micro- and macroalbuminuria. **Level 2+**

Glomerular filtration rate

The study[337] showed that group A presented a significantly higher prevalence of normal and raised GFR (25.8% and 61.3%). Group B had a significantly higher prevalence of low GFR, while prevalence of very low GFR was highest in group C (37.9%).

The GFR had a progressively significant decrement from group A through group B to C ($p<0.01$). **Level 2+**

The study[337] concluded that GFR estimation was the only renal parameter which could singly provide a picture of the actual renal status of Type 2 diabetes patients at any duration irrespective of the status of albuminuria, azotaemia or renal size and morphology as their variability or progression is non-linear.

13.1.24 Diagnostic performance of ACR >120 µmol to detect an eGFR <60 ml/min/1.73 m2 (MDRD)

After ranking 4,303 diabetics based on their eGFR (>90, 90–60, 60–30 and <30 ml/min per 1.73 m^2) one study[338] showed that the proportion of individuals with abnormal serum creatinine rose with progressive fall in eGFR (0%, 1%, 37% and 100% with creatinine >120 µmol/l in eGFR >90, 90–60, 60–30 and <30 ml/min per 1.73 m2 respectively), as did the proportion with abnormal albuminuria (33%, 27%, 42% and 77% with ACR >3.5 mg/mmol). **Level 2+**

The study[338] found that of the 1,296 individuals with an eGFR <60, 539 (42%) had abnormal serum creatinine, 579 (45%) had abnormal albuminuria and 798 (62%) had either abnormal serum creatinine or urine ACR. Thus, a creatinine and ACR based strategy would have missed the renal risk of 498 (38%) individuals since they had normal values of both despite having a significantly impaired eGFR <60 ml/min per 1.73 m^2. **Level 2+**

The same study[338] also demonstrated that the proportion missed by current markers was more marked in women (N=757) where the prevalence of those with abnormal serum

creatinine, urine ACR and either were 20%, 38% and 47% respectively, compared with 72%, 54% and 83% observed in men (N=539). **Level 2+**

When the study analysed the data by ethnic origin, it was found that white people appeared to benefit the most from eGFR, with a greater prevalence of normocreatinaemic and normoalbuminuric renal insufficiency, whereas the majority of the African-Caribbean group with low eGFR had either an abnormal creatinine or ACR 39%, 42% and 59% respectively, with abnormal creatinine, ACR and either in white people (N=997); 62%, 69% and 80% respectively, in African-Caribbeans (N=84); and 44%, 54% and 69% respectively in Indo-Asians (N=210). **Level 2+**

The study did not find difference in performance when data was analysed by the type of diabetes. **Level 2+**

The study[338] concluded that GFR estimates may have a place in routine diabetes clinical care, being a more sensitive marker of risk than serum creatinine or albuminuria. eGFR also appears to eliminate the gender and ethnic bias observed with current markers and also provides an opportunity to monitor longitudinal changes.

Another study[342] using data from 7,596 diabetics found that 27.5% (N=1,715) of the population had an eGFR <60 ml/min/1.73 m^2; of these 19.4% had normoalbuminuria; 20.4% had albuminuria, the remainder not having had albuminuria determined.[aa] The study also reported that serum creatinine was normal (£120 mmol/l) in 54.7% of those with eGFR <60 ml/min/1.73 m^2 and £150 mmol/l in 82.2%. **Level 2+**

This study[342] found that the sensitivity of abnormal serum creatinine levels in identifying eGFR <60 ml/min/1.73 m^2 is 45.3%, albuminuria is 51.2% and either an abnormal serum creatinine or albuminuria is 82.4%. **Level 2+**

The same study also reported that unidentified CKD, defined as the presence of a GFR <60 ml/min/1.73 m^2 but without any evidence of an abnormal creatinine (i.e. serum creatinine £120 mmol/l) was significantly greater in females compared with males adjusting for age, type of diabetes and secondary care setting (OR 8.22, CI 6.56 to 10.29). Using albuminuria as a screening test also failed to identify CKD in females (OR 2.22, CI 1.63 to 3.03). The presence of abnormal serum creatinine and albuminuria to identify CKD continued to display a significant bias against females (OR 7.58, CI 5.44 to 10.57). **Level 2+**

The study[342] concluded that current screening techniques based upon albuminuria and/or abnormal serum creatinine would fail to detect a significant number of participants with an eGFR <60 ml/min/1.73 m^2. Therefore, without eGFR reporting the clinician may not be alerted to the presence of CKD and be falsely reassured that renal function is normal.

13.1.2.5 Association between GFR (by DTPA renal scan) and UAER (timed urine collection)

One study[341] divided 301 Type 2 diabetes patients on the basis of their GFR (i.e., < or ≥60 ml/min 1.73 m2) and albuminuria status (i.e., normo <20 µg/min, micro 20–200 µg/min, macro >200 µg/min). The study found a significant correlation between a decreasing GFR with increasing levels of AER (r=-0.29, p<0.0001). **Level 2+**

Glomerular filtration rate status

The study[341] reported that for the 109 patients with a GFR <60 l/min 1.73 m2 the prevalence of normo-, micro- and macroalbuminuria was 39%, 35% and 26% respectively. For the 192 patients with a GFR ≥60 ml/min 1.73 m^2 the prevalence of normo-, micro- and macroalbuminuria was 60%, 33% and 7% respectively. **Level 2+**

aa Albuminuria was determined in only 39.8% of participants with an eGFR <60 ml/min/1.73m2 over the 2-year period of our study despite current recommendations in the UK for annual screening. A greater proportion of participants (70%) receiving diabetes management in a secondary care setting had albuminuria quantified

UAER status

When the study[341] stratified the 301 patients according to their AER status regardless of their GFR, 52% had normo-, 34% had micro-, and 14% had macroalbuminuria. For the 158 normoalbuminuric patients, 27% had a corresponding GFR <60 ml/min 1.73 m^2 and 73% had a GFR ≥60 ml/min 1.73 m^2. **Level 2+**

The study also demonstrated that normoalbuminuric patients were significantly older ($p<0.01$) and more commonly female ($p<0.01$) in comparison to those with macroalbuminuria. There were no differences in the duration of diabetes, BMI, prevalence of retinopathy, history of CVD, smoking history, HbA1c levels, systolic blood pressure, diastolic blood pressure (DBP), total cholesterol, low-density lipoprotein, high-density lipoprotein and triglyceride levels among patients with a GFR <60 ml/min 1.73 m^2 associated with normo-, micro-, or macroalbuminuria.

Overall, the study did not find significant differences in the use of any antihypertensive agent (specifically renin-angiotensin system inhibitors (RAS-inhibitors)) for patients with a GFR <60 ml/min 1.73 m^2 and normo-, micro- or macroalbuminuria. **Level 2+**

The study[341] calculated the prevalence of a GFR <60 ml/min 1.73 m^2 and normoalbuminuria after excluding 23 of 43 patients whose normoalbuminuric status was possibly altered by the use of RAS inhibitors. After this adjustment the prevalence of a <60 ml/min 1.73 m^2 and normoalbuminuria was 20 of 86 (23%). **Level 2+**

13.15 From evidence to recommendations

The GDG noted the importance to health in delaying or preventing the progression of diabetes renal damage, and the certainty of evidence that this could be done. Detection of early diabetes kidney damage at a stage when therapy could be usefully intensified was now nearly universally through urinary ACR – review of the evidence showed no reason to doubt this was appropriate. This measure is also a CV risk factor, and accordingly features elsewhere in chapter 13.

Some discussion of the logistics of collection of first-pass morning urine samples revealed there was no single right answer to establishing a sound process for ensuring samples were obtained annually. No changes in the process for confirming presence of microalbuminuria were felt necessary.

It was noted that laboratory estimation of serum creatinine was now reported with an eGFR result using the method abbreviated MDRD (4-variable) equation. The group recognised some problems with these calculations (worse overall in people with diabetes than in the general population) but could see no better alternative.

The management of diabetic nephropathy when confirmed was felt not to have changed from that of the previous NICE guideline and that for Type 1 diabetes, centring around renin-angiotensin system blockade, tight blood pressure control, and specialist referral. Non-diabetic renal disease will also occur in people with diabetes and needs not to be confused with diabetic nephropathy. The group noted that there were a series of markers which suggested when renal disease in people with diabetes was not diabetic nephropathy.

The group noted that there is a NICE CKD clinical guideline which also considers people with diabetes. This guideline is due to be published in September 2008.

13.16 Recommendations

R93 Ask all people with or without detected nephropathy to bring in a first-pass morning urine specimen once a year. In the absence of proteinuria/urinary tract

infection (UTI), send this for laboratory estimation of albumin:creatinine ratio. Request a specimen on a subsequent visit if UTI prevents analysis.

R94 Make the measurement on a spot sample if a first-pass sample is not provided (and repeat on a first-pass specimen if abnormal) or make a formal arrangement for a first-pass specimen to be provided.

R95 Measure serum creatinine and estimate the glomerular filtration rate (using the method- abbreviated modification of diet in renal disease (MDRD) four-variable equation) annually at the time of albumin:creatinine ratio estimation.

R96 Repeat the test if an abnormal albumin:creatinine ratio is obtained (in the absence of proteinuria/UTI) at each of the next two clinic visits but within a maximum of 3–4 months. Take the result to be confirming microalbuminuria if a further specimen (out of two more) is also abnormal (>2.5 mg/mmol for men, >3.5 mg/mmol for women).

R97 Suspect renal disease, other than diabetic nephropathy and consider further investigation or referral when the albumin:creatinine ratio (ACR) is raised and any of the following apply:

- **there is no significant or progressive retinopathy**
- **blood pressure is particularly high or resistant to treatment**
- **had a documented normal ACR and develops heavy proteinuria (ACR >100 mg/mmol)**
- **significant haematuria is present**
- **the glomerular filtration rate has worsened rapidly**
- **the person is systemically ill.**

R98 Discuss the significance of a finding of abnormal albumin excretion rate, and its trend over time, with the individual concerned.

R99 Start ACE inhibitors with the usual precautions and titrate to full dose in all individuals with confirmed raised albumin excretion rate (>2.5 mg/mmol for men, >3.5 mg/mmol for women).

R100 Have an informed discussion before starting an ACE inhibitor in a woman for whom there is a possibility of pregnancy, assessing the relative risks and benefits of the use of the ACE inhibitor.

R101 Substitute an angiotensin II-receptor antagonist for an ACE inhibitor for a person with an abnormal albumin:creatinine ratio if an ACE inhibitor is poorly tolerated.

R102 For a person with an abnormal albumin:creatinine ratio, maintain blood pressure below 130/80 mmHg.

R103 Agree referral criteria for specialist renal care between local diabetes specialists and nephrologists.

14 Diabetic neuropathic pain management

14.1 Clinical introduction

Neuropathic pain is a troublesome symptom of chronic exposure to poor blood glucose control that cannot be managed acutely by restoration of blood glucose control. It can take many forms, and is often distressing and sometimes depressing, particularly if symptoms are predominantly nocturnal and disturb sleep. People with diabetes may be reluctant to report the symptoms to those with expertise in diabetes care, because of lack of awareness that the problem is diabetes related. A number of drug and non-drug approaches to management are available, this diversity reflecting that none of them are fully effective.

Clinically the issues are when to start specific drug therapy for neuropathic pain, which medications to use, and in what order to try them.

14.2 Methodological introduction

Tricyclics

There were nine studies identified in this area. All five studies included were double-blind, crossover studies. One study compared desipramine, amitriptyline and active placebo[bb] (benzotropine to mimic dry mouth).[348] One study compared clomipramine with desipramine.[349] One study compared imipramine with mianserin (60 mg/day).[350] One study considered amitriptyline with gabapentin,[351] and the last study compared amitriptyline with lamotrigine.[352] Four studies were excluded for methodological reasons.[353,354,355,356]

One study specified the proportion of patients with Type 2 diabetes, 88%,[351] and a second study was conducted only in patients with Type 2 diabetes.[352]

The different drug and dose comparisons prevented a direct comparison between the studies.

Duloxetine

There were six RCTs and one meta-analysis identified in this area.[357–363] The meta-analysis was excluded for methodological reasons.[360]

Two double-blind studies compared patients on duloxetine 60 mg/day and duloxetine 60 mg twice daily with placebo,[358,362] and a further study compared patients on duloxetine 20 mg/day, 60 mg/day or 60 mg twice daily with placebo[359] all over a 12-week study duration. There were two open-label long-term efficacy studies of 52-weeks duration comparing duloxetine 60 mg twice daily with routine care,[357,363] although in one of these studies the dose of duloxetine could be reduced to 60 mg/day in cases of poor tolerability. Additional medications were allowed in both studies; including gabapentin, amitriptyline, venlafaxine extended release and acetaminophene,[357] and paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS) or opioids.[363] The final study compared duloxetine 60 mg twice daily with duloxetine 120 mg once daily in an open-label study over 28 weeks.[361]

The majority of study participants had Type 2 diabetes; between approximately 88–94% in all studies.[357–359,361–363]

bb Based on the results of two studies amitriptyline compared with desipramine and fluoxetine compared with placebo (N=52).

Gabapentin

There were five studies identified in this area, four of these were RCTs and one was an open- label study.[364]

One study[365] was excluded for methodological reasons.

Two studies compare gabapentin with placebo,[366,367] (the study by Simpson DA[367] reported on a three-phase study. Phases two and three included gabapentin compared with venlafaxine and therefore only phase one, gabapentin compared with placebo, has been included here). One study considered gabapentin and amitriptyline in a crossover study.[351]

The open-label study considered a fixed dose of gabapentin compared with a titrating dose which was titrated until it was perceived to have reached clinical effect – that was a ≥50% reduction in pain.[364]

The majority of study participants had Type 2 diabetes; approximately 75%,[366] 89%,[364] 88%,[351] and 82%.[367]

Pregabalin

There were three studies identified in this area, all were RCTs comparing varying doses of pregabalin (75 mg/day to 600 mg/day) with placebo for those with both Type 1 and Type 2 diabetes, N=729.[368–370]

The majority of the participants in each study were those with Type 2 diabetes; 90.1%,[368] 91%,[369] and 87%.[370]

There were no studies which considered pregabalin in comparison with other treatments for painful diabetic neuropathy. The included studies were all of short duration (6–9 weeks) and there were no studies which considered longer-term effectiveness.

Carbamazepine

There were a limited number of studies identified in this area. It should be noted that studies looking at oxcarbazepine, a new form of carbamazepine which has the same indications but seems to be better tolerated, were also included. All the studies were conducted in diabetic patients.

In relation to carbamazepine, we found three small RCTs with a crossover design. Two of them compared carbamazepine against placebo.[cc371,372] The third RCT[373] compared carbamazepine monotherapy with the combination of nortriptyline-fluphenazine.

There were some methodological quality issues with the two placebo-controlled studies[371,372] which often involved a short follow-up and the absence of a washout period.

Three RCTs were identified comparing oxcarbazepine with placebo using a parallel design.[374–376] One of these studies was excluded due to a high dropout rate.[376]

14.13 Health economic methodological introduction

Three papers were identified from the literature search. One paper was excluded because it was a review and did not include economic evidence. The other two papers were excluded for methodological reasons.[377–379]

cc These two studies were published more than 30 years ago (1969, 1974) reflecting the fact that carbamazepine was one of the first interventions studied for treatment of painful diabetic neuropathy.

14.1.4 Evidence statements

14.1.4.1 Tricyclics

Outcomes

Pain related outcomes were measured using either a six-item neuropathy scale,[349,350] or a pain diary.[348]

Mean pain score

Overall, the results indicate that all of the drugs, with the exception of mianserin,[350] produced reduction in pain scores compared to placebo. However, there are no statistically significant differences between the individuals.[348,349,351] **Level 1+**

There was a significant reduction on the observer and the self-rating neuropathy scale in favour of clomipramine ($p<0.05$) and desipramine ($p<0.05$ and $p<0.01$) both compared to placebo ($p<0.05$). There were no statistically significant differences between the two treatments. The median reduction as compared with placebo was on cloimpramine 39% (95% CI 27 to 79%) and desipramine 32% (0 to 46%).[349] **Level 1+**

Desipramine and amitriptyline resulted in an equivalent reduction in mean pain scores and pain intensity. Both treatments were superior to placebo on mean pain score (mean change 0.47 and 0.35 vs 0.15, $p<0.05$ for both) and pain intensity[dd] (–0.48 and –0.48 vs –0.15, $p<0.05$, one- tailed Dunnett's test).[348] **Level 1+**

There was a significant difference in favour of imipramine compared to placebo ($p=0.03$) and compared to mianserin ($p=0.033$) on the observer-rated score but not the self-rated score. There was no significant difference between mianserin and placebo.[350] **Level 1+**

Although both gabapentin and amitriptyline showed significant reductions in pain intensity scores there was no significant difference between the drugs, this was also found for global pain score.[351] **Level 1+**

Both amitriptyline and lamotrigine resulted in improvements in pain relief on several pain measures, although there was no significant difference between the treatments.[352] **Level 1+**

Adverse events and dropout rates

The total side-effect score was significantly higher for clomimpramine (median 4.0) and desipramine (median 4.5) than during placebo (median 0.02, $p< 0.05$ for both). There were no statistically significant differences between cloimpramine and desipramine. The most common side effects were dry mouth, sweating, orthostatic dizziness and fatigue. Six patients withdrew from the study all due to side effects (three each during clomimpramine and desipramine).[349] **Level 1+**

The proportion of patients who experienced any side effects associated with amitriptyline, desipramine or placebo treatments was 81%, 76% and 68% respectively. Seven patients withdrew whilst on amitriptyline and seven whilst on desipramine, all due to drug-associated side effects.[348] **Level 1+**

The total adverse effect scores were significantly higher during mianserin (median 2.03, $p=0.0093$) and imipramine (median 4.00, $p=0.0001$) than during placebo (median, 0.98) but there were no significant differences between the two active treatments. The most common side effects were dry mouth, orthostatic dizziness and fatigue. One patient withdrew due to side effects whilst taking imipramine.[350] **Level 1+**

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dd The data has been extracted from a graphical representation of the results.

With the exception of weight gain with amitriptyline (p<0.03) there was no significant difference in occurrence of adverse events (AEs) between amitriptyline and gabapentin. Adverse effects included sedation, dry mouth, dizziness, postural hypotension, weight gain, ataxia and lethargy. Two patients (one from each group) crossed over early due to AEs and completed the study.[351] **Level 1+**

Amiptriptyline resulted in significantly more AEs overall than lamotrigine (p<0.001), the major side effect being an increase in sleep. More patients discontinued treatment while on amitriptyline (19/46) than while on lamotrigine (8/46).[352] **Level 1+**

14.1.4.2 Duloxetine

Pain

Pain-related outcomes were measured throughout the papers using recognised and validated tools.

Overall, duloxetine 60 and 120 mg/day (delivered as 60 mg twice daily) were associated with significant reductions in measures of pain (24-hour average pain, brief pain inventory (BPI) and Short-form McGill Pain Questionnaire (SF-MPQ)) when compared with placebo.[358,359,362] Two studies found greater improvements in all pain measures in the duloxetine 120 mg/day arm,[359,362] while the other study found greater improvements in the duloxetine 120 mg daily arm in selected pain measures (BPI interference scores and SF-MPQ).[358] **Level 1++** and **level 1+**

One study found a significantly lower dose of concomitant analgesics (acetaminophen) used in the duloxetine 120 mg daily arm than either the duloxetine 60 mg daily arm (p<0.05) or the placebo arm (p<0.001).[362] **Level 1+**

Table 18.1 Pain related and quality of life measures (mean change (standard error)) for duloxetine 60 mg daily vs duloxetine 120 mg daily (given as 60 mg twice daily)

Measure	Goldstein (2005)[166]	Raskin (2005)[168]	Wernicke (2006)[161]
24-hour average pain	Duloxetine 60 mg vs placebo −1.17 (95% CI −1.84 to −0.50) ps0.001 Duloxetine 120 mg vs placebo −1.45 (95% CI −2.13 to −0.78) ps0.001	Duloxetine 60 mg vs placebo −2.50 (0.18) vs −1.60 (0.18) p<0.001 Duloxetine 120 mg vs placebo −2.45 (0.18) vs −1.60 (0.18) p<0.001	Duloxetine 60 mg vs placebo −2.72 (0.22) vs −1.39 (0.23) p<0.001 Duloxetine 120 mg vs placebo −2.84 (0.23) vs −1.39 (0.23) p<0.001
BPI	Duloxetine 60 mg vs placebo −2.81 (0.21) vs −2.40 (0.21) ps0.01 Duloxetine 120 mg vs placebo −3.07 (0.22) vs −2.40 (0.21) ps0.001	Duloxetine 60 mg vs placebo −2.65 (0.19) vs −1.82 (0.19) p<0.01 Duloxetine 120 mg vs placebo −2.62 (0.19) vs −1.82 (0.19) p<0.01	Duloxetine 60 mg vs placebo −2.66 (0.23) vs −1.48 (0.23) p<0.001 Duloxetine 120 mg vs placebo −3.05 (0.24) vs −1.48 (0.23) p<0.001
BPI interference	–	Duloxetine 60 mg vs placebo −2.43 (0.18) vs −1.56 (0.18) p<0.001 Duloxetine 120 mg vs placebo −2.54 (0.18) vs −1.56 (0.18) p<0.001	Duloxetine 60 mg vs placebo −2.36 (0.19) vs −1.72 (0.19) p<0.05 Duloxetine 120 mg vs placebo −2.79 (0.19) vs −1.72 (0.19) p<0.001
SF-MPQ	Duloxetine 20 mg vs placebo −8.25 (0.65) vs −5.369 (0.66) ps0.05 Duloxetine 60 mg vs placebo −8.25 (0.65) vs −5.39 (0.66) ps0.001 → Duloextine 120 mg vs placebo −9.18 (0.64) vs −5.39 (0.66) ps0.001	Duloxetine 60 mg vs placebo −7.47 (0.61) vs −4.96 (0.60) p<0.01 Duloxetine 120 mg vs placebo −7.82 (0.61) vs −4.96 (0.60) p<0.001	Duloxetine 60 mg vs placebo −7.23 (0.70) vs −4.18 (0.73) p<0.01 Duloxetine 120 mg vs placebo −7.98 (0.71) vs −4.18 (0.73) p<0.001
CGI – severity score	Duloxetine 20 mg vs placebo −1.28 (0.11) vs −0.83 (0.12) ps0.05 Duloxetine 60 mg vs placebo −1.42(0.12) vs −0.83 (0.12) ps0.001 → Duloxetine 120 mg vs placebo −1.70 (0.012) vs −0.83 (0.12) ps0.001	Duloxetine 60 mg vs placebo −1.42 (0.09) vs −0.3 (0.09) p<0.001 Duloxetine 120 mg vs placebo −1.40 (0.10) vs −0.3 (0.09) p<0.001	Duloxetine 60 mg vs placebo −1.37 (0.11) vs −0.98 (0.12) p<0.05 Duloxetine 120 mg vs placebo −1.47 (0.12) vs −0.98 (0.12) p<0.01
PGI – improvement score	Duloxetine 60 mg/d vs placebo 2.21 (0.12) vs 2.91(0.12) ps0.001 Duloxetine 120 mg/d vs placebo 2.24 (0.12) vs 2.91(0.12) ps0.01	Duloxetine 60 mg vs placebo 2.50 (0.10) vs 3.04 (0.10) p<0.001 Duloxetine 120 mg vs placebo 2.54 (0.10) vs 3.04 (0.10) p<0.001	Duloxetine 60 mg vs placebo 2.61 (1.44) vs 3.17 (1.44) p<0.01 Duloxetine 120 mg vs placebo 2.40 (1.29) vs 3.17 (1.44) p<0.001
SF-36	Duloxetine 60 mg vs placebo Bodily pain 18.00 (1.89) vs 10.32 (1.89) ps0.01 Mental health 2.99 (1.65) vs −2.63 (1.69); ps0.05 Duloxetine 120 mg/d vs placebo Mental 1.84 (0.75) vs −1.09 (0.75) ps0.01 Bodily pain 18.32 (0.88) vs 10.32 (1.89) ps0.01 General health perceptions 9.56 (1.62) vs 2.03 (1.61) ps0.001 Mental health 5.14 (1.62) vs −2.63 (1.69) ps0.001	–	Duloxetine 60 mg vs placebo Physical functioning 11.96 (1.81) vs 3.64 (1.90) p<0.01 Vitality 8.47 (1.73) vs 2.79 (1.78) p<0.05 Physical component score 6.85 (0.76) vs 3.67 (0.78) p<0.01 Duloxetine 120 mg vs placebo Physical functioning 11.20 (1.86) vs 3.64 (1.90) p<0.01 Physical component score 7.46 (0.77) vs 3.67 (0.78) p<0.001 Bodily pain 20.59(2.04) vs 12.17(2.10) p<0.01 General health perceptions 7.73 (1.39) vs 2.39(1.42) p<0.01 Mental health 3.82 (1.49) vs −0.31 (1.52) p<0.05
EQ-5D	Duloxetine 60 mg and 120 mg vs placebo 0.13 (0.02) vs 0.08 (0.02) ps0.05		Duloxetine 60 mg and 120 mg vs placebo 0.15 (0.02) vs 0.08 (0.02) p<0.05

CGI, clinical global impression; EQ-5D, EuroQol 5-Dimensional outcomes questionnaire; PGI, patient global impression; SF-36, short-form 36

CGI, PGI and quality of life

Overall, duloxetine 60 and 120 mg/day were associated with significant improvements on the CGI and PGI compared with placebo-treated patients.[358,359,362] **Level 1++** and **level 1+**

Two studies reported a significant improvement in favour of duloxetine 60 and 120 mg/day compared to placebo on the SF-36 and EQ-5D.[359,362] **Level 1++** and **level 1+**

One long-term efficacy study reported no significant differences between duloxetine and routine care on the SF-36 or EQ-5D.[357] The other study found significant differences between duloxetine and routine care arms in SF-36 bodily pain (p=0.021) and in the EQ-5D (p=0.001).[363] **Level 1+**

A 28-week open-label study comparing duloxetine 60 mg twice daily with 120 mg once daily found that both treatment groups showed improvement from baseline to endpoint on all subscales of the BPI and clinical global impression of change score (CGIC-S) (p<0.001 for both). (Results taken from graph.)[361] **Level 1+**

Adverse events

Three studies reported higher treatment-related AEs and discontinuation rate due to AEs, in duloxetine dose treatment arms compared with placebo or routine care.[358,359,362] Two studies reported higher AEs in the routine care or placebo arms, which was significant in one of the studies,[357] although both these studies also reported higher discontinuation due to AEs in the duloxetine arm.[357,363] **Level 1++** and **level 1+**

Three studies reported significant differences in treatment-emergent AEs in duloxetine groups compared with placebo.[358,359,362] In these studies the following treatment-emergent AEs were reported to occur significantly more in one or both duloxetine groups (60 mg daily or 60 mg twice daily); nausea, somnolence, increased sweating, dizziness, constipation, fatigue, insomnia, vomiting, dry mouth, anorexia and decreased appetite. Most AEs were mild or moderate. **Level 1++** and **level 1+**

In three studies, including the two studies with 52 weeks of follow-up,[357,363] there were no treatment related AEs that were reported to occur significantly more in the duloxetine group than in routine care groups. Most AEs were moderate or mild. **Level 1++** and **level 1+**

14.1.2.3 Gabapentin

Outcomes

Pain-related outcomes were measured throughout the papers using recognised and validated tools.

Mean pain score

Both placebo-based studies found significant decreases in pain score with gabapentin compared with placebo; –1.2 (–1.9 to –0.6), p<0.001[366] and –2 vs –0.5, p<0.01.[367]

For the titration to clinical effect doses (range from 900–3600 mg/day) gabapentin showed significantly greater reductions in final mean pain scores than the fixed dose of 900 mg/day, 53.6% vs 43.3%, p=0.009.[364]

Although both gabapentin and amitriptyline showed significant reductions in pain intensity scores there was no significant difference between the drugs, this was also found for global pain score.[351] **Level 1+**

Short-form McGill pain questionnaire

There was a significant decrease in total SF-MPQ scores for gabapentin compared with placebo,–5.9 (–8.8 to –3.1), p<0.001 which was also noted in the VAS, –16.9 (–25.3 to –8.4), p<0.001 and the present pain intensity score (PPI), –0.6 (–0.9 to –0.3), p<0.001.366 This significant difference between gabapentin and placebo for the total SF-MPQ was also noted in the other placebo-based study, though further detail was not reported.[367]

The titration to clinical effect group showed a significant decrease in the short-form McGill Pain Questionnaire visual analogue scale (SF-MPQ VAS) compared with fixed dose (p<0.001) but was not significant in the total or PPI scores.[364] **Level 1+**

Sleep interference

There was a significant decrease in sleep interference, at endpoint, compared with placebo for gabapentin, –1.47 (–2.2 to –0.8), p<0.001.[366] Changes in sleep interference also showed significant improvement in the gabapentin-treated group against placebo, further details were not reported.[367]

The titration to clinical effect study showed significant improvements in sleep interference compared with the fixed dose group (57% vs 37.2%, p=0.013).[364] **Level 1+**

Short-form 36

The gabapentin compared with placebo studies showed significant increases (denotes improvement) in SF-36 results for; bodily pain 7.8 (1.8–13.8), p=0.01; mental health 5.4 (0.5–10.3), p=0.03 and vitality 9.7 (3.9–5.5), p=0.001.[366] Again, Simpson DA[367] stated there had been significant differences without further details.

There was no significant differences found in the SF-36 results for the titration to clinical effect compared with fixed-dose study.[364] **Level 1+**

PGIC and CGIC

Gabapentin compared with placebo showed significant improvements in pain for both the patient perception score and the clinician perception score (p=0.001).[366] Differences were also identified for PGIC and CGIC in the other placebo-based study with 55.5% in the much/moderately improved category for gabapentin compared with 25.9% for placebo. Significance not reported.[367]

The titration to clinical effect group identified a significant improvement in the clinician assessed score CGIC compared with the fixed dose, p=0.02. However, there was no significant difference found between the two groups in the PGIC.[364] **Level 1+**

Adverse events and dropout rates

There were a significantly higher number of AEs of dizziness and somnolence experienced by those in the gabapentin group than with placebo.[366]

The titration to clinical effect group showed higher occurrences of somnolence (20.1% vs 15.3%) and dizziness (16.6% vs 13.5%) than those in the fixed-dose group.[364]

For gabapentin compared with amitriptyline there was no significant difference in the occurrence of the main AEs, such as sedation, dry mouth and dizziness.

14.1.244 Pregablin

Outcomes

Pain-related outcomes were measured throughout the papers using recognised and validated tools.

Mean pain score (recorded via pain diaries)

Pregabalin was significantly effective in reducing the mean pain score at the 300 mg/day and 600 mg/day doses compared with placebo, this effect was seen from the end of the first

week of treatment and throughout the studies, this was identified in all three studies.[368–370] **Level 1++**

For those studies which included lower doses, 75 mg/day[368] and 150 mg/day,[369] there was no significant decrease in mean pain score found. **Level 1++**

Short form McGill pain questionnaire

Significant decreases were identified with pregabalin 300 and 600 mg/day, compared with placebo but not with the lower doses (see table 18.2). **Level 1++**

Table 18.2 Pregablin 300 and 600 mg/day compared to placebo

	Study	Total	VAS	PPI
Pregabalin 75 mg/day	Lesser (2004)[368]	NS	NS	NS
Pregabalin 150 mg/day	Richter (2005)[369]	NS	NS	NS
Pregabalin 300 mg/day	Lesser (2004)[368]	–4.89 (–7.29 to –2.48) p=0.0001	–16.09 (–23.11 to –9.08) p=0.0001	–1.59 (–0.88 to –0.30) p=0.0001
	Rosenstock (2004)[370]	–4.41 (–732 to –1.49) p=0.033	–16.19 (–24.52 to –7.86) p=0.0002	–0.37 (–0.72 to –0.02) p=0.0364
Pregabalin 600 mg/day	Lesser (2004)[368]	–5.18 (–7.58 to –2.79) p=0.0001	–19.01 (–26.00 to –12.01) p=0.0001	–0.61 (–0.90 to –0.32) p=0.0001
	Richter (2005)[369]	–5.83 (–8.43 to –3.23) p=0.002	–14.67 (–21.92 to –7.41) p=0.0002	–0.66 (–0.97 to –0.35) p=0.0002

Sleep interference

There was a significant reduction in sleep interference at the 300 mg/day and 600 mg/day doses compared with placebo; p=0.001 for both,[368] 600 mg/day –1.152 (–1.752 to –0.551), p=0.0004[369] and p<0.0001, 300 mg/day.[370] Again there was no significant reduction in sleep interference for the 75 and 150 mg/day groups.[368,369] **Level 1++**

Short-form 36

This efficacy parameter was used in two of the papers and identified that there were significant improvements in the vitality domain for the 75 mg/day (p<0.02) and 300 mg/day (p<0.01) compared with placebo, while in the social functioning and bodily pain domains there were significant improvements in the 300 mg/day (p<0.05 and p=0.005) and 600 mg/day (p<0.01 and p<0.0005) groups.[368] For 300 mg/day compared with placebo,[370] improvements were identified in the bodily pain domain, 6.87 (0.70 to 13.04, p=0.0294). No significant changes were found in the other domains. **Level 1++**

Patient global impression of change

There were significant improvements in the patient perception for 300 mg/day and 600 mg/day, compared with placebo:

- 300 mg/day (p=0.001, both studies)[368,370]
- 600 mg/day (p=0.001,368 p=0.002).[370]

Level 1++

Clinical global impression of change

Results showed that clinician perceptions echoed those of the patients:

- 300 mg/day (p=0.001 both studies)368,370

- 600 mg/day (p=0.001,368 p=0.004).370

Level 1++

Adverse events and dropout rates

There were no major differences in the AE and dropout rates between the drug dosages than placebo. AEs did occur more frequently in the treatment groups, with the most common being dizziness and somnolence.

Carbamazepine

One RCT[372] reported a significant relief of pain in patients treated with carbamazepine compared to those receiving placebo ($p<0.05$). No significant differences were found in terms of ability to sleep and reduction of numbness when the two groups were compared. Another RCT[371] showed that carbamazepine users experienced greater relief of pain compared to placebo-treated patients. However, no statistical analysis was performed. **Level 1+**

The study comparing carbamazepine monotherapy with the combination of nortriptyline–fluphenazine[373] showed that both interventions produced significant reductions of pain and paraesthesia. However, the study did not find a significant difference between the two interventions. **Level 1+**

Oxcarbazepine

One RCT[375] with a sample size of 146 reported that patients treated with oxcarbazepine experienced a significantly larger decrease from baseline in average VAS-pain scores compared with placebo (p=0.0108). The study also found a significantly greater number of oxcarbazepine-treated patients reporting some improvement from baseline on the patient's global assessment of therapeutic effect, compared to those receiving placebo (p=0.0003). No significant differences were found in terms of quality of life. Level 1+

In contrast, the other RCT[374] with a sample size of [347], did not find any significant difference between oxcarbazepine (600 mg, 1,200 mg and 1,800 mg) and placebo in terms of pain (VAS scale), assessment of therapeutic efficacy and quality of life. **Level 1+**

All five studies [371–375] demonstrated a higher incidence of AEs reported by patients receiving the active intervention (carbamazepine or oxcarbazepine) compared to placebo. The most common AEs reported were dizziness, headache and somnolence. No statistical analyses were performed. **Level 1+**

14.1.15 From evidence to recommendations

The evidence reported suggested that tricyclic drugs, duloxetine, gabapentin, and pregabalin, were all effective in at least some people with neuropathic pain of diabetes origin. The evidence included very few comparative studies, and what there was suggested no advantage for the newer drugs over the tricyclics. Clinical experience confirmed both the limited efficacy of all of the drugs in some people, but also that failure with tricyclics did not often predict failure with other drugs. In these circumstances, and given that side effects were a common problem with all drugs, the GDG felt that first-line specific therapy should be with a tricyclic drug on cost grounds, but that lack of necessary efficacy or problematic side effects should then lead onto a trial of a new drug, with a trial of a third drug if side effects again intervened. The GDG felt that carbamazepine should not be offered to patients due to the drug interactions and intolerance. It was noted that these drug interactions make it difficult for prescribers to monitor patients safely.

It was noted that for milder problems simple analgesia was sometimes all that is needed, and that local measures including contact materials or relief from beddings were sometimes

helpful. Specific topical creams were not formally appraised, but it was noted these had not entered widespread use.

A more holistic approach was often needed at discovery of the problem in helping people to understand it, where secondary psychological problems occurred, and when onward referral was needed to specialist pain teams for lack of response to conventional measures.

21. Recommendations

For the management of foot problems relating to Type 2 diabetes, follow recommendations in 'Type 2 diabetes: prevention and management of foot problems'.380

R113 Make a formal enquiry annually about the development of neuropathic symptoms causing distress.

- Discuss the cause and prognosis (including possible medium-term remission) of troublesome neuropathic symptoms, if present (bearing in mind alternative diagnoses).
- Agree appropriate therapeutic options and review understanding at each clinical contact.

R114 Be alert to the psychological consequences of chronic painful diabetic neuropathy and offer psychological support according to the needs of the individual.

R115 Use a tricyclic drug to treat neuropathic discomfort (start with low doses, titrated as tolerated) if standard analgesic measures have not worked, timing the medication to be taken before the time of day when the symptoms are troublesome; advise that this is a trial of therapy.

R116 Offer a trial of duloxetine, gabapentin or pregabalin if a trial of tricyclic drug does not provide effective pain relief. The choice of drug should be determined by current drug prices. Trials of these therapies should be stopped if the maximally tolerated drug dose is ineffective. If side effects limit effective dose titration, try another one of the drugs.

R117 Consider a trial of opiate analgesia if severe chronic pain persists despite trials of other measures. If there is inadequate relief of the pain associated with diabetic neuropathic symptoms, seek the assistance of the local chronic pain management service following a discussion with the person concerned.

R118 If drug management of diabetic neuropathic pain has been successful, consider reducing the dose and stopping therapy following discussion and agreement with the individual.

R119 If neuropathic symptoms cannot be controlled adequately, it may be helpful to further discuss:

- the reasons for the problem
- the likelihood of remission in the medium term
- the role of improved blood glucose control.

15 Areas for future research

Metformin: confirmatory studies of the advantage in terms of cardiovascular outcome studies.

Studies of the role of sulfonylureas when starting a pre-mix.

Longer term studies of the role of self-monitoring as part of an integrated package with patient education and therapies used to target.

The use of ACEI and A2RBS in combination in early diabetic nephropathy.

Comparison studies on tricyclics, duloxetine, gabapentin, and pregabalin

Appendix B: Clinical questions and search strategies for CG66

Question ID	Question wording	Study type filters used	Database and years
PAT 1	Are patient education models effective for people with Type 2 diabetes?	All study types	Medline 2002–2006 Embase 2002–2006 Cochrane 2002–2006 CINAHL 2002–2006
DIET 1	Which forms of dietary advice are effective treatments for people with Type 2 diabetes?	All study types	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
TARG 2	In people with Type 2 diabetes, what should be the target value for HbA_{1c}?	Systematic reviews, RCTs and observational studies	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
MET 1	Is metformin as monotherapy or in combination with oral antidiabetic drugs effective in the control of blood glucose in people with Type 2 diabetes compared to other oral antidiabetic drugs regimens or placebo?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
SEC 1	Are the insulin secretagogues (sulphonylureas and nateglinide and repaglinide) as monotherapy or in combination with oral antidiabetic drugs effective in the control of blood glucose in people with Type 2 diabetes compared to other oral antidiabetic drugs regimens or placebo?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
GLIT 1	Are the glitazones (pioglitazone and rosiglitazone) effective in the control of blood glucose in people with Type 2 diabetes either alone or in combination compared to other antidiabetic treatment regimens?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
ACAR 1	Are the alphaglucosidases inhibitors (acarbose or miglitol) as monotherapy or in combination with oral antidiabetic drugs effective in the control of blood glucose in people with Type 2 diabetes compared to other oral antidiabetic drugs regimens or placebo?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
EXEN 1	Is exenatide effective in the control of blood glucose in people with Type 2 diabetes either alone or in combination compared to other antidiabetic treatment regimens?	Systematic reviews and RCTs	Medline 1966–2007 Embase 1980–2007 Cochrane 1800–2007 CINAHL 1982–2007
INS 2	Are the biphasic insulin preparations (premixes) effective in the control of blood glucose compared to NPH in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
INS 3	Are the biphasic human insulin preparations effective in the control of blood glucose compared to biphasic analogue preparations in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007

continued

Question ID	Question wording	Study type filters used	Database and years
INS 4	Are multiple analogue insulin injection regimens effective (meal time and basal insulin) compared to basal insulin or biphasic insulin regimes?	All study types	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
INS 5	Are long acting insulin analogues (insulin glargine (Lantus®) effective in the control of blood glucose compared to NPH insulin, biphasic insulins or multiple daily injections?	Systematic reviews and RCTs	Medline 2002–2007 Embase 2002–2007 Cochrane 2002–2007 CINAHL 2002–2007
INS 6	Is insulin in combination with oral antidiabetic drugs effective in the control of blood glucose compared to insulin alone in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
INS 7	What methods of delivery of insulin therapy are effective at improving clinical outcomes in Type 2 diabetes?	All study types	Medline 1995–2007 Embase 1995–2007 Cochrane 1995–2007 CINAHL 1995–2007
SM 1	Is self-monitoring effective for blood glucose control in patients with Type 2 diabetes?	Systematic reviews, RCTs and qualitative studies	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
BP 1	In people with Type 2 diabetes (with and without nephropathy), what should be the target value for blood pressure?	Systematic reviews, RCTs and observational studies	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
ACE 1	Are ACE inhibitors (alone or in combination) effective in the lowering of blood pressure and/or reduction of cardiovascular disease compared with other treatments in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
ALPH 1	Are alpha blockers (alone or in combination) effective in the lowering of blood pressure and/or reduction of cardiovascular disease compared with other treatments in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
ANG 1	Are angiotensin II receptor antagonists (alone or in combination) effective in the lowering of blood pressure and/or reduction of cardiovascular disease compared with other treatments in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
BETA 1	Are beta blockers (alone or in combination) effective in the lowering of blood pressure and/or reduction of cardiovascular disease compared with other treatments in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
CALC 1	Are dihydropyridine and non-dihydropyridine calcium channel blockers (alone or in combination) effective in the lowering of blood pressure and/or reduction of cardiovascular disease compared with other treatments in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007

Question ID	Question wording	Study type filters used	Database and years
THIA 1	Are thiazide and loop diuretics (alone or in combination) effective in the lowering of blood pressure and/or reduction of cardiovascular disease compared with other treatments in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
TARG 1	In people with Type 2 diabetes, what should be the target value for lipid levels?	All study types	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
STAT 1	Are statins effective in improving lipid profiles and other outcomes compared to other treatments or placebo in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
FIB 1	Are fibrates effective in improving lipid profiles and other outcomes compared to other treatments or placebo in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
NICO 1	Are nicotinic acid derivatives effective in improving lipid profiles and other outcomes compared to other treatments or placebos in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 1966–2007 Embase 1980–2007 Cochrane 1800–2007 CINAHL 1982–2007
OMEG 1	Are omega 3s (fish oils) effective in improving lipid profiles and other outcomes compared to other treatments or placebo in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 1966–2007 Embase 1980–2007 Cochrane 1800–2007 CINAHL 1982–2007 AMED 1985–2007
RISK 1	Which arterial risk tables, equations or engines for calculation of arterial risk are most predictive of arterial disease in people with Type 2 diabetes?	Systematic reviews, RCTs and observational studies	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
PREV 1	Does aspirin prevent vascular disease in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
PREV 2	Does clopidogrel prevent vascular disease in people with Type 2 diabetes compared to aspirin or in combination with aspirin?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
NEPH 1	Which tests should be used in the diagnosis and management of renal disease?	Systematic reviews, RCTs and observational studies	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
NEUR 1	Are tricyclic drugs effective for the treatment of painful neuropathy in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
NEUR 2	Is gabapentin effective for the treatment of painful neuropathy in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007

continued

Question ID	Question wording	Study type filters used	Database and years
NEUR 3	Is pregabalin effective for the treatment of painful neuropathy in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
NEUR 4	Is carbamazepine effective for the treatment of painful neuropathy in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 2001–2007 Embase 2001–2007 Cochrane 2001–2007 CINAHL 2001–2007
GAST 1	In people with Type 2 diabetes, can gastroparesis be effectively treated with a prokinetic drug (metoclopramide or domperidone)?	Systematic reviews and RCTs	Medline 1966–2007 Embase 1980–2007 Cochrane 1800–2007 CINAHL 1982–2007
EREC 1	Are PDE5 inhibitors effective for the treatment of erectile dysfunction in people with Type 2 diabetes?	Systematic reviews and RCTs	Medline 1966–2007 Embase 1980–2007 Cochrane 1800–2007 CINAHL 1982–2007

Appendix C: Health economic analysis of third-line therapy with insulins, glitazones or exenatide in Type 2 diabetes

Introduction to the UKPDS outcomes model

The purpose of economic modelling is to present the available evidence in a logical way to inform decisions.400 An economic evaluation of a healthcare programme is only as good as the effectiveness data it is built upon, so it is important to consider the quality and relevance of the medical evidence. It also is important to consider how close the situation to be modelled is to the situation where the published clinical studies were conducted.[181]

The clinical trials of insulins, glitazones or exenatide were run for approximately 3 months to 2 years and intermediate outcomes were measured, for example change in HbA1c from baseline. In order to look at the cost effectiveness of these treatments it is necessary to extrapolate these intermediate outcomes to quality adjusted life years (QALYs) saved. Diabetes is a complicated disease and poor control can lead to the development of macrovascular and microvascular complications, which affect both quality of life and survival. In order to provide useful cost- effectiveness analysis, a model should take costs and health consequences of these complications into account.

Using one model to analyse various treatments for diabetes will provide consistency and allow the results to be compared. This will be beneficial for making decisions regarding treatment algorithms.

The United Kingdom Prospective Diabetes Study (UKPDS) was conducted between 1977 and 1991.[401] 5,102 patients with newly diagnosed Type 2 diabetes were recruited aged between 25 and 65 years. Patients had fasting plasma glucose (FPG) of above 6 mmol/l on two occasions, had no recent history of myocardial infarction (MI), ischaemic heart disease (IHD) or congestive heart failure (CHF), and had never had more than one major vascular event or a severe concurrent illness that would limit life expectancy. Biochemical measurements were taken, including HbA1c, systolic blood pressure, and lipid and lipoprotein fractions.

Observational data on 3,642 patients, for whom annual data on potential risk factors was available, were used to develop the UKPDS outcomes model. The model estimates the relationship between exposure over time to glycaemia and other risk factors to the development of macrovascular and microvascular complications (cardiovascular disease, kidney failure etc.).

The model allows the following baseline population characteristics to be inputted:

- age at diagnosis
- ethnicity
- gender
- duration of diabetes
- body mass index (BMI)
- HbA1c (glycosylated haemoglobin)
- total: high density lipoprotein (HDL) cholesterol
- blood pressure (BP)
- smoking status
- atrial fibrillation at diagnosis

- peripheral vascular disease at diagnosis
- history of diabetes-related events.

The following risk factors can be inputted for each year the patient is in the model:

- HbA1c
- systolic blood pressure (SBP)
- total: HDL cholesterol
- smoking status.

All the inputs are used to estimate first occurrence of each of seven diabetes-related complications:

1. fatal or non-fatal MI
2. other IHD
3. stroke
4. heart failure
5. amputation
6. renal failure
7. eye disease.

The outcomes of the model are:

- life expectancy
- quality adjusted life expectancy
- costs
- cumulative event rate of all seven complications.

Quality adjusted life expectancy attaches a utility to each life year gained by effective treatment. A utility score of 1 is given to perfect health, and 0 to death. So a treatment, which extends the life of a person with diabetes by 4 years and gives perfect quality of life (4 yrs x 1) results in 4 quality adjusted life years (QALYs). A treatment that extends that person's life by 5 years but does not improve their quality of life (if people with diabetes give their quality of life a utility score of 0.8, due to pain etc) may result in the same number of QALYs (5 yrs x 0.8=4 QALYs).

C.1.1 UKPDS population

Table C1 Baseline characteristic of patients from the UKPDS

Demographic	Number of patients (N=3,867)
Age in years – mean (SD)	53.3 (8.6)
Male/female	2359/1508 (61%/39%)
Ethnicity (%) Caucasian/Indian Asian/African-Caribbean/other	81/10/8/1
Clinical	
Weight in kg – mean (SD)	77.5 (15.5)
BMI – mean (SD)	27.5 (5.2)
Systolic blood pressure (mmHg) – mean (SD)	135 (20)
Diastolic blood pressure (mmHg) – mean (SD)	82 (10)
Smoking (%) never/ex/current	34/35/31
Alcohol (%) none/social/regular/dependent	22/56/18/1
Exercise (%) sedentary/moderately active/active/fit	20/35/40/5
Biochemical	
FPG (mmol/l) – median (IQR)	8.0 (7.1–9.7)
HbA_{1c} (%) – mean (SD)	7.08 (1.51)
Plasma insulin (pmol/l) – geometric mean (±1SD)	92 (52–160)
Triglyceride (mmol/l) – geometric mean (±1SD)	2.35 (0.84–6.55)
Total cholesterol (mmol/l) – mean (SD)	5.4 (1.1)
LDL-cholesterol (mmol/l) – mean (SD)	3.5 (1.0)
HDL-cholesterol (mmol/l) – mean (SD)	1.07 (0.24)

Costs

A cost analysis was conducted alongside the UKPDS.402 All patients attended clinics every 3 or 4 months for the duration of the study. At each visit they were assessed to determine the occurrence of any clinical events or hospital episodes since the previous visit. Where an inpatient stay had occurred, details were obtained from the relevant hospital of dates of admission and discharge, reasons for admission, and any major procedures undertaken. Within the cost analysis, the cost of each episode of hospitalisation was estimated by multiplying the length of stay by the average cost of the respective specialty, based on an average of the Department of Health's (DH) National Health Service (NHS) Trust Financial returns for 1997/8 and 1998/9. We have updated the costs to 2004 prices in the model using the Hospital and Health Services Price Index.[403]

Information on non-inpatient healthcare resources was obtained using a cross-sectional survey of 3,488 UKPDS patients conducted between January 1996 and September 1997. A questionnaire was distributed at clinic visits or by post to patients who did not attend clinics during the survey period. This survey recorded information on all home, clinic and telephone contacts with general practitioners, nurses, podiatrists, opticians and dieticians, and with eye and other hospital outpatient clinics over the 4 months prior to the survey.[402]

It was assumed that patient characteristics and complications had a multiplicative effect on costs.

The results of this cost analysis represented an estimate of the increase in all healthcare costs in the year in which the complication occurs. The hospital inpatient costs reported for a non-fatal stroke would capture any inpatient stays directly associated with the stroke, but also the potential indirect impact of the stroke, e.g. on lengths of inpatient stay for other conditions.

Table C2 Costs used for complications in UKPDS model, 2004

Complication	Cost in year of event (£)		Cost in subsequent years (£)
	Fatal	Non-fatal	
IHD		2,696	891
MI	1,366	5,199	856
Heart failure	3,007	3,007	1,054
Stroke	4,011	3,180	601
Amputation	10,354	10,354	598
Blindness	–	1,358	575
Renal failure	30,000	30,000	30,000
Cost in absence of complications			374

Utilities

EuroQol EQ-5D (EQ-5D) data from 3,192 UKPDS patients in 1996 was used to measure the impact of diabetic complications on quality of life. It was assumed that multiple complications would have an additive effect on utility.[33]

Table C3 Utility decrements used in UKPDS

Complication	Utility in year of event	Utility in subsequent years
IHD	–0.090	–0.090
MI	–0.055	–0.055
Heart failure	–0.108	–0.108
Stroke	-0.164	–0.164
Amputation	–0.280	–0.280
Blindness	–0.074	–0.074
Renal failure	–0.263	–0.263
Initial utility	0.785	

Limitations

Limitations of the UKPDS outcomes model were identified by the authors. Only the first event is predicted in any single category of diabetes-related complications. Multiple events in the UKPDS were relatively infrequent and subsequent fatal events in specific categories of diabetes- related complications were included in the diabetes-related mortality equation.[401]

Not all relevant complications are included in the model; peripheral neuropathy and ulceration were not included as major endpoints in the UKPDS and so could not be easily incorporated as outcomes in the model. Hypoglycaemia and hyperglycaemia were also excluded.[401]

Some of the complications are represented in the model using a single state, e.g. the only state representing eye disease in the model is the endpoint of blindness in one eye. This is unlikely to fully describe the complex process of disease progression.[401]

Limitations in the costing study identified were that the UKPDS patients were newly diagnosed and tended to be younger than people with Type 2 diabetes in the general population and the costs reported may not reflect the resource use associated with complications of some older patients in the general population.[402] The inpatient costs were based on clinical practice in the UK from 1977 to 1997, although treatment protocols may have changed, for example coronary stents are increasingly used in the treatment of patients with IHD.

Aims of analysis

The standard pathway of pharmacological treatment used in this model for a person with Type 2 diabetes is to start with metformin (unless intolerant or contraindicated) which has been shown to be cost-saving compared to conventional therapy primarily of dietary changes.[33,34] After metformin the next step is to add a sulfonylurea, which was also shown to be cost effective as a monotherapy compared to conventional therapy.[33]

Uncertainty arises in the third-line therapy. There are a number of insulins available in different forms, which work in different ways. Alternatively patients could be given a glitazone (rosiglitazone or pioglitazone) or the newly licensed exenatide. Sitagliptin and vildagliptin will not be covered in this guideline and so have not been included in this analysis.

The aim of this analysis is to determine what the third-line therapy should be, given the following options:

- human insulin – neutral protamine Hagedorn (NPH) or a premix of NPH/regular 30/70
- biphasic analogues (either lispro or aspart) – twice daily
- insulin glargine – once daily
- glitazones (pioglitazone and rosiglitazone)
- exenatide

The perspective of the analysis was that of the NHS. This includes direct costs to the NHS, not to the patients or their carers.

A cost-utility analysis was conducted with an outcome of cost per QALY gained.

Population

The following characteristics for the population were based on expert opinion agreed among the GDG as the UKPDS population characteristics were not thought to reflect the current characteristics of people with diabetes at the point at which third-line therapy was being considered.

Table C4 Population characteristics for a hypothetical Type 2 diabetes population at the point of choosing a third-line therapy

Characteristic	Base case	Range for sensitivity analyses
Age	58 yrs	+10 yrs
Duration of diabetes	5 yrs	+5 yrs
HbA_{1c}	7.5%	
BMI (kg/m^2)	30.42*	±3 kg/m^2
SBP	140 mmHg	±10 mmHg
Total cholesterol	4.4 mmol/l	±0.6mmol/l
HDL cholesterol	1 mmol/l	

* UKPDS inputs are height and weight (1.72 m and 90 kg were used)

The SBP, total cholesterol, HDL cholesterol and HbA1c were set to be the same at diagnosis as for current values. It was assumed that at diagnosis of diabetes people had no history of atrial fibrillation or peripheral vascular disease, and they were non-smokers.

A recent study by Calvert et al. 2007[404] used data from 154 general practices in the UK between 1995 and 2005, which included 14,824 people with Type 2 diabetes. Patients' characteristics were as follows:

- mean age of 64.2 years (12.5 yrs)
- mean BMI of 30.1 kg/m2 (SD 6.8 kg/m^2)
- median time from initiation of the last oral agent to insulin for patients prescribed two or more types of oral agents concurrently was 7.7 years (95% CI=7.4 to 8.5 yrs)
- mean HbA1c prior to insulin was 9.85% (SD 1.96%).

These population characteristics were used in a sensitivity analysis as the Calvert et al. paper was identified after the main analysis had been conducted.

Discounting

Both costs and benefits were discounted by 3.5% for the first 30 years, and after 30 years by 3%. The discount rate reflects that people prefer to receive a benefit earlier and to incur a cost later, even in a world with zero inflation and no bank interest.[181]

Time horizon

The model was run for 40 years to capture a lifespan time horizon. The costs were applied for 40 years as people with diabetes are likely to need treatment for the rest of their lives. As the clinical evidence available was for a maximum of 2 years, it seems likely that the benefits of treatment would persist for some time beyond this. As a conservative estimate, we assumed that treatment effects would persist for 3 years in the base case model (e.g. where a treatment reduced HbA1c, HbA1c would be reduced in each of the first 3 years of treatment when this reduction was assumed to stop). The median time from initiation of the last oral agent to insulin was 7.7 years in the study by Calvert et al. 2007[404] (see above for description of this study). This suggests that the treatment effect from third-line therapy might last for longer than 3 years. After the initial 3 years, the model was run with no additional

treatment effect, HbA1c would therefore gradually increase over time. The duration of effect was tested in a sensitivity analysis.

Treatments included

Meta-analysis was conducted where more than one study was available for a comparison. The following comparisons were found in published papers:

- biphasic analogue vs human insulin: 6 studies, total N=1,001 [182,183,186–189]
- glargine vs human insulin: 2 studies, total N=591 [196,199]
- biphasic analogue vs glargine: 3 studies, total N=435 [198,201,202]
- glargine vs rosiglitazone: 1 study, N=216 [139]
- rosiglitazone vs pioglitazone: 1 study, N=91 [133]
- exenatide vs glargine: 1 study, N=549 [405]
- exenatide vs biphasic analogue: 1 study, N=501. [405]

After oral antidiabetics, the next option was human insulin premix or NPH (personal communication, Philip Home 2 April 2007). It was not felt that the choice between NPH or human insulin premix was a question that would need to be addressed by this analysis. As human insulin premix could include NPH, the studies with NPH as a comparator were combined with the human insulin premix studies to give the baseline treatment.

A random effect MA was used for glargine vs human premix comparisons.[196,199]

Human premix was used as the baseline. Direct evidence from good-quality RCTs is considered the gold standard. As there were no studies which had all comparators, a simple indirect comparison was carried out using the results of a meta-analysis by adding weighted mean differences in the treatment effects.

Insulins (human, biphasic analogue, insulin glargine)

See figure C1 for the meta-analysis results.

None of the papers included treatment effect on SBP or lipid profiles. It was assumed in the base case that there was no difference in these outcomes between the insulins.[406]

A meta-analysis was identified by Rosenstock et al.[194] which found that there was no difference in the level of HbA1c reduction between insulin glargine and NPH insulin. The results of this meta-analysis were used in a sensitivity analysis, it was assumed that the change in HbA1c for insulin glargine would be equal to that for human insulin in the sensitivity analysis.

It was not possible to include all the treatment effects associated with the drugs evaluated using the UKPDS model. Hypoglycaemic events are included in the UKPDS model based on those observed but it was not possible to change the RR of events occurring for different treatments. A simple sensitivity analysis was conducted with an increased quality of life for patients receiving glargine, which is associated with decreased hypoglycaemic events. Only one paper reviewed for clinical evidence reported the number of hypoglycaemic events.[213]

Table C5 Hypoglycaemic events per patient year, insulin glargine vs NPH

	Glargine	NPH	Difference
All symptomatic events	13.9	17.7	3.8
Confirmed events ≤72 mg/dl	9.2	12.9	3.7
Confirmed events ≤56 mg/dl (severe)	3.0	5.1	2.1

In the long-acting insulin technology appraisal (TA)[193] a utility decrement of 0.15 was applied to each day in a severe hypoglycaemic event which was assumed to last for 4 days each (0.0016 QALY loss per severe event). It was assumed that insulin glargine avoided three episodes of symptomatic hypoglycaemia per person per year, and no reduction in HbA1c levels compared to NPH insulin they also applied a utility decrement to represent fear of hypoglycaemia, although this information was submitted as 'commercial in confidence'. The TA analysis was updated by the TA group with new evidence on the utility associated with hypoglycaemic events, and 0.0052 was applied to each hypoglycaemic event avoided.[407] The cost of a severe hypoglycaemic event was £218.34. This gave a cost-effectiveness ratio of £32,508 compared to NPH insulin, using the price of a vial of glargine. Using cartridges or pens gave higher cost- effectiveness ratios, £41,236 and £43,411 respectively. The results were most sensitive to the assumption on utility gained from reducing fear of hypoglycaemia. If it was assumed that there was no utility gain from this, then the cost-effectiveness ratio rose to approximately £10million per QALY.

Review: Insulins in Type 2 diabetes
Comparison: 01 Biphasic vs human
Outcome: 01 HbA_{1c}

Study or sub-category	N	Biphasic mean (SD)	N	Human mean (SD)	WMD (fixed) 95% CI	Weight (%)	WMD (fixed) 95% CI	Quality
Boehm 2002	85	-0.13(0.73)	102	-0.13(0.80)		28.32	0.00 [-0.22, 0.22]	D
Christiansen 2003	201	-0.67(1.00)	202	-0.61(1.00)		35.79	-0.06 [-0.26, 0.14]	D
Kilo 2003	46	-1.30(1.00)	47	-1.10(1.00)		8.26	-0.20 [-0.61, 0.21]	D
Boehm 2004	58	0.24(1.00)	67	-0.09(1.00)		11.04	0.33 [-0.02, 0.68]	D
Schernthaner 2004	18	-0.80(1.10)	17	-0.30(1.10)		2.57	-0.50 [-1.23, 0.23]	D
Abrahamian 2005	80	-2.20(1.00)	78	-2.15(1.00)		14.03	-0.05 [-0.36, 0.26]	D
Total (95% CI)	488		513			100.00	-0.02 [-0.14, 0.10]	

Test for heterogeneity: Chi^2=6.45, df=5 (p=0.26), I^2=22.5%
Test for overall effect: Z=0.36 (p=0.72)

-1 -0.5 0 0.5 1
Favours biphasic Favours human

Review: Insulins in Type 2 diabetes
Comparison: 02 Glargine vs human
Outcome: 01 HbA_{1c}

Study or sub-category	N	Glargine mean (SD)	N	Human mean (SD)	WMD (random) 95% CI	Weight (%)	WMD (random) 95% CI	Quality
Eliaschewitz 2006	231	-1.38(1.32)	250	-1.44(1.33)		71.57	0.06 [-0.18, 0.30]	D
Yki 2006	61	7.14(1.00)	49	7.16(1.00)		28.43	-0.02 [-0.40, 0.36]	D
Total (95% CI)	292		299			100.00	0.04 [-0.16, 0.24]	

Test for heterogeneity: Chi^2=0.12, df=1 (p=0.72), I^2=0%
Test for overall effect: Z=0.36 (p=0.72)

-1 -0.5 0 0.5 1
Favours glargine Favours human

Review: Insulins in Type 2 diabetes
Comparison: 03 Biphasic vs glargine
Outcome: 01 HbA_{1c}

Study or sub-category	N	Biphasic mean (SD)	N	Glargine mean (SD)	WMD (fixed) 95% CI	Weight (%)	WMD (fixed) 95% CI	Quality
Malone 2004	52	-1.30(1.00)	53	-0.90(0.90)		0.59	-0.40 [-0.76, -0.04]	D
Malone 2005	50	-1.00(0.85)	47	-0.42(0.92)		0.63	-0.58 [-0.93, -0.23]	D
Raskin 2005	117	-2.79(0.11)	116	-2.36(0.11)		98.77	-0.43 [-0.46, -0.40]	D
Total (95% CI)	219		216			100.00	-0.43 [-0.46, -0.40]	

Test for heterogeneity: Chi^2=0.72, df=2 (p=0.70), I^2=0%
Test for overall effect: Z=30.07 (p<0.00001)

-1 -0.5 0 0.5 1
Favours biphasic Favours glargine

Figure C1 Meta-analysis

A recent study of utility related to fear of hypoglycaemia used pooled data from two postal surveys of subjects with confirmed diabetes (both Type 1 and Type 2), (N=1,305 responses), conducted in the UK.[408] The Hypoglycaemia Fear Survey (HFS) (values from 0 to 52, 0=least worry) and the EQ-5D were used to characterise the fear of hypoglycaemia. They found that each severe hypoglycaemic event resulted in a change of 5.881 units of the HFS and one or more symptomatic events resulted in a change of 1.773 units on the HFS. They found that a 1-unit decrease on the HFS resulted in a 0.008 unit decrease on the EQ-5D.

Table C6 Utility increments associated with avoiding hypoglycaemic events

	HFS score[408]	EQ5D score for fear of hypoglycaemic events avoided (applied to whole year)	EQ5D score for hypoglycaemic event avoided[193]	Total utility increment from hypoglycaemic events over a year
Severe hypoglycaemic event	5.881	0.047	0.0016	0.05
Symptomatic hypoglycaemic event	1.773	0.014		0.014

Based on the Riddle et al. study[213] it was assumed that there would be 2.1 severe hypoglycaemic events per person per year and 3.7 non-severe symptomatic events. For each day in a severe hypoglycaemic event, we assumed a utility loss of 0.15 directly due to the symptoms for 4 days. In addition, we assumed a utility loss due to fear of hypoglycaemia of 0.047 and 0.014 respectively with severe and symptomatic events applied over the year. This gave an estimated QALY gain of 0.064 per year due to avoided hypoglycaemic events for each person treated with glargine rather than other insulins. Additionally using the updated TA evidence, a 0.52% reduction in utility per severe hypoglycaemic event was tested (0.0052 x 2.1 events=0.011 utility increased over a year treated with glargine).

Glitazones

Most studies examining the glitazones were placebo controlled. As the glitazones have only recently gained the license for triple therapy, there were very few studies available that had suitable comparators. One study was available that compared rosiglitazone (4 mg/day) to insulin glargine (10 IU).[139] Another study compared pioglitazone (15 mg/day) to rosiglitazone (4 mg/day).[133]

Table C7 Rosiglitazone compared to glargine in a 24-week study. Percentage changes from baseline

	Rosiglitazone	Glargine
HbA_{1c} (%)	–1.51	–1.66
TC (%)	10.1	–4.4
HDL (%)	4.4	0

Table C8 Rosiglitazone compared to pioglitazone in a 12-month study

	Rosiglitazone	Pioglitazone
Baseline HbA_{1c} %	8.1	8.20
12-month HbA_{1c} change	–1.3	–1.40
lower	–0.8	–1.10
upper	–1.8	–1.70
Baseline TC mmol/l	4.92	5.03
12-month TC	0.21	–0.50
lower	0.83	–0.01
upper	–0.41	–0.99
Baseline HDL mmol/l	1.09	1.14
12-month HDL mmol/l	–0.03	0.1
lower	–0.16	–0.06
upper	0.1	0.26

Exenatide

The GWAD[166] compared exenatide (10 µg BID) to biphasic insulin aspart 30/70 (BiAsp) twice daily over 52 weeks. The inputs for change in the ratio of total cholesterol to HDL for the model are reported in tables C53–55 at the end of the appendix. The population included in this study had maximised their treatment on metformin and sulfonylurea treatment but were unable to achieve optimal blood glucose levels, and would normally begin insulin treatment.[164,166,405] The whole intent-to-treat (ITT) population was used to estimate the unadjusted treatment effects in the industry-submitted economic analysis. It was reported that this would ensure consistency across the endpoints. This assumption led to a less favourable change in HbA1c for exenatide.[405] The inputs for change in the ratio of total cholesterol to HDL for the model are reported in tables C53–55 at the end of the appendix.

Table C9 Treatment effects from clinical trial data – changes from baseline to 52 weeks. Data are unadjusted means based on whole ITT population

	Exenatide		Biphasic insulin aspart	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Change in HbA_{1c} %	–0.97 (1.25)	–1.13, –0.81	–0.88 (1.05)	–1.01, –0.75
Change in SBP mmHg	–4.85 (11.15)	–6.73, –2.97	1.37 (15.60)	–0.58, 3.32
Change in triglycerides (mg/dl)	–1.77 (135.51)	–18.61, 12.40	2.66 (99.2)	–9.75, 15.96
Change in BMI (kg/m^2)	–0.83 (1.19)	–0.93, –0.66	0.98 (1.21)	0.83, 1.13
All hypoglycaemia**	4.63		5.24	

*The population characteristics are reported at the end of this appendix (C56)
**Events per patient year

A total of 33.2% of exenatide patients and 0.4% of BiAsp patients reported nausea during the study period. The nausea was generally mild/moderate and transient in nature and only a small proportion of patients (4%) withdrew from the study due to nausea, 40–50% of patients reported at least one episode of nausea.[405]

The GWAA[164] study compared exenatide (10 µg BID) treatment to insulin treatment; insulin glargine once daily over 26 weeks (table C10).

Table C10 Unadjusted* treatment effects taken from the clinical trial data reflecting changes from baseline to 26 weeks

	Exenatide		Insulin glargine	
	Mean (SD)	95% CI	Mean (SD)	95% CI
Change in HbA_{1c} %	–0.99	–1.11, –0.87	–1.07	–1.19, –0.96
Change in SBP mmHg	–4.15	–6.24, –2.06	–0.57	–2.49, 1.36
Change in triglycerides (mg/dl)	–15.04	–28.34, –1.77	–30.08	–46.06, –13.29
Change in BMI (kg/m^2)	–0.80	–0.93, –0.66	0.55	0.42, 0.68
All hypoglycaemia**	6.94		5.84	

* The results are for the whole ITT population. The population characteristics are reported at the end of this appendix in table C57
** Events per patient year

The EQ5D was given at baseline and at the 26-week endpoint in the trial with insulin glargine as a comparator. Although the data showed a significant improvement in quality of life for both treatment groups, there was no significant difference between the treatments (the mean differences were not reported in the SMC submission).405 As it was felt that more data were required as the clinical trial had demonstrated treatment differences which were felt to impact quality of life, more data were collected by a stakeholder. A study was carried out in 129 people with diabetes using an initial set of health states developed based on clinical trial data and clinical expertise (table C11). They used the standard gamble method using one-month durations for the health states compared to perfect health.[409]

The utility changes used in the industry basecase model were:

- exenatide
  - year 1=0.006
  - year 2=0.032 (this appears to be assuming 5% weight loss, and no nausea or hypoglycaemia)
- glargine:
  - year 1=–0.045
  - year 2=–0.065 (assuming 5% weight gain, and no nausea or hypoglycaemia)

The following description was provided as a comment during consultation by a stakeholder:

The health state utilities from the UK utility study were applied in the simulations according to the following assumptions, based on data from the GWAA clinical trial, with weight change referred to as a percentage change from baseline:

- exenatide
  - year 1: utility for 3% weight loss (mean baseline body weight=87.5 kg, mean weight change=–2.3 kg, a 3% reduction); 57.1% patients experienced nausea with exenatide (assumed to last for 6 months)

- exenatide
  - year 2: utilities for 5% weight loss (2 year clinical trial data show mean loss of –4.4 kg from a baseline weight of 99 kg). No patients assumed to experience nausea
- insulin glargine
  - year 1: utility for 3% weight gain (mean baseline body weight=88.3 kg, mean weight change=+1.8 kg, a 2% increase); 8.6% of patients experienced nausea (assumed to last for 6 months)
- insulin glargine
  - year 2: utility for 5% weight gain based on a review of weight gain with insulin therapy which found that weight continues to increase over time from insulin initiation with insulin-treated patients found to gain an average of 5% of their body weight during the first 2 years of treatment (UKPDS 24, 1998) in line with a recent review which shows an average weight gain of 4.9 kg after insulin initiation (Heller, 2004). From a baseline weight of 88.3 kg (GWAA) this equates to 5.5% weight gain. No patients were assumed to experience nausea.

From year 3 onwards, patients in both treatment groups would be assumed to have a disutility value of –0.0061 per unit difference in BMI over 25 (as per CODE-2 TTO) and no disutility for nausea.

Using the assumptions from above and the values from table C11, the resulting utility/disutility values for exenatide and insulin glargine in the GWAA model are therefore:

- exenatide
  - year 1: utility=57.1%* 0.5 (years)* G+57.1%* 0.5 (years)* I+42.9%* I=0.006
  - year 2: utility=100%* J=0.032
- insulin glargine
  - year 1: utility=8.6%* 0.5 (years)* C+8.6%* 0.5 (years)* E+91.4%* E=–0.045
  - year 2: utility=100%* F=–0.065

The utility/disutility values for exenatide and BiAsp in the GWAD model are based on similar patterns of short-term weight change for exenatide (mean baseline body weight=85.5 kg, mean change=–2.5 kg, 3% reduction and BiAsp (mean baseline body weight=83.4 kg, mean change=+2.9 kg, 3% gain) as in the GWAA base case analysis. As for the base case, year 2 weight change was assumed to be 5% loss for exenatide patients, 5% gain for BiAsp patients. The resulting treatment-related utility values are:

- exenatide
  - year 1: utility=33.2%* 0.5 (years)* G+33.2%* 0.5 (years)* I+42.9% *I=0.012
  - year 2: utility=100%* J=0.032
- biphasic insulin aspart
  - year 1: utility=0.4%* 0.5 (years)* C+0.4%* 0.5 (years)* E+99.6%* E=–0.044
  - year 2: utility=100%* F=–0.065

Table C11 Utility scores reported in the SMC submission for exenatide

Health states	Standard gamble adjusted		Difference from A	
	Mean	(SD)	Mean	(SD)
A: Basic HS* (current weight)	0.891	0.132		
B: Basis HS + nausea	0.848	0.158	–0.043	0.07
C: Basic HS + 3% higher weight, nausea	0.819	0.188	–0.073	0.1
D: Basic HS + 5% higher weight, nausea	0.796	0.211	–0.095	0.14
E: Basic HS + 3% higher weight, no nausea	0.847	0.177	–0.044	0.08
F: Basic HS + 5% higher weight, no nausea	0.827	0.190	–0.065	0.1
G: Basic HS + 3% lower weight, nausea	0.864	0.148	–0.028	0.09
H: Basic HS + 5% lower weight, nausea	0.881	0.128	–0.010	0.09
I: Basic HS + 3% lower weight, no nausea	0.912	0.110	0.020	0.07
J: Basic HS + 5% lower weight, no nausea	0.923	0.104	0.032	0.07
Own current health state	0.873	0.154		
Other health states				
K: Basic HS + rare hypoglycaemia	0.878	0.141	–0.014	0.04
L: Basic HS + sometimes hypoglycaemia	0.864	0.148	–0.027	0.06

*Basic health state (HS) refers to a basic Type 2 diabetes health state (description not included in the copy of the SMC submission sent to the NCC-CC)

Treatment inputs to model

Human insulin was the baseline treatment. The clinical evidence of human insulin compared to placebo (oral antidiabetic agents alone) was not reviewed in the guideline and so it was assumed that UKPDS observational data with no added treatment effect would approximate to human insulin, treatments in the UKPDS included metformin, sulfonylurea and insulin. The studies including insulins did not report changes in TC:HDL or SBP. The GDG agreed that this was because there would be no difference in TC:HDL or SBP with insulin therapies and that these did not need to be tested in a sensitivity analysis.

Table C12 Base case drug efficacy inputs

	Weighted mean difference % change in HbA_{1c}	Change in TC:HDL*	Change in SBP
Biphasic analogue vs human insulin	–0.02	0	0
Glargine vs human insulin	0.04	0	0
Glargine vs biphasic analogue	0.43	0	0
Exenatide vs glargine	0.08	–0.12	–3.58
Exenatide vs biphasic analogue	–0.09	0.1	–6.22
Rosiglitazone vs glargine	0.15	0.42	0
Pioglitazone vs rosiglitazone	–0.1	–1.08	0

* Calculations for the change in TC:HDL are shown in tables 52 to 54 at the end of this appendix. Conversion rate of mg/dl to mmol/l=0.0259.[410]

1

Table C13 Lower values for drug efficacy – using the difference between the worse 95% confidence limits for the treatment and the better 95% confidence limit for their comparator (for rosiglitazone vs glargine CIs were not reported and so it was assumed that there was no difference in change in HDL between the treatment, but the mean change in TC would remain the same)

	Weighted mean difference % change in HbA_{1c}	Change in TC:HDL	Change in SBP
Biphasic analogue vs human insulin	0.1	0	0
Glargine vs human insulin	0.24	0	0
Glargine vs biphasic analogue	0.46	0	0
Exenatide vs glargine	0.32	0.2	0.43
Exenatide vs biphasic analogue	0.2	0.42	–2.39
Rosiglitazone vs glargine	0.2	0.61	0
Rosiglitazone vs pioglitazone	0.7	0.96	0

2

Table C14 Upper values for drug efficacy – using the difference between lowest 95% confidence limits for the treatment compared to the highest 95% confidence limit for their comparator. Although the studies available for the glitazones did not report on change in SBP, it was thought that the glitazones may reduce SBP and so this was tested in this sensitivity analysis

	Weighted mean difference % change in HbA_{1c}	Change in TC:HDL	Change in SBP
Biphasic analogue vs human insulin	–0.14	0	0
Glargine vs human insulin	–0.16	0	0
Glargine vs biphasic analogue	0.4	0	0
Exenatide vs glargine	–0.15	–0.4	–7.6
Exenatide vs biphasic analogue	–0.38	–0.22	–10.05
Rosiglitazone vs glargine	0	–0.17	–3
Rosiglitazone vs pioglitazone	–0.9	–3.19	–3

Base case treatment pathway

The following diagram shows the comparisons available from the clinical evidence. All the treatments were compared to human insulin. For the analysis one pathway needs to be chosen from the available options for biphasic analogues, insulin glargine and exenatide. Rather than discard the other studies, different pathways were tested in the sensitivity analyses, these are listed below.

The weighted mean differences in treatments were added along the pathways, for example exenatide was not directly compared to human insulin in a RCT, it was compared to biphasic analogue insulin (weighted mean difference in HbA1c reduction –0.09%), and there were studies in which biphasic analogue was directly compared to human insulin (weighted mean difference in HbA1c reduction –0.02%), therefore making an indirect comparison gives a mean difference in HbA1c reduction between human insulin and exenatide of –0.11%).

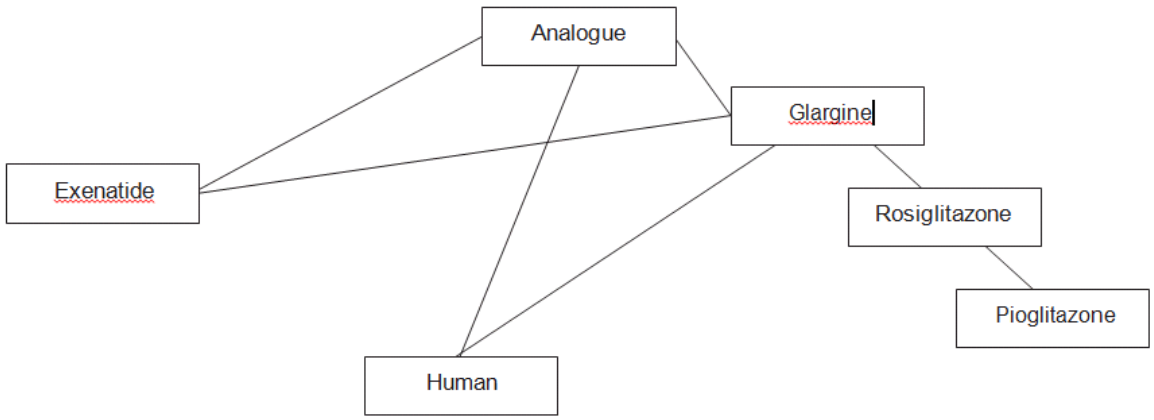

Figure C1 Human insulin vs biphasic analogue, biphasic analogue vs glargine, exenatide vs biphasic, rosiglitazone vs glargine, pioglitazone vs rosiglitazone

Sensitivity analysis

- Human insulin vs biphasic analogue, biphasic analogue vs glargine, exenatide vs glargine, rosiglitazone vs glargine, pioglitazone vs rosiglitazone
- Human insulin vs biphasic analogue, human insulin vs glargine, exenatide vs biphasic, rosiglitazone vs glargine, pioglitazone vs rosiglitazone
- Human insulin vs biphasic analogue, human insulin vs glargine, exenatide vs glargine, rosiglitazone vs glargine, pioglitazone vs rosiglitazone

The HTA on indirect comparisons by Glenny et al. (2005)[411] highlighted issues that would be of concern, these included methodological quality of the trials, the degree of comparability of the treatments, participants and protocols of the trials. All the trials included in the HTA indirect analysis were given a positive score by the HTA clinical reviewers, which ensure good methodological quality.

The comparability of the insulins and glitazones seems to be acceptable as their main effectiveness is on HbA1c levels. Exenatide has other effects, on lipid levels, SBP, and weight, which may mean the indirect comparisons are not appropriate. A sensitivity analysis with only treatment effects on HbA1c was carried out.

Studies from the Type 2 diabetes guideline and the update were quickly scanned to identify those which reported a change in HbA1c, or the baseline and endpoint HbA1c values. All studies that were given a positive score and reported the change in HbA1c results were included in a series of meta-analyses. The studies varied in size (35 to 549 participants), and in duration (12 weeks to 24 months). There may be bias in the measurement of outcomes or the efficacy of treatment may differ in subpopulations of patients, for example if patients are more severely affected, older or younger, or more compliant with treatment. None of the trials were highlighted for particularly different inclusion and exclusion criteria, and so it is assumed that the efficacy data can be generalised to the Type 2 diabetes population as a whole.[411]

The model was run with 10,000 iterations to take into account variability in the population, i.e. that people with Type 2 diabetes who have the same characteristics can experience different outcomes. Also the model was run with 100 bootstraps in order to give approximate CIs around the UKPDS outcomes.

Daily doses

Table C15 Mean and range of daily doses taken from available studies (not weighted)

	Mean dose	Lowest dose	Highest dose
Human insulin	50 IU	31 IU	70 IU
Biphasic analogue	56 IU	38 IU	79 IU
Glargine	46 IU	32 IU	68 IU
Rosiglitazone	8 mg	4 mg	
Pioglitazone	30 mg	15 mg	45 mg
Exenatide	20 µg		

Cost input to model

Table C16 Costs of drugs used in the model (taken from British National Formulary (BNF) March 2007; price for exenatide taken from SMC submission)

	Name (company)	Description	Price per pack (£)
Human insulin	Mixtard® 30 (Novo Nordisk)	30% soluble, 70% isophane, 100 units/ml, Mixtard 30 Penfill® cartridge (for Innovo® or Novopen® devices) 5x3 ml	20.08
	Insulatard® (Novo Nordisk)	Penfill® cartridge (for Innovo®, or Novopen® devices) 5x3 ml, 100 units/ml	20.08
Biphasic analogue	NovoMix®30 (NovoNordisk)	100 units/ml, 5x3 ml Penfill® cartridges for Novopen®	29.43
Insulin glargine	Lantus® (Aventis Pharma)	10 ml vial	26.00
		5x3 ml Lantus® OptiSet® prefilled disposable injection devices, 100 units/ml	39.00
Pioglitazone	Actos® (Takeda)	15 mg 28-tablet pack	24.74
		30 mg 28-tablet pack	33.54
		45 mg 28-tablet pack	36.96
Pioglitazone plus metformin	Competact®	15 mg pioglitazone/850 mg metformin 56-tablet pack	31.56
Rosiglitazone	Avandia® (GSK)	4 mg, 28-tablet pack	24.74
		4 mg, 56-tablet pack	49.48
		8 mg, 28-tablet pack	50.78
Rosiglitazone plus metformin	Avandamet®	2 mg rosiglitazone/500 mg metformin 112 tablets	52.45
		2 mg/1 g 56 tablets	27.71
		4 mg/1 g 56 tablets	52.45
Exenatide		60-dose (30-day) pen	68.24
Pens	NovoPen®		24.07
	OptiPen Pro 1®		22.00

Table C17 Costs of blood glucose monitoring (BNF March 2007)

	Mean (£)	Min (£)	Max (£)
Cost per strip	0.29	0.24	0.32
Cost of meter	16.91	5.63	35

It was decided by the GDG the following frequencies of blood glucose monitoring represented the average use:

- insulin glargine – one strip per day
- biphasic analogue and human – two strips per day
- exenatide and glitazones – three strips per week.

Table C18 Annual costs of blood glucose monitoring*

	Annual costs of strips		
	Mean (£)	Min (£)	Max (£)
Glargine	105.52	87.60	117.75
Biphasic analogue and human	211.04	175.20	235.50
Exenatide and glitazones	45.10	37.44	50.33

*Average blood glucose monitoring costs were included in the UKPDS costing analysis, so there will be some double counting in adding the annual costs shown in the table

Table C19 Annual costs of treatments

	Annual costs of drugs		
	Mean (£)	Min (lowest dose) (£)	Max (highest dose) (£)
Human insulin	245	152	342
Biphasic analogue	400	271	562
Glargine	434	307	645
Rosiglitazone	645	323	
Pioglitazone	437	315	
Exenatide	830	623*	

*75% of cost reported in the SMC submission

Results

NB; net benefit

Net benefit; (total QALYs x £30,000 – total cost
where £30,000 = NICE threshold for willingness-to-pay for one QALY (one year of life in perfect health).

Dominated; another drug is more effective and less expensive.

ED; extended dominance
A drug is more effective and more expensive, but if you use another more cost-effective drug you will get more health benefits for the same budget.

Using the base case inputs human insulin was the most cost-effective treatment for third-line therapy, either dominating the other options, or with the other options having very high incremental costs per QALYs (table C20).

Table C20 Base case analysis: drug costs and additional blood glucose monitoring costs

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.018	300	dominated
Glargine	8.00	21,467	–0.041	1,940	dominated
Biphasic analogue	8.05	23,033	0.004	3,505	ED
Rosiglitazone	7.94	24,978	–0.110	5,451	dominated
Exenatide	8.08	29,001	0.034	9,474	£280,495

Table C21 Net benefit results for the base case analysis

	Total QALYs	Total costs (£)	NB (£) (threshold £30,000)	NB (£) (threshold £20,000)
Human insulin	8.05	19,527	221,826	141,375
Pioglitazone	8.03	19,828	220,992	140,719
Glargine	8.00	21,467	218,649	138,610
Biphasic analogue	8.05	23,033	218,441	137,950
Rosiglitazone	7.94	24,978	213,080	133,72
Exenatide	8.08	29,001	213,365	132,577

Table C22 UKPDS model outcomes, mean and 95% confidence intervals

	Total QALYs	95% confidence intervals		Costs of complications* (£)	95% confidence intervals (£)	
		Lower	Upper		Lower	Upper
Human insulin	8.05	7.56	8.53	9,153	7,200	11,105
Pioglitazone	8.03	7.55	8.51	8,884	6,957	10,810
Glargine	8.00	7.53	8.48	9,215	7,269	11,162
Biphasic analogue	8.05	7.57	8.53	9,153	7,192	11,114
Rosiglitazone	7.94	7.47	8.40	9,326	7,375	11,278
Exenatide	8.08	7.60	8.55	9,152	7,235	11,070

* Treatment costs are not included, they were added on to the cost outcomes of the UKPDS

Sensitivity analysis

These analyses involve changing one characteristic of the base case population at a time. Human insulin remained the most cost effective option for third line therapy when the population characteristics were changed. For people with high systolic blood pressure or high cholesterol levels, pioglitazone was cost effective at £12,184 and £16,139 per QALY respectively.

Table C23 68-year-old patient

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	5.52	17,089			
Pioglitazone	5.51	17,524	–0.010	436	dominated
Glargine	5.47	18,922	–0.050	1,833	dominated
Biphasic analogue	5.52	20,600	–0.003	3,511	dominated
Rosiglitazone	5.40	22,385	–0.119	5,297	dominated
Exenatide	5.58	26,430	0.061	9,341	£152,770

Table C24 10-year diabetes duration

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	6.55	17,880			
Pioglitazone	6.55	18,416	0.008	535	£65,963
Glargine	6.48	19,730	–0.077	1,314	dominated
Biphasic analogue	6.55	21,385	–0.003	2,970	dominated
Rosiglitazone	6.40	23,191	–0.153	4,775	dominated
Exenatide	6.59	26,970	0.032	8,554	£268,091

Table C25 Body mass index 33 kg/m^2

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.01	19,746			
Pioglitazone	7.97	20,123	–0.034	377	dominated
Glargine	7.96	21,611	–0.052	1,865	dominated
Biphasic analogue	8.01	23,241	–0.001	3,496	dominated
Rosiglitazone	7.89	25,045	–0.118	5,299	dominated
Exenatide	8.05	29,167	0.038	9,421	£246,497

1

Table C26 Body mass index 27 kg/m^2

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.07	19,440			
Pioglitazone	8.07	19,964	–0.000	523	dominated
Glargine	8.04	21,428	–0.025	1,988	dominated
Biphasic analogue	8.07	22,954	0.002	3,514	ED
Rosiglitazone	7.98	24,958	–0.086	5,518	dominated
Exenatide	8.13	28,975	0.064	9,535	£149,868

2

Table C27 SBP 130 mmHg

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.12	19,247			
Pioglitazone	8.12	19,602	0.003	355	£117,468
Glargine	8.09	21,033	–0.030	1,431	dominated
Biphasic analogue	8.12	22,714	–0.004	3,112	dominated
Rosiglitazone	8.03	24,520	–0.085	4,918	dominated
Exenatide	8.13	28,679	0.012	9,077	£741,145

3

Table C28 SBP 150 mmHg

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	7.87	20,372			
Pioglitazone	7.91	20,863	0.040	491	£12,184
Glargine	7.83	22,198	–0.074	1,335	dominated
Biphasic analogue	7.87	23,894	–0.035	3,031	dominated
Rosiglitazone	7.77	25,603	–0.136	4,740	dominated
Exenatide	8.00	29,201	0.089	8,338	£94,111

1

Table C29 Total cholesterol 5 mmol/l

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	7.93	19,795			
Pioglitazone	7.95	20,264	0.029	468	£16,139
Glargine	7.88	21,815	–0.075	1,551	dominated
Biphasic analogue	7.93	23,282	–0.026	3,018	dominated
Rosiglitazone	7.85	25,137	–0.105	4,873	dominated
Exenatide	8.02	28,856	0.069	8,592	£123,875

2

Table C30 Total cholesterol 3.8 mmol/l

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.10	19,551			
Pioglitazone	8.13	19,972	0.034	421	£12,386
Glargine	8.06	21,503	–0.072	1,531	dominated
Biphasic analogue	8.10	23,003	–0.032	3,031	dominated
Rosiglitazone	8.04	25,071	–0.092	5,099	dominated
Exenatide	8.16	28,999	0.024	9,027	£372,421

3

Table C31 Alternative characteristics taken from Calvert et al. 2007[404]

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	4.05	15,754			
Pioglitazone	4.06	16,283	0.01	529	£54,719
Glargine	3.99	17,754	–0.06	1,471	dominated
Biphasic analogue	4.05	19,260	–0.01	2,978	dominated
Rosiglitazone	3.94	21,180	–0.12	4,897	dominated
Exenatide	4.08	24,966	0.02	8,683	£370,580

Clinical inputs

Table C32 It is assumed that the insulin glargine and human insulin have the same efficacy as reported in the Rosenstock et al. meta-analysis[134]

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	8.05	21,467	0.00	1,940	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	ED
Rosiglitazone	7.94	24,978	–0.11	5,451	dominated
Exenatide	8.08	29,001	0.03	9,474	£280,495

Increasing the initial utility for patients on glargine as a simple estimation of the effects of glargine on hypoglycaemic events had no effect on the ranking of the results. Assuming an additional gain of 0.065 due to reduced hypoglycaemic events and reduced fear of hypoglycaemia over the three years of treatment effect, and a reduction in costs by £1,300 for 2.1 severe events avoided per year for 3 years, the estimated cost per QALY for glargine was £4,352.

Table C33 Initial QALY gain for glargine increased by 0.065 for 3 years to represent increased quality of life due to fewer hypoglycaemic events and reduced fear of hypoglycaemia

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	8.19	20,167	0.15	639	£4,352
Biphasic analogue	8.05	23,033	–0.14	2,866	dominated
Rosiglitazone	7.94	24,978	–0.26	4,811	dominated
Exenatide	8.08	29,001	–0.11	8,834	dominated

Table C34 Utility for glargine increased by 0.011 for 3 years to represent increased quality of life due to fewer hypoglycaemic events using an increase of 0.52% per severe hypoglycaemic event avoided

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	8.04	20,167	–0.01	639	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	ED
Rosiglitazone	7.94	24,978	–0.11	5,451	dominated
Exenatide	8.08	29,001	0.03	9,474	£280,495

It was not possible to include changes in weight in the model. As exenatide was associated with weight reduction and this is considered an important benefit, a sensitivity analysis was conducted in which the patients receiving exenatide were given a lower BMI than other patients to allow for the health and quality of life benefits associated with a lower weight. These results include additional benefits for exenatide from avoided microvascular and macrovascular events estimated to result from an initial 3 kg/m^2 reduction in BMI. It can be seen that this does not change the results, as the incremental cost-effectiveness ratio for exenatide compared with the next best alternative (human insulin) remains over £100,000 per QALY.

Table C35 Exenatide patients with a body mass index of 27 kg/m^2 compared to a 30 kg/m^2 for people treated with other treatments

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	8.00	21,467	–0.04	1,940	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	ED
Rosiglitazone	7.94	24,978	–0.11	5,451	dominated
Exenatide	8.13	28,975	0.08	9,448	£111,784

Further sensitivity analyses were conducted assuming additional utility benefits for exenatide based on the survey results in table C8 above. Although the cost effectiveness of exenatide was reduced to £29,865 if exenatide use resulted in a weight loss with no nausea.

Table C36 Exenatide patients with a BMI of 27 kg/m^2 (exenatide results in a 0.016 utility increase due to 3% weight loss, and nausea compared to 3% increased weight gain and no nausea in other treatments applied for first 3 yrs), compared to a BMI 33 kg/m^2

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.01	19,746			
Pioglitazone	7.97	20,123	–0.03	377	dominated
Glargine	7.96	21,611	–0.05	1,865	dominated
Biphasic analogue	8.01	23,241	0.00	3,496	dominated
Rosiglitazone	7.89	25,045	–0.12	5,299	dominated
Exenatide	8.18	28,975	0.17	9,230	£54,550

Table C37 Exenatide patients with a BMI of 27 kg/m^2 (utility gain of 0.064 due to 3% weight loss on exenatide, no nausea, compared to weight gain for other treatments), compared to a 33 kg/m^2

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.01	19,746			
Pioglitazone	7.97	20,123	–0.03	377	dominated
Glargine	7.96	21,611	–0.05	1,865	dominated
Biphasic analogue	8.01	23,241	0.00	3,496	dominated
Rosiglitazone	7.89	25,045	–0.12	5,299	dominated
Exenatide	8.32	28,975	0.31	9,230	£29,865

When the clinical evidence was presented for exenatide, the doses for the insulins were questioned as the GDG thought they were lower than would normally be given. Lower treatment efficacy was used to investigate if the reported results may overestimate the effectiveness of exenatide. As can be seen in table 39, a 0.29% reduction in the weighted mean difference for exenatide compared with biphasic analogue insulin (HbA1c levels would increased by 0.2% compared to analogue insulin) led to a large increase in its estimated cost per QALY compared with the next best alternative (biphasic analogue insulin).

Table C38 Lower treatment efficacy on HbA_{1c} levels for exenatide patients

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	8.00	21,467	–0.04	1,940	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	£872,187
Rosiglitazone	7.94	24,978	–0.11	1,945	dominated
Exenatide	8.03	29,001	–0.02	5,968	dominated

It was highlighted by the GDG that exenatide would be an option for overweight or obese patients who would have to take large doses of insulins. No clinical evidence was available in this specific subgroup and so it was assumed the treatment efficacy was the same as reported in the studies available. The following sensitivity analysis compares the costs of the highest insulin dose reported in the studies available (70 IU per day) and higher monitoring costs with the mean doses of exenatide and glitazones. As no clinical evidence was available it is unknown whether patients who would require higher insulin doses would also require higher exenatide or glitazone doses to maintain their HbA1c levels.

Table C39 Maximum daily dose of insulin to represent the doses given to overweight people with Type 2 diabetes (BMI 33 kg/m^2)

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Pioglitazone	7.97	20,123			
Human insulin	8.01	22,514	0.03	2,392	£70,163
Rosiglitazone	7.89	25,045	–0.12	2,531	dominated
Biphasic analogue	8.01	27,492	–0.00	4,977	dominated
Glargine	7.96	26,704	–0.05	4,190	dominated
Exenatide	8.05	29,167	0.04	6,652	£174,053

Recent publications have highlighted increased risks with the glitazones for cardiac outcomes. Details of these studies can be found in the clinical evidence (chapter 10). A study comparing pioglitazone to placebo in 2,445 patients with Type 2 diabetes and previous MI reported that the incidence of CHF was significantly higher in patients receiving pioglitazone (13.5 vs 9.6%; p=0.003). The incidence of serious CHF (requiring hospitalisation) was also significantly higher in the pioglitazone group (7.5% vs 5.2%; p=0.022).[150]

In a study comparing rosiglitazone in combination with metformin or sulfonylurea, compared to metformin in combination with sulfonylurea, patients in the rosiglitazone group had a significantly higher risk of CHF than patients did in the control group, with 38 versus 17 adjudicated events (hazard ratio, 2.24; 95% CI 1.27 to 3.97).[116] In a study comparing the rosiglitazone to a control group the odds ratio for MI was 1.43 in the rosiglitazone group (95% CI 1.03 to 1.98; p=0.03).[115]

It is not possible to change the RR for cardiac events in the UKPDS, but as an indirect indication of the potential sensitivity of the results to uncertainty over the cardiac risk associated with glitazones, we investigated in the impact of hypothetical differences in SBP between the insulins and glitazones (tables 41 and 42). Human insulin remained the most cost- effective option.

Table C40 An initial SBP of 150 mmHg for people taking glitazones compared to 140 mmHg for people taking other treatments

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	7.83	20,890	–0.21	1,363	dominated
Glargine	8.00	21,467	–0.04	1,940	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	ED
Rosiglitazone	7.77	25,603	–0.27	6,076	dominated
Exenatide	8.08	29,001	0.03	9,474	£280,495

Table C41 Reducing SBP by 3 mmHg for people taking insulin

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,514			
Pioglitazone	8.03	19,828	–0.02	313	dominated
Glargine	8.02	21,351	–0.03	1,836	dominated
Biphasic analogue	8.05	23,019	0.00	3,505	ED
Rosiglitazone	7.94	24,978	–0.12	5,463	dominated
Exenatide	8.08	29,001	0.03	9,486	£337,888

Indirect comparisons – sensitivity analysis

As there were studies available that had different comparators which could not be grouped together in a meta-analysis, it was important to test whether using different pathways for the comparisons would affect the results. Using the different indirect comparison results did not change the results and human insulin remained the most cost-effective option for third-line therapy.

Table C42 Human premix vs biphasic analogue, biphasic analogue vs glargine, exenatide vs glargine, rosiglitazone vs glargine, pioglitazone vs rosiglitazone

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	8.00	21,467	–0.04	1,940	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	£872,187
Rosiglitazone	7.94	24,978	–0.11	5,451	dominated
Exenatide	8.03	28,900	–0.01	9,373	dominated

1

Table C43 Human premix vs biphasic analogue, human premix vs glargine, exenatide vs biphasic, rosiglitazone vs glargine, pioglitazone vs rosiglitazone

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.06	20,041	0.02	513	£30,708
Glargine	8.04	21,405	–0.02	1,364	dominated
Biphasic analogue	8.05	23,033	–0.01	2,992	dominated
Rosiglitazone	7.99	24,989	–0.07	4,948	dominate
Exenatide	8.05	28,948	–0.01	8,907	dominated

2

Table C44 Human premix vs biphasic analogue, human premix vs glargine, exenatide vs glargine, rosiglitazone vs glargine, pioglitazone vs rosiglitazone

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	8.04	21,405	–0.01	1,877	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	ED
Rosiglitazone	7.94	24,978	–0.11	5,451	dominated
Exenatide	8.08	29,001	0.03	9,474	£280,495

3

4 **Time horizon**

5 The baseline assumption for the treatment effects was fairly conservative, only assuming the
6 treatment effects would be seen for a year longer than the length of the longest clinical trial.

Based on the median time from initiation of the last oral agent to insulin for patients prescribed two or more types of oral agents concurrently which was 7.7 years in the study by Calvert et al. 2007, a longer treatment effect for the third-line therapies was tested. Assuming a 10-year treatment effect had no impact of the results and human insulin remained the most cost- effective option.

Table C45 10-year treatment effect – 40-year time horizon

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.07	20,293	0.02	766	£35,506
Glargine	7.95	21,760	–0.12	1,467	dominated
Biphasic analogue	8.05	23,028	–0.02	2,735	dominated
Rosiglitazone	7.85	25,100	–0.21	4,807	dominated
Exenatide	8.12	28,882	0.06	8,589	£150,017

Costs – sensitivity analysis

Table C46 Base case patient – drug costs only as monitoring was included in the UKPDS costing analysis and so adding on monitoring costs would result in a degree of double-counting

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	14,729			
Biphasic analogue	8.05	18,234	0.004	3,505	ED
Pioglitazone	8.03	18,547	–0.018	3,818	dominated
Glargine	8.00	19,059	–0.041	4,330	dominated
Rosiglitazone	7.94	23,939	–0.110	9,210	dominated
Exenatide	8.08	27,962	0.034	13,233	£391,806

Treatment efficacy – sensitivity analysis

These analyses were carried out to test the generalisability of the results, if the treatments prove to be less effective in practice than in the trials. Using lower efficacy values for the insulins and the glitazones made no effect on the results. Increasing the efficacy of glargine and biphasic analogue did not improve their cost-effectiveness compared to human insulin. Increasing the efficacy of the glitazones did make pioglitazone cost effective, £1,447 per QALY. Although this seems to be driven mainly by reduction of the TC:HDL by –3.19 which seems unlikely.

Table C47 Lower efficacy values for insulins

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	7.98	21,625	–0.06	2,098	dominated
Biphasic analogue	8.04	23,051	0.00	3,524	dominated
Rosiglitazone	7.94	24,978	–0.11	5,451	dominated
Exenatide	8.08	29,001	0.03	9,474	£280,495

1

Table C48 Lower efficacy values for glitazones

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	7.71	20,658	–0.33	1,130	dominated
Glargine	8.00	21,467	–0.04	1,940	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	ED
Rosiglitazone	7.90	25,186	–0.14	5,659	dominated
Exenatide	8.08	29,001	0.03	9,474	£280,495

2

Table C49 Upper efficacy values for insulins

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	8.02	21,380	–0.02	1,853	dominated
Biphasic analogue	8.06	23,093	0.01	3,566	£263,257
Rosiglitazone	7.94	24,978	–0.12	1,884	dominated
Exenatide	8.08	29,001	0.02	5,907	£292,039

3

Table C50 Upper efficacy values for glitazones

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.35	19,970	0.31	443	£1,447
Glargine	8.00	21,467	–0.35	1,497	dominated
Biphasic analogue	8.05	23,033	–0.30	3,063	dominated
Rosiglitazone	8.04	24,710	–0.31	4,741	dominated
Exenatide	8.08	29,001	–0.27	9,031	dominated

Table C51 Upper efficacy values for exenatide

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.03	19,828	–0.02	300	dominated
Glargine	8.00	21,467	–0.04	1,940	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	ED
Rosiglitazone	7.94	24,978	–0.11	5,451	dominated
Exenatide	8.18	28,786	0.13	9,259	£69,791

Table C52 Treatment effects on HbA_{1c} only, as there was limited evidence on the other treatment effects on lipid ratios and SBP this tests the external generalisability of the clinical evidence

	Total QALYs	Total costs (£)	Inc. QALY	Inc. cost (£)	ICER
Human insulin	8.05	19,527			
Pioglitazone	8.00	20,172	–0.05	645	dominated
Glargine	8.00	21,467	–0.04	1,940	dominated
Biphasic analogue	8.05	23,033	0.00	3,505	ED
Rosiglitazone	7.98	25,026	–0.07	1,993	dominated
Exenatide	8.06	29,042	0.01	9,515	£828,786

Conclusions

Human insulin was consistently the most cost-effective option (table C20). It remained so in different subgroups where one characteristic of the population was changed at a time (tables

C23 to C31). It also remained the most cost-effective option if it was assumed that the treatment effect of all the therapies lasted for 10 years instead of only 3 years.

Clinical evidence has shown glargine to reduce hypoglycaemic events. If it was assumed that people experienced a utility increment due to events avoided, and also a utility increment due to reduction in fear of hypoglycaemic events, then glargine became cost effective: £4,352 per QALY. Using the utility increments used in the TA update of 0.52% increment per hypoglycaemic event avoided did not improve the results of glargine enough to make it cost effective (table C33 to C34).

The UKPDS was chosen for the analysis before it was decided to include exenatide in the guideline. The studies available that include exenatide have reported treatment effects on weight reduction, lipid ratios and blood pressure. Treatment effect on weight loss could only be tested in the model by changing the initial weight and the actual treatment effects may not be represented accurately. From the results of the sensitivity analyses, giving people on exenatide a lower initial BMI and a higher quality of life to represent the potential weight loss, exenatide was unlikely to be cost-effective at current NICE thresholds[1] (lowest cost per QALY was £29,865). Pioglitazone became the most cost-effective option when the daily dose of insulin was increased to reflect that given to overweight or obese people with Type 2 diabetes (tables C35 to 41).

The glitazones were only recently licensed for third-line therapy and as such few clinical studies were available for evidence. Pioglitazone became cost-effective in a number of the sensitivity analyses (changing the initial total cholesterol and the initial SBP). Using the combined pioglitazone/metformin tablet was cheaper than giving these separately (saving approximately £60 per year) and it is likely if this combined tablet was given then pioglitazone would be cost effective. Only one study[133] was available comparing pioglitazone to rosiglitazone which showed pioglitazone to have a considerable effect on the TC:HDL ratio (-1.08 compared to rosiglitazone). This treatment effect appears to have been driving the results of pioglitazone. When only treatment effects on HbA1c were taken into account pioglitazone was dominated by human insulin (table C52). The relative risks for heart failure could not be incorporated into the UKPDS as inputs, and a sensitivity analysis was carried out by raising the initial SBP levels of people on glitazones (150 mm/Hg compared to 140 mm/Hg for other treatments). Both pioglitazone and rosiglitazone were dominated by human insulin in this sensitivity analysis (tables C40 to 41).

Table C53 Calculations for change in TC:HDL – mean differences based on adjusted data from the exenatide SMC submission

Exenatide vs glargine			SMC submission			
	Baseline		Endpoint		Difference	
	Exenatide	Glargine	Exenatide	Glargine	Exenatide	Glargine
TC (mmol/l)	4.80	4.9	4.72	4.93		
HDL (mmol/l)	1.10	1.2	1.14	1.24		
Ratios	4.36	4.08	4.14	3.98	–0.22	–0.11
Mean difference						–0.12
Exenatide vs biphasic analogue			**SMC submission**			
	Baseline		Endpoint		Difference	
	Exenatide	Biphasic analogue	Exenatide	Biphasic analogue	Exenatide	Biphasic analogue
TC (mmol/l)	5.08	5.02	5.01	4.99		
HDL (mmol/l)	1.23	1.21	1.24	1.26		
Ratios	4.13	4.15	4.04	3.96	–0.09	–0.19
Mean difference						0.10

continued

1

Table C53 Calculations for change in TC:HDL – mean differences based on adjusted data from the exenatide SMC submission – *continued*

Glargine vs rosiglitazone			Rosenstock 2006[139]			
	Baseline		Endpoint		Difference	
	Glargine	Rosi	Glargine	Rosi	Glargine	Rosi
TC mg/dl	196	196	186	215		
TC mmol/l	5.08	5.08	4.82	5.57	–0.26	0.49
HDL mmol/l	1.23	1.23	1.23	1.28	0	0.05412
Ratio	4.13	4.13	3.92	4.34	–0.21	0.21
Mean difference						0.42
Rosiglitazone vs pioglitazone			**Derosa 2007[133]**			
Derosa 2007	**Baseline**		**12mon**		**Difference**	
	Rosi	Pio	Rosi	Pio	Rosi	Pio
TC mmol/l	4.92	5.02	5.13	4.53		
HDL mmol/l	1.09	1.14	1.06	1.24		
Ratio	4.51	4.40	4.84	3.65	0.33	–0.75
Mean difference						–1.08

2

Table C54 Calculations for change in TC:HDL – lower differences

Lower	Baseline		Endpoint		Difference	
Exenatide vs glargine	**Exenatide**	**Glargine**	**Exenatide**	**Glargine**	**Exenatide**	**Glargine**
TC (mmol/l)	4.80	4.9	4.80	4.79		
HDL (mmol/l)	1.1	1.2	1.12	1.26		
Ratios	4.36	4.08	4.29	3.80	–0.08	–0.28
Mean difference						0.20
Exenatide vs biphasic analogue	**Baseline**		**Endpoint**		**Difference**	
	Exenatide	**Biphasic analogue**	**Exenatide**	**Biphasic analogue**	**Exenatide**	**Biphasic analogue**
TC (mmol/l)	5.08	5.02	5.17	4.95		
HDL (mmol/l)	1.23	1.21	1.22	1.29		
Ratios	4.13	4.15	4.24	3.84	0.11	–0.31
Mean difference						0.42

continued

Table C54 Calculations for change in TC:HDL – lower differences – *continued*

Glargine vs rosiglitazone	Baseline		Endpoint		Difference	
	Glargine	**Rosi**	**Glargine**	**Rosi**	**Glargine**	**Rosi**
TC mmol/l	5.08	5.08	4.82	5.57		
HDL mmol/l	1.23	1.23	1.23	1.23		
Ratio	4.13	4.13	3.92	4.53	–0.21	0.40
Mean difference						0.61
Rosiglitazone vs pioglitazone	**Baseline**		**12mon**		**Difference**	
	Rosi	**Pio**	**Rosi**	**Pio**	**Rosi**	**Pio**
TC mmol/l	4.92	5.02	4.51	5.02		
HDL mmol/l	1.09	1.14	1.19	1.08		
Ratio	4.51	4.40	3.79	4.64	–0.72	0.24
Mean difference						0.96

Table C55 Calculations for change in TC:HDL – upper differences

Upper	Baseline		Endpoint		Difference	
Exenatide vs glargine	**Exenatide**	**Glargine**	**Exenatide**	**Glargine**	**Exenatide**	**Glargine**
TC (mmol/l)	4.80	4.9	4.62	5.00		
HDL (mmol/l)	1.1	1.2	1.16	1.22		
Ratios	4.36	4.08	3.98	4.10	–0.38	0.02
Mean difference					–0.40	
Exenatide vs biphasic analogue	**Baseline**		**Endpoint**		**Difference**	
	Exenatide	**Biphasic analogue**	**Exenatide**	**Biphasic analogue**	**Exenatide**	**Biphasic analogue**
TC (mmol/l)	5.08	5.02	4.94	5.16		
HDL (mmol/l)	1.23	1.21	1.27	1.25		
Ratios	4.13	4.15	3.89	4.13	–0.24	–0.02
Mean difference					–0.22	

continued

Table C55 Calculations for change in TC:HDL – upper differences – *continued*

Glargine vs rosiglitazone	Baseline		Endpoint		Difference	
	Glargine	**Rosi**	**Glargine**	**Rosi**	**Glargine**	**Rosi**
TC mmol/l	5.08	5.08	5.08	5.08		
HDL mmol/l	1.23	1.23	1.23	1.28		
Ratio	4.13	4.13	4.13	3.95	0.00	–0.17
Mean difference					–0.17	
Rosiglitazone vs pioglitazone	**Baseline**		**12mon**		**Difference**	
	Rosi	**Pio**	**Rosi**	**Pio**	**Rosi**	**Pio**
TC mmol/l	4.92	5.02	5.75	4.04		
HDL mmol/l	1.09	1.14	0.93	1.4		
Ratio	4.51	4.40	6.18	2.88	1.67	–1.52
Mean difference					–3.19	

Table C56 Baseline demographic and metabolic characteristics of ITT population for GWAD study

Baseline demographics	Exenatide	Biphasic Insulin
Number of patients	253	248
Age (y)	59 (9)	58 (9)
Male (%)	53	49
Weight (kg)	85.5 (15.7)	83.4 (15.6)
BMI (kg/m^2)	30.6 (4.0)	30.2 (4.2)
Fasting serum glucose (mmol/l)	11.0 (2.7)	11.3 (2.8)
HbA_{1c} (%)	8.6 (1.0)	8.6 (1.1)
Duration of diabetes (y)	9.8 (6.3)	10.0 (6.2)

Table C57 Baseline demographics from the GWAA study of exenatide vs insulin glargine (values are mean±SD)

Baseline demographics	Exenatide	Biphasic insulin
Number of patients	282	267
Male (%)	55.0	56.6
Caucasian (%)	79.8	80.5
Age (y)	59.8±8.8	58.0±9.5
Weight (kg)	87.5±16.9	88.3±17.9
BMI (kg/m^2)	31.4±4.4	31.3±4.6
HbA_{1c} (%)	8.2±1.0	8.3±1.0
Fasting plasma glucose (mmol/l)	10.1±2.6	10.4±2.9
Duration of diabetes (yrs)	9.9±6.0	9.2±5.7

Appendix D: The cost-effectiveness of treating to target compared to a fixed-dose statin in patients with Type 2 diabetes

Introduction

There were no published studies found considering the cost effectiveness of treatment using statins to pre-specified cholesterol level targets in patients with Type 2 diabetes. A denovo

model was built in to estimate the cost per QALY of titrating using pre-specified targets to a maximum dose, compared with a fixed-dose treatment strategy using simvastatin 40 mg. Two separate models were constructed for adults with Type 2 diabetes with prior or no prior cardiovascular (CV) event/MI. The model takes a UK NHS costing and healthcare perspective.

Model assumptions

Treatment strategies

The model compared five different strategies. The first one was a fixed-dose treatment strategy. Patients are given simvastatin 40 mg and there is no further titration and no targets are measured. We modelled four titration strategies using targets of 5 or 4 mmol/l total cholesterol (TC), and using both one- and two-step titration strategies. In the one-step treatment strategy, the model assumes that patients not reaching target on simvastatin 40 mg are then treated with the higher intensity simvastatin 80 mg with no further measurement against target, and no further dose increase to follow. In the two-step model, patients not reaching target on simvastatin 80 mg are assumed to be treated with atorvastatin 80 mg with no further measurement against target, and no further dose increase to follow. Each increase in dose is assumed to be preceded by a GP consultation and blood test.

Patient population

The population is defined with an initial distribution of TC levels corresponding to results from The Health Improvement Network (THIN) database (see table D1). The average age of these patients is 65 years and the average initial TC level is 6.0 mmol/l. This distribution was assumed to be the average across people with prior or no prior cardiovascular disease (CVD).

Table D1 Distribution of initial total cholesterol for patients with Type 2 diabetes

TC mmol/l	Distribution (%) with specified cholesterol levels in patients with Type 2 diabetes and no prior CVD	Distribution (%) with specified cholesterol levels in patients with Type 2 diabetes and with prior CVD
2	0.05	0.08
2.5	0.03	0.09
3	0.17	0.48
3.5	0.56	1.04
4	1.64	2.95
4.5	4.60	6.68
5	10.91	12.60
5.5	19.43	19.84
6	20.45	18.67
6.5	16.87	14.73
7	11.21	9.75
7.5	6.64	5.73
8	3.45	3.34
8.5	1.74	1.62
9	0.95	0.94
9.5	0.46	0.66
10	0.27	0.25
10.5	0.58	0.54

Data table provided by Professor Alistair Gray, University of Oxford, obtained from THIN database (personal communication)

Treatment effects

We estimated the reduction in CV risk associated with each of the five treatment strategies for the two population groups using a two-stage process.

Cholesterol reduction and statin use

First, we estimated the proportions of patients who would be expected to achieve the defined TC targets of 4 and 5 mmol/l. The percentage reductions in TC associated with different doses of simvastatin and atorvastatin were taken from the STELLAR trial (Jones PH, Hunninghake DB, Ferdinand KC et al. 2004) (see table D1) in which 50% of the randomised population had Type 1 and Type 2 diabetes.

This data was combined with the initial cholesterol distributions in table D1 to estimate the proportion of patients achieving the target TC levels, table D3 for patients with diabetes and no prior CVD, and table D4 for patients with diabetes and prior CVD.

Table D2 The estimated reduction in total cholesterol obtained by simvastatin and atorvastatin from the STELLAR trial

	STELLAR reductions (%)	Standard deviation of % reduction in TC
Atorvastatin 10 mg	27	9
Atorvastatin 20 mg	32	6
Atorvastatin 40 mg	36	8
Atorvastatin 80 mg	39	7
Simvastatin 10 mg	20	9
Simvastatin 20 mg	26	8
Simvastatin 40 mg	28	10
Simvastatin 80 mg	33	1

Source: STELLAR trial, Jones et al. 2004

Table D3 Cumulative proportion of modelled cohort estimated to reach target on each of the modelled drugs in diabetic patients with no prior CVD

Statin dose	Cumulative percentage (%) achieving target (5 mmol/l)	Cumulative percentage (%) achieving target (4 mmol/l)
Simvastatin 40 mg	74.2	35.1
Simvastatin 80 mg	88.12	44.18
Atorvastatin 80 mg	93.07	65.69

Data table provided by Professor Alistair Gray, University of Oxford, obtained from THIN database (personal communication)

Table D4 Cumulative proportion of modelled cohort estimated to reach target on each of the modelled drugs in diabetic patients with prior CVD

Statin dose	Cumulative percentage (%) achieving target (5 mmol/l)	Cumulative percentage (%) achieving target (4 mmol/l)
Simvastatin 40 mg	76.50	39.8
Simvastatin 80 mg	88.81	49.96
Atorvastatin 80 mg	93.39	68.96

Data table provided by Professor Alistair Gray, University of Oxford, obtained from THIN database (personal communication)

These estimates then allow us to predict the proportion of patients who would be treated with each drug and dose under the five strategies: Tables D6 and D7 show these results for diabetic patients without and with prior CVD respectively. With the fixed-dose strategy, all

patients would be treated with simvastatin 40 mg. With one-step titration to a TC target of 5 mmol/l, 24–26% of patients are expected to require the higher dose of simvastatin 80 mg. This rises to 60–65% if a lower target of 4 mmol/l is used. Introducing a second titration step, 11–12% of patients would need atorvastatin 80 mg to reach the 5 mol/l target, and 50–56% to reach 4 mmol/l.

Table D5 Proportion of patients with diabetes but no prior CVD modelled to be on each of the three included drugs under four treatment strategies

	Fixed dose Sim 40 mg (%)	One-step (%)		Two-step (%)	
		Target 5	Target 4	Target 5	Target 4
Simvastatin 40 mg	100	74.2	35.1	74.2	35.1
Simvastatin 80 mg	–	25.8	64.9	13.92	9.1
Atorvastatin 80 mg	–	–	–	11.88	55.8

Table D6 Proportion of patients with diabetes and prior CVD modelled to be on each of the three included drugs under four treatment strategies

	Fixed dose Sim 40 mg (%)	One-step (%)		Two-step (%)	
		Target 5	Target 4	Target 5	Target 4
Simvastatin 40 mg	100	76.5	39.8	76.5	39.8
Simvastatin 80 mg	–	23.5	60.2	12.31	10.16
Atorvastatin 80 mg	–	–	–	11.19	50.40

Reduction in cardiovascular risk

We then estimated the reduction in CVD risk associated with the predicted use of each statin in tables D6 and D7 using equations derived from a meta-analysis by Law et al. 2003. The equations were applied in a two-stage procedure.

Firstly, the cholesterol lowering effects using both simvastatin and atorvastatin were measured using the following equations:

Reduction in TC by drug and dosage is given by:

= –1.123+0.238TC+0.384□Logn (dose of simvastatin)

= –2.205+0.419TC+0.475LN (dose of atorvastatin)

Then the relative risks of CVD/CVA events were estimated using the following equations respectively:

RR of CHD is given by:

RR of CHD per 1.2 mmol/l reduction in TC=–0.745□Logn (Age)+3.47, so RR of CHD=(–0.745□Logn (Age)+3.47) (Reduction in TC/1.2)

Where age=mean age of patient cohort in years RR of cerebrovascular disease/PAD is given by: RR of PAD/cerebrovascular disease per 1.2 mmol/l reduction in TC=0.94, so RR=0.94(Reduction in TC/1.2)

The resulting RR estimates from statin treatment effect for 65-year-old patient with a starting TC of 6 mmol/l (the mean for the diabetic populations in table D1) are presented in table D5 by drug and dose. Only CHD and not cerebrovascular disease/PAD risk is age dependant as specified by the Law and Wald equations.

Table D7 Effectiveness of different statins for a 65-year-old patient with a starting cholesterol level of 6 mmol/l

Statin	RR on CHD	RR on CVA (stroke/PAD/TIA)
Simvastatin 40 mg	0.529	0.915
Simvastatin 80 mg	0.479	0.903
Atorvastatin 80 mg	0.386	0.876

Markov model assumptions

A Markov model was built to estimate the impact of statin treatment on CVD events (defined as MI, stroke, PAD, TIA, heart failure, revascularisation, unstable angina, CV death, and death from other causes). The Markov model is a lifetime model which uses transitional probabilities (annual cycles) to estimate the number of CVD events from the initiation of statin treatment until death, or until the patient reaches an age of 100, whichever is the earlier of these two events. Using health state utility values assigned to each of the above health states, the model then calculates QALY for each of the modelled treatment strategies. The model also estimates the cost of each strategy, including healthcare costs of CVD as well as statin treatment.

Transition probabilities

Primary prevention

Baseline probabilities for the primary prevention model were taken from the statins technology appraisal (TA) 94. Data on PAD, heart failure and revascularisation were taken from Miejer et al. 1998, ONS 2000, and Johansen 1998 respectively. The baseline risk of CVD events was assumed to be 2% per year for a 65-year-old person without diabetes or prior CVD.

The GDG estimated that the risk of CVD events in people without existing CVD was between twofold to fourfold for diabetics compared with non-diabetics. For the purpose of this model we used an estimate of 2.5 fold and tested this assumption in a sensitivity analysis.

The model assumes the risk of CVD increases with age. The NICE statins TA 94 used data from the Health Survey for England 1998, and estimated a mathematical relationship between age and risk increase. For all males (all males, non-diabetic males and diabetic males) a linear relationship was the best-fitting mathematical model and the slope of the linear relationship was 0.0003. This represents an increase in the one year risk of 0.03% for a one year increase in age. For all females and non-diabetic females the best mathematical relationship was also found to be linear but the model fit was not as good as for males. No clear relationship between age and risk was found for diabetic females. The rate of increase was assumed to be the same for diabetic females as for all females, in the same way that the rate of increase was the same for all three male groups. The rate of increase used in the model is therefore 0.0002 which was the average between males and females. Table D2, appendix D1, shows the annual transition probabilities without treatment. Once patients had a first event, recurrent events were modelled as in the secondary prevention population.

Secondary prevention

Baseline annual transitional probabilities of CVD events following a previous MI are estimated from data reported in the TNT, LaRosa et al. 2005 and IDEAL, Pedersen et al. 2005 clinical trials which were done in non-diabetic populations. These transitional probabilities were then apportioned across patient age bands using data reported in the literature. Kaplan 2002, Bots et al. 1997, ONS 2000, Miejer et al. 1998.

Data on patients with Type 2 diabetes was not readily available. We used evidence from literature which suggests that diabetic patients have at least 1.5–2.6 fold increase in the risk of CVD events compared with non-diabetics. The evidence was taken from the statin trials CARE study Sacks et al. 1996, LIPID study 1998, and the 4S study Pyorala et al. 1997 and one observational study from Finland by Haffner et al. 1998. These studies demonstrated that there is increased risk of morbidity and mortality compared with the general population or patients with prior CVD. For the purposes of this model, we have increased the observed baseline risks in people after MI by factor of 1.9 which is the average of the risks reported across the four studies mentioned above. These transitional probabilities are presented in table D3, appendix D1.

Non-CVD mortality is modelled by using the age adjusted 'all cause mortality' rates from Government Actuarial Department (GAD) 2006, and adjusting for CVD mortality. It is assumed that diabetics have the same risk of dying from other causes as the general population (table D5, appendix D1).

Modelled costs

Statin drug costs are taken from prices quoted on March 26 2008 by the Prescription Pricing Authority (Drug Tariff 2008). Costs of treatment for CVD events are taken from published literature (table D7, appendix D1).

Each uptitration in the target treatment arm of the model is assumed to be preceded by a standard (approximately 10 minute) GP consultation and a blood test (assumed total cost per uptitration of £26). Unit costs of GP visits and blood test are taken from literature Curtis et al. 2007 (table D8, appendix D1). In line with current NICE guidance (NICE technical manual 2006), an annual discount rate of 3.5% has been applied to future costs in the Markov model

Quality of life (utility)

In order for the model to estimate QALYs, each of the modelled CVD health states has been assigned an assumed health-related quality of life utility score using previously published values (table D9, appendix D1). Utility has been adjusted for age using data from the Health Survey of England 1996 (table D10, appendix D1). Future QALY values are discounted at 3.5% per annum as recommended by NICE, (NICE technical manual 2006).

Cost-effectiveness analysis

The results of the cost-effectiveness analysis are summarised using an ICER – comparing each strategy with the next most expensive, non-dominated strategy.

Sensitivity analysis

In addition to the deterministic base cases, which use the mean values of the included model variables, the sensitivity of the base case ICER results to a range of univariate deterministic sensitivity analyses have been tested.

Base case results

The base case results are presented for the hypothetical cohort with a mean age of 65 years and a mean TC level of 6 mmol/l and CVD risk of 5% pa before treatment. Results are presented separately for Type 2 diabetes patients with and without prior CVD. The fixed-dose treatment strategy is the strategy which is least costly, but also generates the smallest number of QALYs. As expected, the two-step titration strategies are more costly than the one-step titration strategies and having a target of 4 mmol/l is more expensive than a target of 5 mmol/l in both models, see figures D1 and D2. Results are interpreted using the £20,000/QALY threshold.

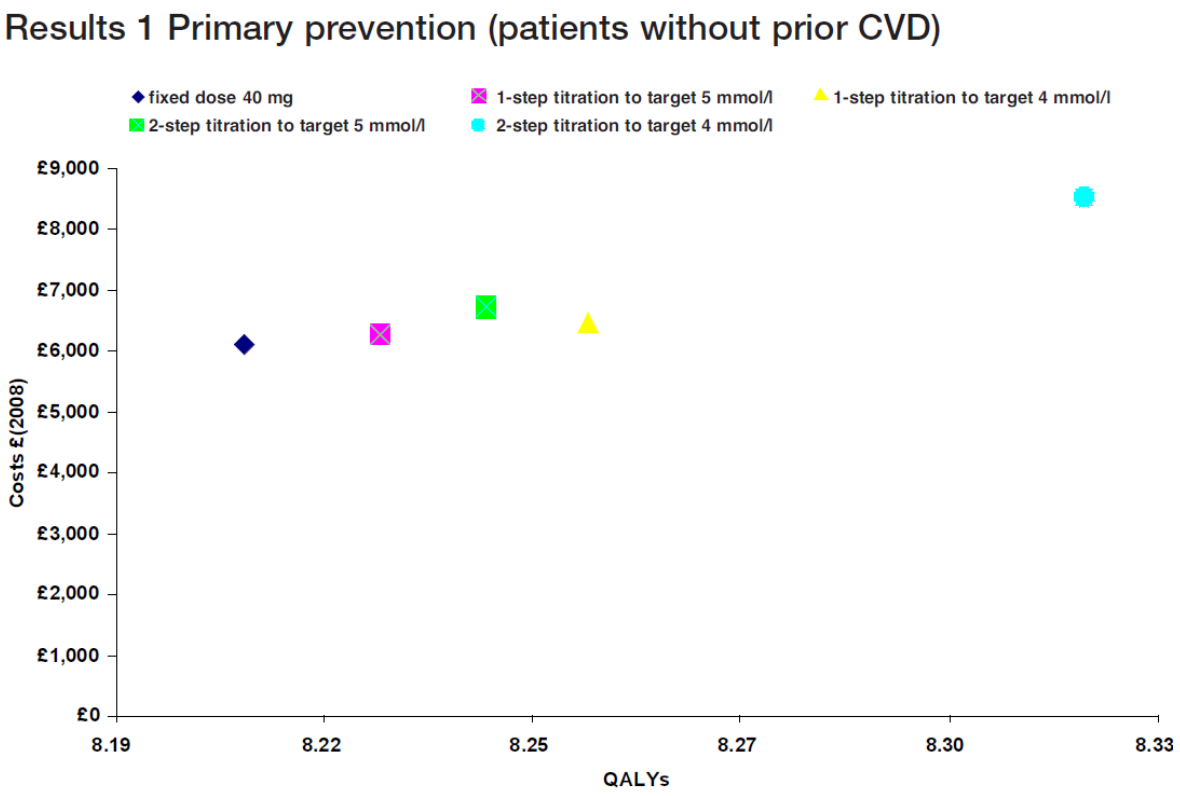

Figure D1 Cost-effectiveness plane, showing the costs and QALYs for the five strategies in patients with Type 2 diabetes without prior CVD

Table D8 Incremental cost-effectiveness results for the primary prevention model in patients with Type 2 diabetes

Treatment Strategy	Total cost (£)	QALYS	Inc. costs (£)	Incr. QALY	ICER (Cost/QALY)
Fixed dose 40 mg	6,119	8.21	–	–	–
One-step titration to target 5 mmol/l	6,281	8.22	–	–	ED**
One-step titration to target 4 mmol/	6,487	8.25	368	0.05	£7,878
Two-step titration to target 5 mmol/l	6,719	8.24	–	–	D*
Two-step titration to target 4 mmol/l	8,530	8.32	2,043	0.07	£30,321

The model indicates that the one-step target four treatment strategy has extended dominance over the one-step target five strategy and has an ICER of about £7,878/QALY compared to the fixed-dose strategy. The two-step titration to 5 mmol strategy is dominated by the one-step 4 mmol strategy (that is, it costs more and produces less QALYs) and so both 5 mmol target strategies are excluded due to dominance. The ICER of the two-step target 4 mmol/l compared to the one-step target 4 mmol/l strategy is £30,321 and is therefore not cost-effective using the £20,000/QALY thresholds. Thus for primary prevention the most cost-effective strategy in patients with Type 2 diabetes is one-step titration to a target of 4 mmol/l with an estimated ICER of £7,878/QALY compared to the fixed-dose strategy for 65-year-old patients with an initial CVD risk of 5% pa.

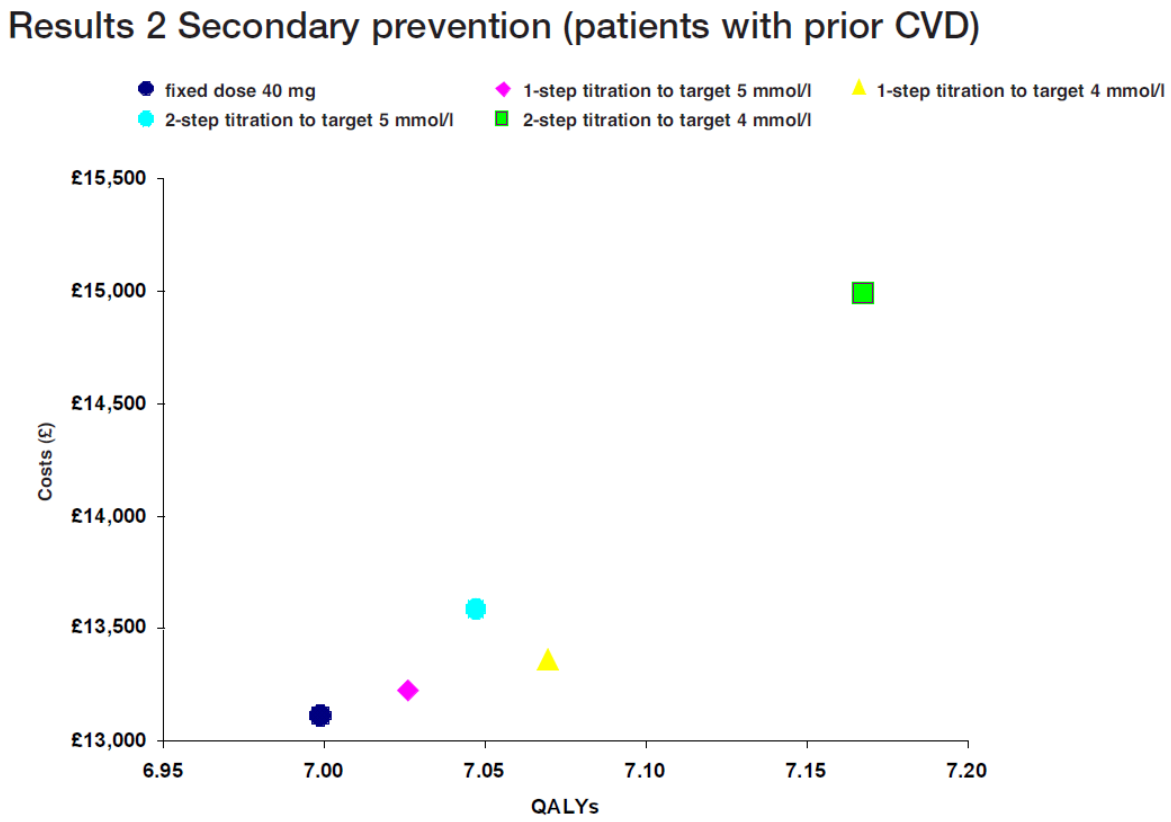

Figure D2 Cost-effectiveness plane, showing the costs and QALYs for the five strategies in patients with Type 2 diabetes and prior CVD

Table D9 Base case ICER for Type 2 diabetes patients with prior CVD

Treatment Strategy	Total cost (£)	QALYS	Inc. costs (£)	Incr. QALY	ICER (Cost/QALY)
Fixed dose 40 mg	13,116	7.00	–	–	–
One-step titration to target 5 mmol/l	13,228	7.03	–	–	ED
One-step titration to target 4 mmol/l	13,366	7.07	250	0.07	£3,534
Two-step titration to target 5 mmol/l	13,583	7.05	–	–	D
Two-step titration to target 4 mmol/l	14,987	7.17	1,622	0.10	£16,482

D, simple dominance; ED, extended dominance

The model indicates that the one-step target 4 treatment strategy has extended dominance over the one-step target 5 strategy and has an ICER of about £3,534 per QALY compared to the fixed-dose strategy. The two-step titration to 5 mmol strategy is dominated by the one-step 4 mmol strategy (that is, it costs more and produces less QALYs) and so both 5 mmol target strategies are excluded due to dominance. The ICER of the two-step target 4 mmol/l compared to the one-step target 4 mmol/l strategy is £16,482/QALY and is therefore cost-effective using the £20,000/QALY threshold. Thus for secondary prevention two-step target 4 mmol/l is the most cost-effective treatment strategy using a threshold of £20,000 per QALY with an estimated ICER of about £16,482/QALY.

Univariate sensitivity analyses

Sensitivity analysis: RR of CVD events for diabetic population compared to non-diabetic population with/without prior CVD.

The base model assumed that people with Type 2 diabetes without prior CVD have a 2.5 fold increase in risk of CVD/CVA events compared to non-diabetics. This assumption was tested using the range provided by the GDG of between 2–4 fold. The ICER ranged between £9,188 to £6,110 when a risk of 2 and 4 were used respectively, when one-step titration to a target of 4 mmol/l is compared with fixed-dose strategy.

In patients with prior CVD in the base case, we assumed the risk of developing CVD events in patients with Type 2 diabetes compared with non-diabetics was 1.9 fold. Evidence from literature suggested the risk could be between 1.5 to 2.6 fold. We used these ranges in sensitivity analysis and the ICER for the two-step titration to a target of 4 mmol/l compared with one-step titration to a target of 4 mmol/l ranged from £21,500 to £11,670/QALY. These results suggest that risk of developing CVD events has to be at least 1.6 fold for two-step titration to 4 mmol/l to be cost-effective at £20,000/QALY.

Table D10 Sensitivity analysis relative risk of CVD events diabetic population compared to non-diabetic population with/without prior CVD

	ICER (£/QALY) RR=1.5	Prior CVD RR=2.6	ICER (£/QALY) RR=2	No prior CVD RR=4
Age 65	£21,514	£11,667	£9,188	£6,110

Sensitivity analysis: RR of non-CVD mortality for diabetic population compared with non-diabetic population with/without prior CVD

The base model assumed that people with Type 2 diabetes with or without prior CVD have the same risk of dying from non-CVD causes compared with the general population. This assumption was tested by assuming that the risk of non-CVD mortality is twofold compared to the general population. For primary prevention the ICER slightly increased to £9,480/QALY when one-step titration to a target of 4 mmol/l is compared with fixed-dose strategy. In patients with prior CVD the ICER for the two-step titration to a target of 4 mmol/l compared with one- step titration to a target of 4 mmol/l also increased to £19,335/QALY. The base case conclusions are not changed by this sensitivity analysis.

Sensitivity analysis: costs of CV events

Increasing the costs of treatments for CV events will improve the cost-effectiveness of interventions for CVD all else being equal. Using the upper range of the assumed base case costs of CVD treatments (table D7, appendix D1) only marginally lowers the incremental cost per QALY. For primary prevention the ICERs remained below £9,000/QALY when one-step titration to a target of 4 mmol/l is compared with fixed-dose strategy. In patients with prior CVD the ICERs for the two-step titration to a target of 4 mmol/l compared with one-step titration to a target of 4 mmol/l remained below £18,000/QALY. Thus, the base case model results are insensitive to the CVD event cost assumptions.

Sensitivity analysis: health state utilities

The health state utilities used in the model were obtained from literature. We used the ranges provided for the upper and lower limit of utility scores. Where the ranges were not provided we varied the mean values by 20% in sensitivity analyses. For primary prevention the ICERs ranged between £7,600 to £8,400/QALY when one-step titration to a target of 4 mmol/l is compared with fixed-dose strategy. In patients with prior CVD the ICERs for the two-step titration to a target of 4 mmol/l compared with one-step titration to a target of 4 mmol/l ranged between

£16–19,000/QALY. This is still under the £20,000 per QALY threshold. As such, although the modelled ICERs are relatively sensitive to changes in health state utility values, our sensitivity analyses indicates that the base case conclusion regarding cost-effectiveness are not affected by changes in health state utility values.

Sensitivity analyses: starting age

The sensitivity of the ICERs was also tested against changes in the assumed starting age of the patient cohort. We varied the starting age of the starting cohort from 45 years to 75 years, assuming fixed initial CVD risk. For primary prevention the ICER ranges from £6,632 to

£10,280/QALY when one-step titration to a target of 4 mmol/l is compared with fixed-dose strategy. In patients with prior CVD the ICER for the two-step titration to a target of 4 mmol/l compared with one-step titration to a target of 4 mmol/l varies from £16,400 to £18,200/QALY. In all cases ICERs were increasing by age. The ICERs are thus relatively stable to changes in patient age with a trend to slightly higher ICERs for older patient groups. The conclusions of the base case analyses are however unchanged by this sensitivity analysis

Table D11 Impact of age on cost-effectiveness results

Age	Prior CVD, ICER (£/QALY)	No prior CVD, ICER (£/QALY)
Age 45	£17,963	£6,632
Age 55	£17,330	£7,361
Age 65	£16,482	£7,878
Age 75	£18,174	£10,280

Sensitivity analyses: starting CVD risk

The above analysis does not take account of the relationship between CVD risk and age. In our base case primary prevention model, we assume an initial CVD risk of 2% per year in the absence of diabetes (hence 5% per year with diabetes). This is appropriate for an average cohort aged 65, but the levels of risk is generally higher in older patients and lower in younger patients, Hippisley-Cox et al. 2007. For diabetic patients with a baseline risk of CVD events below 1.5% per year, titration is no longer cost-effective at the £20,000 per QALY level for primary prevention. Conversely, two-stage titration to a target of 4 mmol/l becomes cost-effective for primary prevention in people with diabetes if their baseline CVD is greater than about 10.5% per year.

Sensitivity analysis, discounting cost and health benefits

NICE recommends that both future costs and future benefits are discounted at a rate of 3.5% per annum in order to allow for societal time preference. We tested the sensitivity of the base case ICERs to the discounting assumption using rates of 0% and 6%. Using these assumptions, for primary prevention the ICER ranges from £6,514 to £9,074/QALY when one-step titration to a target of 4 mmol/l is compared with fixed-dose strategy. In patients with prior CVD the ICER for the two-step titration to a target of 4 mmol/l compared with one-step titration to a target of 4 mmol/l varies from £13,870 to £18,690/QALY. The higher the discount rate, the higher the ICER, however the base case cost-effectiveness conclusions are not affected by this sensitivity analysis.

In summary, the sensitivity analyses have indicated that the base case ICERs are relatively stable to changes in input variable values. In primary prevention one-step titration is cost-effective when compared with a fixed-dose strategy at levels of risk usual for most diabetic patients. In secondary prevention, two-step titration appears cost-effective for most diabetic patients, although the ICER rises above £20,000 per QALY if the RR of developing CVD in patients with diabetes compared with those without diabetes is below 1.5.

Discussion and conclusion

Our model indicates that for primary prevention one-step titration to a target of 4 mmol/l is the most cost-effective strategy when compared with a fixed-dose strategy for most patients with Type 2 diabetes. The estimated ICER is about £7,878/QALY. Our model indicates that it is not cost-effective to try to get more patients to target by adding atorvastatin 80 mg because the ICER then increases to over £30,000 per QALY. These results were stable in sensitivity analysis, except for patients at unusually low or high levels of CVD risk. Titration was not cost-effective for primary prevention in diabetic patients with an initial CVD risk below 1.5% per year, whereas two-step titration (including atorvastatin 80 mg) to a target of 4 mmol/l became cost- effective above an initial CVD risk of 10.5% per year.

In the secondary prevention model, for patients with Type 2 diabetes who had a prior CVD event, a two-step titration to a target of 4 mmol/l is the most cost-effective strategy compared to one-step titration to a target of 4 mmol/l with an estimated ICER of about £16,482/QALY.

This result was stable in sensitivity analysis. The model was slightly sensitive to assumption about the RR of CVD disease between diabetics compared to non-diabetics.

In both models (for people with prior or no prior CVD) both treatment strategies using a target of 5 mmol/l are either extendedly dominated or dominated by the one-step titration strategy using a target of 4 mmol/l.

Our model results for primary prevention in people with diabetes are consistent with the model results for the Lipid guideline which demonstrated that one-step titration is cost-effective in secondary prevention patients without diabetes. Haffner et al. 1998 demonstrated that patients without diabetes but with prior CVD will benefit the same as patients with diabetes but without a prior CVD. In the Lipids model a two-step titration was not cost-effective with ICERs well above £60,000/QALY. Our secondary prevention model differs from the Lipids model in that people with diabetes are assumed to have an almost twofold increase in risk of CVD compared with non-diabetics as described in the methods section. If this risk is assumed to be less than 1.5 fold, then our model results will conclude the same as the Lipids guideline model, suggesting that two-step titration will not be cost-effective.

The Law and Wald equations used in the analysis estimated treatment benefit from cholesterol reduction in the non-diabetic population. We assumed the benefits to be the same in the diabetic population. This might not necessarily be the case, and people with diabetes may tend to have higher absolute benefit than the non-diabetic population. This will make our model conservative as it will underestimate treatment benefit.

Economic models are by definition a simplification of the real world. There is a lack of long-term clinical trials comparing titration strategies with fixed lower-intensity statin treatment strategies. As such, our model is predicated on the assumption that reductions in CVD events, resulting from reductions in TC levels from statin treatment are adequately represented by the Law and Wald equations. These equations are themselves predicated on the Framingham risk equations. The equations reflect the fact that higher intensity statins lead to greater reductions in cholesterol. RR reductions are greater for patients with a higher starting cholesterol level and for younger patients. Our base case model assumes a hypothetical cohort of patients with average starting TC of 6 mmol/l and average age of 65 years.

The guideline group acknowledged that the results of the Law et al. 2003 meta-analysis overestimate reduction in cholesterol and CVD events in comparison to the longer-term trial results described by the Cholesterol Trialists Collaboration, and may yield over-optimistic estimates of treatment effects. However, it is reassuring that the cholesterol reduction estimates from the Law and Wald equations yielded similar answers to those observed in the STELLAR trial, Jones et al. 2004. The external validity of our model should be tested if and when long- term outcome data becomes available from trials comparing a fixed-dose treatment strategy with a target driven strategy.

There is also lack of good long-term safety and utility data for statin use. Although a number of safety studies and a meta-analysis on statin use were identified, the GDG felt the recruitment in these trials made it difficult to demonstrate any significant difference in side effects, since only those who could tolerate statins were included in the trials. As a result the trials reported that there was no significant difference between higher intensity and lower intensity statins with regards to major side effects, though there is a trend of greater ‘minor’ adverse events with increasing dose. There is also lack of health-related quality of life utility data, with which to estimate quality of life reductions resulting from adverse events associated with higher intensity statin treatment. Consequently, and in line with previously

published cost-effectiveness analyses in hyperlipidemia statins TA 94, our model assumes no adverse events from treatment with higher intensity stations.

Another limitation of the model arises because of the nature of Markov models. These assume that the probability of an individual moving to any given health state in one time period depends only on their current health state (there is no 'memory' in the model). Thus the probability of HF for a patient whose last CVD event was an MI is assumed to be the same irrespective of how many CVD events they have previously had. Similarly, a patient's health outcome and healthcare costs incurred are assumed to depend only on their current health state. These assumptions are unlikely to be strictly true, and will tend to underestimate overall costs and overestimate health outcomes for the cohort. Thus, interventions that prevent more CVD events will tend to appear rather less cost-effective than they may be in reality. So the model is conservative in this respect.

In conclusion, for primary prevention one-step titration to 4 mmol/l compared to fixed-dose strategy is cost-effective and in secondary prevention a two-step titration strategy compared to one-step titration is cost-effective in patients with Type 2 diabetes. These results were relatively robust to sensitivity analyses.

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Appendix D

Table D1.1 Distribution of primary CVD events without taking statins in general population

Age	MI (%)	Stroke (%)	TIA (%)	PAD (%)	HF (%)	Rev (%)	UNA (%)	CV death (%)
45	18.75	17.90	11.00	7.50	0.25	7.88	11.20	4.80
55	13.20	24.70	9.20	10.50	1.15	6.88	7.20	6.00
65	14.70	32.60	8.65	15.50	4.05	9.00	6.75	8.28
75	13.15	40.35	8.90	25.50	10.43	3.50	5.75	7.38
85	14.30	42.60	5.15	57.00	10.43	0.63	6.25	7.10

Table D1.2 Annual probability of primary CVD events without taking statins in diabetic population with no prior CVD

Age	MI (%)	Stroke (%)	TIA (%)	PAD (%)	HF (%)	Rev (%)	UNA (%)	CV death (%)
45	0.94	0.90	0.55	0.38	0.01	0.39	0.56	0.24
55	0.73	1.36	0.51	0.58	0.06	0.38	0.40	0.33
65	0.88	1.96	0.52	0.930	0.24	0.54	0.41	0.50
75	0.85	2.62	0.58	1.66	0.68	0.23	0.37	0.48
85	1.001	2.98	0.36	3.99	0.73	0.04	0.44	0.50

All the rates above include a 2.5 multiplier to reflect the increased risk of CVD seen in diabetic patients compared to non-diabetics

Table D1.3 Baseline annual transition probabilities, in diabetic patients with stable coronary artery disease

Estimated annual rates by age – assuming mean age of 65 in cohorts

From MI year 1 to	45	55	65	75	85	Source
MI	0.041	0.042	0.051	0.075	0.075	TNT/IDEAL Kaplan
SK	0.012	0.015	0.026	0.044	0.044	ibid
TIA	0.021	0.021	0.038	0.047	0.055	ibid
PAD	0.017	0.024	0.036	0.059	0.133	Ibid
HF	0.001	0.007	0.023	0.060	0.060	Ibid
REV	0.110	0.110	0.127	0.053	0.010	Ibid
USA	0.006	0.020	0.040	0.055	0.055	Ibid
CVD	0.009	0.013	0.028	0.057	0.057	ibid

continued

Table D1.3 Baseline annual transition probabilities, in diabetic patients with stable coronary artery disease – *continued*

Estimated annual rates by age – assuming mean age of 65 in cohorts						
Post MI year 2 onwards to						
MI	0.016	0.017	0.020	0.030	0.030	Ibid
SK	0.005	0.006	0.010	0.017	0.017	Ibid
TIA	0.008	0.008	0.015	0.018	0.022	Ibid
PAD	0.007	0.010	0.014	0.023	0.052	Ibid
HF	0.001	0.003	0.009	0.023	0.023	Ibid
REV	0.045	0.045	0.052	0.022	0.004	Ibid
USA	0.002	0.008	0.016	0.022	0.022	Ibid
CVD	0.004	0.005	0.011	0.022	0.022	ibid
From stroke to						
SK	0.1462	0.3167	0.3931	0.5000	0.6333	Hardie 2004
MI	0.0070	0.0135	0.0240	0.0350	0.0454	NICE TA 94
HF	0.0188	0.0194	0.0231	0.0342	0.0342	Assumed to be 1/2 of MI to HF
REV	0.0000	0.0000	0.0000	0.0000	0.0000	Assumed no transition
USA	0.0070	0.0135	0.0240	0.0350	0.0454	Same as stroke to MI
CVD	0.0201	0.0485	0.1136	0.2561	0.5310	NICE TA 94
Post SK to SK						
SK	0.0088	0.0196	0.0246	0.0318	0.0411	Hardie 2004
MI	0.0070	0.0135	0.0240	0.0350	0.0454	NICE TA 94
HF	0.0188	0.0194	0.0231	0.0342	0.0342	Assumed to be 1/2 of MI to HF
REV	0.0000	0.0000	0.0000	0.0000	0.0000	Assumed no transition
USA	0.0070	0.0135	0.0240	0.0350	0.0454	Same as stroke to MI
CVD	0.0092	0.0214	0.0454	0.0900	0.1639	NICE TA 94
From TIA to						
MI	0.0070	0.0135	0.0240	0.0350	0.0454	NICE TA 94
SK	0.0153	0.0791	0.1849	0.3618	0.4200	NICE TA 94
CVD	0.0057	0.0306	0.0712	0.1394	0.1617	NICE TA 94

continued

Table D1.3 Baseline annual transition probabilities, in diabetic patients with stable coronary artery disease – *continued*

Estimated annual rates by age – assuming mean age of 65 in cohorts						
From PAD to						
MI	0.0704	0.0704	0.0704	0.0704	0.0704	Caro 2005
SK	0.0716	0.0716	0.0716	0.0716	0.0716	Caro 2005
CVD	0.3592	0.3592	0.3592	0.3592	0.3592	Caro 2005
From HF to						
HF	0.1818	0.1818	0.1818	0.1818	0.1818	SOLVD Investigators 1991
MI	0.0352	0.0352	0.0352	0.0352	0.0352	SOLVD Investigators 1991
SK	0.0085	0.0085	0.0085	0.0085	0.0085	SOLVD Investigators 1991
REV	0.0000	0.0000	0.0000	0.0000	0.0000	Assumed no transition
UNA	0.0352	0.0352	0.0352	0.0352	0.0352	Assumed to be 1/2 of MI to HF
CVD	0.1988	0.1988	0.1988	0.1988	0.1988	SOLVD Investigators 1991
From REV to						
REV	0.1697	0.1697	0.1697	0.1697	0.1697	Henderson 2003
MI	0.1311	0.1311	0.1311	0.1311	0.1311	Hartwell 2005
SK	0.0437	0.0437	0.0437	0.0437	0.0437	Hartwell 2005
HF	0.0656	0.0656	0.0656	0.0656	0.0656	Assumed to be 1/2 of revascularisation to MI
CVD	0.0248	0.0248	0.0248	0.0248	0.0248	Henderson 2003
From UNA to						
REV	0.6205	0.6205	0.6205	0.6205	0.6205	Mehta S 2001
MI	0.2163	0.2172	0.2133	0.2036	0.1857	NICE TA 94
SK	0.0287	0.0339	0.0608	0.1013	0.1013	Assumed to be same as MI to Stroke
HF	0.1923	0.1923	0.1923	0.1923	0.1923	CURE study 2001
CVD	0.0118	0.0118	0.0201	0.0323	0.0503	NICE TA 94
Post UNA to						
REV	0.6205	0.6205	0.6205	0.6205	0.6205	Mehta S 2001
MI	0.0813	0.1521	0.2762	0.4903	0.8543	NICE TA 94
SK	0.0113	0.0133	0.0239	0.0398	0.0398	Assumed to be same as MI to stroke
HF	0.1923	0.1923	0.1923	0.1923	0.1923	CURE study 2001
CVD	0.0017	0.0017	0.0022	0.0026	0.0031	NICE TA 94

All the rates above include a 1.9 multiplier to reflect the increased risk of CVD seen in diabetic patients compared to non-diabetics

Table D1.4 Deaths by age, sex and underlying cause, 2004 registrations, England and Wales in the general population

	Deaths								
	All cause ICD10: A00-R99			Circulatory ICD: I00-I99			Proportion of non-circulatory deaths to all deaths		
	M	F	ALL	M	F	ALL	M	F	ALL
45	12,417	8,139	20,556	3,930	1,362	5,292	68%	83%	74%
55	27,117	17,649	44,766	9,330	3,541	12,871	66%	80%	71%
65	52,709	37,041	89,750	19,783	11,304	31,087	62%	69%	65%
75	87,367	88,404	175,771	35,607	35,958	71,565	59%	59%	59%
85	51,329	109,488	160,817	20,816	46,470	67,286	59%	58%	58%

Source: GAD

Table D1.5 Estimated non-CVD death rates used in the model

	All cause * (%)	Non-CVD (%)
45	0.35	0.26
55	0.88	0.63
65	2.37	1.55
75	6.75	4.00
85	36.29	21.11

Table D1.6 Treatment effect (RR of cardiovascular events) by age, starting cholesterol level and dose of statin

RR of CVD events with simvastatin 40 mg			CHD				Stroke/PAD/TIA
	Patient	Age					
Starting TC	55	60	65	70	75	80	
4	0.504	0.570	0.631	0.687	0.740	0.790	0.938
5.5	0.414	0.485	0.553	0.617	0.679	0.738	0.921
6	0.388	0.460	0.529	0.596	0.660	0.721	0.915
6.5	0.364	0.436	0.506	0.575	0.641	0.705	0.909
7	0.341	0.413	0.484	0.554	0.623	0.689	0.904

continued

Table D1.6 Treatment effect (RR of cardiovascular events) by age, starting cholesterol level and dose of statin – *continued*

RR of CVD events with simvastatin 40 mg			CHD				Stroke/PAD/TIA
	Patient	Age					
Starting TC	55	60	65	70	75	80	
4	0.436	0.506	0.572	0.634	0.694	0.751	0.925
5.5	0.358	0.430	0.501	0.570	0.637	0.701	0.908
6	0.335	0.408	0.479	0.550	0.619	0.686	0.903
6.5	0.314	0.387	0.459	0.530	0.601	0.670	0.897
7	0.294	0.366	0.439	0.512	0.584	0.656	0.892
RR of CVD events with atorvastatin 40 mg			**CHD**				**Stroke/PAD/TIA**
	Patient	Age					
Starting TC	55	60	65	70	75	80	
4	0.386	0.458	0.527	0.594	0.658	0.720	0.915
5.5	0.273	0.345	0.418	0.491	0.565	0.639	0.885
6	0.243	0.314	0.386	0.461	0.537	0.614	0.876
6.5	0.217	0.285	0.358	0.433	0.511	0.590	0.866
7	0.193	0.260	0.331	0.407	0.486	0.567	0.857

Table D1.7 Costs of CVD events

Health state	Mean (£)	Lower (£)	Upper (£)	Source
Diabetes	0	0	0	GDG assumption (same across all comparators)
MI (first year)	1,291	804	1,986	NHS ref cost 2007
MI (subsequent)	500	200	650	NICE CG 34 2006
Stroke (first year)	8,046	5,886	11,539	NICE TA 94
Stroke (subsequent)	2,163	1,100	3,000	NICE TA 94
TIA (first year)	756	536	1,216	NHS ref cost 2007
TIA (subsequent)	264	200	400	NICE TA 94
PAD (first year)	1,000	612	1,388	Karnon 2005
PAD (subsequent)	264	200	400	Assumption same as TIA
Heart failure	2,303	1,255	3,434	NHS ref cost 2007

continued

Table D1.7 Costs of CVD events – *continued*

Health state	Mean (£)	Lower (£)	Upper (£)	Source
Diabetes	0	0	0	GDG assumption (same across all comparators)
Heart failure (subsequent)	500	200	650	Assumed same as post MI
Revascularisation	10,456	8,012	11,925	NHS ref cost 2007
Revascularisation (subsequent)	500	200	650	Assumed same as post MI
Unstable angina (first year)	1,059	448	1,521	NHS ref cost 2007
Unstable angina (subsequent)	500	200	600	Assumed same as post MI

Table D1.8 Costs of drugs and GP visits

Drug	Number of tablets	Cost/packet (£)	Cost per year (£)
Sim 40 mg	28	1.39	18.12
Sim 80 mg	28	4.95	64.53
Artova 80 mg	28	28.21	367.74
Source: PPA Drug Tariff March 2008			
	Mean unit costs (£)	**Consultation time (min)**	**Source**
Cost of GP visit	2.20/minute	11	Netten 2007
Biochemical test x2	1.59	–	NHS ref costs 2007
Lipid profile	3.56	–	GDG
Nurse	30/hr	–	Netten 2007

Table D1.9 Health state utilities

Health state	Mean	Lower limit	Upper limit	Source
Well	0.95	0.9	1	Chen 2001
MI	0.76	0.56	0.96	NICE TA 94
Post MI	0.88	0.76	1.00	Mason J 2005
Stroke	0.63	0.43	0.83	NICE TA 94
Post stroke	0.63	0.43	0.83	NICE TA 94
TIA	0.90	0.85	1.00	Lavender 1998
Post TIA	0.90	0.85	1.00	Assumption
PAD	0.90	0.86	0.98	Karnon 2005

continued

Table D1.9 Health state utilities – *continued*

Health state	Mean	Lower limit	Upper limit	Source
Post PAD	0.90	0.86	0.98	Assumption
Heart failure	0.68	0.48	0.88	Davies 2006
Post-heart failure	0.68	0.48	0.88	Assumption
Revascularisation	0.93	0.74	1.00	Yorck 2003
Post revascularisation	0.93	0.74	1.00	Assumption
Unstable angina	0.77	0.57	0.97	NICE TA 94
Post unstable angina	0.88	0.60	1.00	Assumed same as post MI

Table D1.10 Age-related utility from Health Survey for England 1996

Age specific quality of life

Age group	Mean	SE
45–54	0.85	0.004
55–64	0.79	0.006
65–74	0.78	0.006
75+	0.73	0.007

Source: Health survey of England 1996

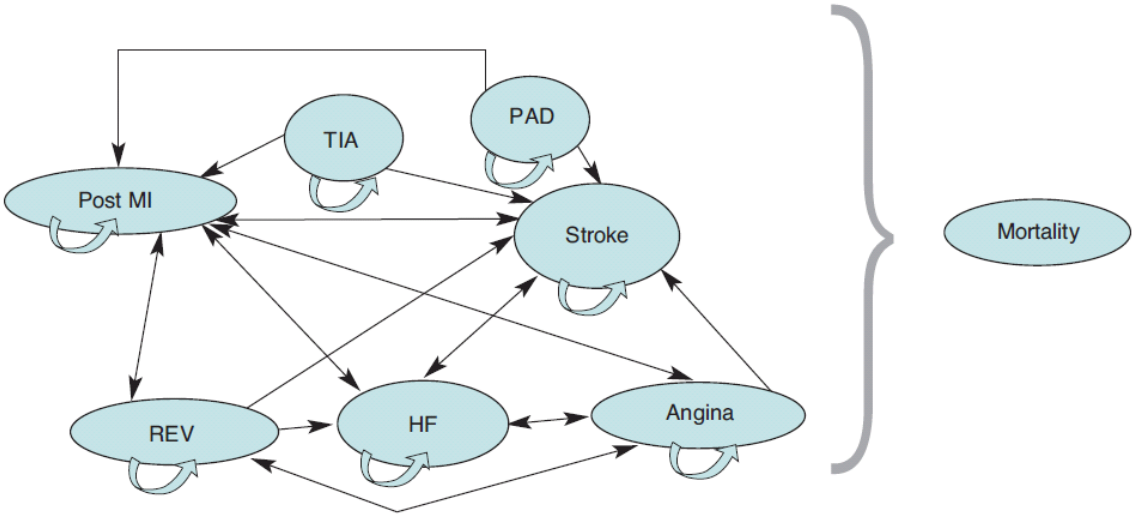

Figure D1.1 Model structure for cost-effectiveness of lower intensity statins versus higher intensity in the secondary prevention of CVD (used for the high low dose and treat to target models)