

1 **Appendix G: NICE Clinical Guideline 66**

2 **Deleted Text**

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

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

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1 **Table 1: Deleted recommendations from CG66 & CG87**
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Recommendation in 2009 guideline	Comment
<p>Follow the recommendations in Depression: management of depression in primary and secondary care clinical guideline (NICE clinical guideline 23). [1.2.2.1]</p>	<p>This statement has been deleted because this is now mentioned in the 'Related guidance' section. 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.</p>
<p>When setting a target glycated haemoglobin (HbA1c):</p> <ul style="list-style-type: none"> • 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] 	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>Self-monitoring of plasma glucose should be available:</p> <ul style="list-style-type: none"> • 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 	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>

<ul style="list-style-type: none"> to monitor changes during intercurrent illness to ensure safety during activities, including driving. [1.4.2] 	
<p>If self-monitoring is appropriate but blood glucose monitoring is unacceptable to the individual, discuss the use of urine glucose monitoring.</p>	<p>The recommendation has been deleted because the guideline development group working on the update believed it was not supported by the evidence.</p>
<p>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]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight. [1.5.1.2]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that:</p> <ul style="list-style-type: none"> 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] 	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>Consider a sulfonylurea as an option for first-line glucose-lowering therapy if:</p> <ul style="list-style-type: none"> 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] 	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>Add a sulfonylurea as second-line therapy when blood glucose control</p>	<p>This recommendation has been deleted because this entire section has been</p>

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 \geq 6.5%, or other higher level agreed with the individual) if: <ul style="list-style-type: none"> 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 \geq 6.5%, or other higher level agreed with the individual) if: <ul style="list-style-type: none"> 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 \geq 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.
<p>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.</p> <p>A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to a thiazolidinedione (pioglitazone) if:</p> <ul style="list-style-type: none"> • 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). <p>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]</p>	This recommendation has been deleted because this entire section has been updated in 2015.
<p>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 \geq 6.5%, or other higher level agreed with the individual) if:</p> <ul style="list-style-type: none"> • 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.

<p>sulfonylurea or a sulfonylurea is contraindicated.</p> <p>[1.6.2.1]</p>	
<p>Consider adding a thiazolidinedione (pioglitazone) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c \geq 6.5%, or other higher level agreed with the individual) if:</p> <ul style="list-style-type: none"> the person does not tolerate metformin or metformin is contraindicated. [1.6.2.2] 	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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 \geq 7.5%, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[7].</p> <p>[1.6.2.3]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>Consider combining pioglitazone with insulin therapy[6] for a person:</p> <ul style="list-style-type: none"> 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] 	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>Discuss the potential benefits and risks of treatment with a thiazolidinedione (pioglitazone) with the person to enable them to make an informed decision. A</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>

<p>thiazolidinedione (pioglitazone) may be preferable to a DPP-4 inhibitor (sitagliptin, vildagliptin) if:</p> <ul style="list-style-type: none"> 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). <p>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]</p>	
<p>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 \geq 7.5%, or other higher level agreed with the individual), and the person has:</p> <ul style="list-style-type: none"> a body mass index (BMI) \geq 35.0 kg/m² 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/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities. [1.6.3.1] 	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>When starting basal insulin therapy:</p> <ul style="list-style-type: none"> continue with metformin and the sulfonylurea (and acarbose, if used) review the use of the sulfonylurea if hypoglycaemia occurs. [1.7.1.1] 	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>When starting pre-mixed insulin therapy (or mealtime plus basal insulin</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>

<p>regimens):</p> <ul style="list-style-type: none"> • continue with metformin • continue the sulfonylurea initially, but review and discontinue if hypoglycaemia occurs. [1.7.1.2] 	
<p>Discuss the benefits and risks of insulin therapy when control of blood glucose remains or becomes inadequate (HbA1c \geq 7.5% or other higher level agreed with the individual) with other measures. Start insulin therapy if the person agrees. [1.7.2.1]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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]</p>	<p>This recommendation has been deleted because this entire section has been updated in 2015.</p>
<p>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]</p>	<p>NICE took the decision to stand down this recommendation because the Type 1 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.</p>
<p>Appropriate local arrangements should be in place for the disposal of sharps.</p>	<p>NICE took the decision to stand down this recommendation because the Type 1 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.</p>
<p>If a person has a manual or visual disability and requires insulin, offer a device or adaptation that:</p> <ul style="list-style-type: none"> • takes into account his or her individual needs • he or she can use successfully 	<p>NICE took the decision to stand down this recommendation because the Type 1 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.</p>
<p>Review cardiovascular risk status annually by assessment of cardiovascular risk factors, including</p>	<p>The type 2 diabetes Guideline Development Group (GDG) wanted to stand down the outstanding lipids recs</p>

<p>features of the metabolic syndrome and waist circumference, and change in personal or family cardiovascular history. [1.10.1.1]</p>	<p>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.</p>
<p>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]</p>	<p>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.</p>
<p>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]</p>	<p>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.</p>
<p>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]</p>	<p>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</p>

	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]	
<p>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:</p> <ul style="list-style-type: none"> • 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

<p>development of neuropathic symptoms causing distress.</p> <ul style="list-style-type: none"> • 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] 	<p>neuropathic pain (NICE clinical guideline 173).</p>
<p>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]</p>	<p>Will be deleted and will cross refer to neuropathic pain (NICE clinical guideline 173).</p>
<p>If neuropathic symptoms cannot be controlled adequately, it may be helpful to further discuss:</p> <ul style="list-style-type: none"> • the reasons for the problem • the likelihood of remission in the medium term • the role of improved blood glucose control. [1.14.2.7] 	<p>Will be deleted and will cross refer to neuropathic pain (NICE clinical guideline 173).</p>

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1 Preface

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

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

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

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

42

43 Dr Bernard Higgins MD FRCP

44 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

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

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

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

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

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

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

1.2 Definition

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

- 1 People are normally thought to have Type 2 diabetes if they do not have Type 1 diabetes
 2 (rapid onset, often in childhood, insulin-dependent, ketoacidosis if neglected) or other
 3 medical conditions or treatment suggestive of secondary diabetes. However, there can be
 4 uncertainty in the diagnosis particularly in overweight people of younger age. A further area
 5 of confusion is the group of disorders classified as monogenetic diabetes – formally Maturity
 6 Onset Diabetes of the Young (MODY) – which are usually not insulin requiring but which
 7 present in the first decades of life.
- 8 It is noted that Type 1 diabetes with onset after childhood can be confused with Type 2
 9 diabetes. However, lower body weight, more rapid progression to insulin therapy, and
 10 absence of features of the metabolic syndrome often give useful distinguishing clues.

1.3 Prevalence

- 12 The prevalence of diabetes in the UK is increasing as is the prevalence of obesity,
 13 decreased physical activity, but also increased longevity after diagnosis thanks to better
 14 cardiovascular risk protection. The current prevalence of Type 2 diabetes is unknown, and
 15 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

- 16
- 17 Prevalence estimates vary from around 3.5 to 5.0%, the third edition of the International
 18 Diabetes Federation (IDF) Atlas suggesting 4.0%, being 1.71 million in the 20- to 79-year-old
 19 age group, of whom it is conventional to assume 85% have Type 2 diabetes.⁴ Current
 20 prevalence estimates are a poor pointer to future burden of diabetes due to their continuing
 21 increase. The healthcare burden is also affected by the improved longevity of people with
 22 diabetes with better management, which means that overall they carry a larger burden of
 23 complications and insulin deficiency needing more complex care.

1.4 Health and resource burden

- 25 Mortality attributed to people with diabetes is suggested as 4.2% of deaths in men and 7.7%
 26 of deaths in women in the UK. These are likely to be underestimates as deaths from vascular
 27 events such as stroke and myocardial infarction (MI) are notorious for under-recording of the
 28 underlying causative disease. In a population-based study in Cardiff, at a time when
 29 population prevalence was only 2.5%, deaths in people with diabetes accounted for over
 30 10% of the total, with around 60% attributable to diabetes.⁵ Life years lost vary considerably
 31 with factors such as blood glucose, blood pressure and blood lipid control, and smoking, as
 32 well as age, and can be estimated by comparing United Kingdom Prospective Diabetes

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

 - 4 The direct cost of Type 2 diabetes to the NHS is unknown, as much is classified as
 - 5 cardiovascular or renal disease. However, with prevalence estimates of 3.5–5.0%, and
 - 6 healthcare costs double those of the background population or more, estimates of 7–12% of
 - 7 total NHS expenditure seem not unreasonable. The IDF Atlas notes that in industrialised
 - 8 countries healthcare costs in people with diabetes tend to be double those of the background
 - 9 population. This suggests a £2.8 billion attributable cost for the UK for 2007.⁴
- 10

2 Methodology

2.1 Aim

- 3 The aim of the National Collaborating Centre for Chronic Conditions (NCC-CC) is to provide
4 a user-friendly, clinical, evidence-based guideline for the NHS in England and Wales that:
- 5 • offers best clinical advice for the management of Type 2 diabetes
 - 6 • is based on best published clinical and economic evidence, alongside expert consensus
 - 7 • takes into account patient choice and informed decision making
 - 8 • defines the major components of NHS care provision for Type 2 diabetes
 - 9 • details areas of uncertainty or controversy requiring further research
 - 10 • provides a choice of guideline versions for differing audiences.

2.2 Scope

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

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

2.3 Audience

- 25 The guideline is intended for use by the following people or organisations:
- 26 • all healthcare professionals
 - 27 • people with Type 2 diabetes and their parents and carers
 - 28 • patient support groups
 - 29 • commissioning organisations
 - 30 • service providers.

2.4 Involvement of people with type 2 diabetes

- 32 The NCC-CC was keen to ensure the views and preferences of people with Type 2 diabetes
33 and their carers informed all stages of the guideline. This was achieved by:
- 34 • having two people with Type 2 diabetes as patient representatives on the GDG
 - 35 • consulting the Patient and Public Involvement Programme (PPIP) housed within NICE
36 during the pre-development (scoping) and final validation stages of the guideline project
 - 37 • the inclusion of patient groups as registered stakeholders for the guideline.

2.5 Guideline limitations

2 The guideline has the following limitations.

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

2.6 Other work relevant to the guideline

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

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

23 Related NICE public health guidance:

- 24 • 'Smoking cessation services, including the use of pharmacotherapies, in primary care,
25 pharmacies, local authorities and workplaces, with particular reference to manual working
26 groups, pregnant smokers and hard to reach communities', Public health programme
27 guidance no. PH010 (February 2008)
- 28 • 'Physical activity guidance for the Highways Agency, local authorities, primary care,
29 pharmacists, health visitors and community nurses, schools, workplaces, the leisure and
30 fitness industry and sports clubs', Public health programme guidance no. PH008 (January
31 2007).

32 Related NICE clinical guidelines:

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

45

1

2

3 Related TA guidance:

4 • 'Guidance on the use of ezetimibe for the treatment of primary (heterozygous-familial and
5 non-familial) hypercholesterolaemia', NICE technology appraisal guidance no. 132 (2007)

6 • 'Guidance on the use of statins for the prevention of cardiovascular events in patients at
7 increased risk of developing cardiovascular disease or those with established
8 cardiovascular disease', NICE technology appraisal guidance no. 94 (2006)

9 • 'Guidance on the use of inhaled insulin for the treatment of Type 1 and Type 2 diabetes',

10 NICE technology appraisal guidance no. 113 (2006)

11 • 'Guidance on the use of clopidogrel and dipyridamole for the prevention of arteriosclerotic
12 events', NICE technology appraisal guidance no. 90 (2005)

13 • 'Guidance on the use of the clinical effectiveness and cost effectiveness of insulin pump
14 therapy', NICE technology appraisal guidance no. 57 (2003).

2.7 Background

16 The development of this evidence-based clinical guideline draws upon the methods
17 described by the NICE's 'Guideline development methods manual'¹ and the methodology
18 pack⁷ specifically developed by the NCC-CC for each chronic condition guideline (see
19 www.rcplondon.ac.uk/clinical-standards/ncc-cc/Pages/NCC-CC.aspx). The developers' role
20 and remit is summarised in table 2.1.

Table 2.1 Role and remit of the developers

NCC-CC	<p>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.</p> <p>A multiprofessional partners' board inclusive of patient groups and NHS management governs the NCC-CC.</p>
NCC-CC Technical Team	<p>The technical team met approximately two weeks before each GDG meeting and comprised the following members:</p> <ul style="list-style-type: none"> GDG Chair GDG Clinical Adviser Information Scientist Two Research Fellows Health Economist Project Manager.
GDG	<p>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.</p> <p>The GDG membership details including patient representation and professional groups are detailed in the GDG membership table at the front of this guideline.</p>
Guideline Project Executive	<p>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.</p> <p>The Project Executive comprises: NCC-CC Director NCC-CC Assistant Director NCC-CC Manager NICE Commissioning Manager Technical Team.</p>
Formal consensus	<p>At the end of the guideline development process the GDG met to review and agree the guideline recommendations.</p>

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

1

2.8 The process of guideline development

- 3 The basic steps in the process of producing a guideline are:
- 4 • developing clinical evidence-based questions
 - 5 • systematically searching for the evidence
 - 6 • critically appraising the evidence
 - 7 • incorporating health economic evidence
 - 8 • distilling and synthesising the evidence and writing recommendations
 - 9 • grading the evidence statements
 - 10 • agreeing the recommendations

- 1 • structuring and writing the guideline
- 2 • updating the guideline.

3 **Developing evidence-based questions**

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

7 **Searching for the evidence**

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

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

21 **Appraising the evidence**

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

28 All procedures are fully compliant with the:

- 29 • NICE methodology as detailed in the 'Guideline Development Methods – Information for
30 National Collaborating Centres and Guideline Developers' Manual¹
- 31 • NCC-CC quality assurance document and systematic review chart available at
32 www.rcplondon.ac.uk/clinical-standards/ncc-cc/Pages/NCC-CC.aspx.

33 **Health economic evidence**

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

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

41 **Distilling and synthesising the evidence and developing recommendations**

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

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

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

4 **Grading the evidence statements**

Table 2.2 Grading the evidence statements¹

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

5

6 **Agreeing the recommendations**

7 The GDG employed formal consensus techniques to:

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

13 The GDG also reached agreement on the following:

- 14 • five recommendations as key priorities for implementation
- 15 • five key research recommendations
- 16 • algorithms.

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

- 19 • high clinical impact
- 20 • high impact on reducing variation
- 21 • more efficient use of NHS resources

- 1 • allowing the patient to reach critical points in the care pathway more quickly.
- 2 Audit criteria for this guideline will be produced for NICE by Clinical Accountability Service
3 Planning and Evaluation (CASPE) Research following publication in order to provide
4 suggestions of areas for audit in line with the key recommendations for implementation.

5 Structuring and writing the guideline

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

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

21 Writing the guideline

22 The first draft version of the guideline was drawn up by the technical team in accord with the
23 decisions of the GDG, incorporating contributions from individual GDG members in their
24 expert areas and edited for consistency of style and terminology. The guideline was then
25 submitted for a formal public and stakeholder consultation prior to publication. The registered
26 stakeholders for this guideline are detailed on the NICE website, www.nice.org.uk. Editorial
27 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

28

29 Updating the guideline

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

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

2.9 Disclaimer

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

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

2.10 Funding

- 14 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

- 3 Offer structured education to every person and/or their carer at and around the time of
4 diagnosis, with annual reinforcement and review. Inform people and their carers that
5 structured education is an integral part of diabetes care.
- 6 Provide individualised and ongoing nutritional advice from a healthcare professional with
7 specific expertise and competencies in nutrition.
- 8 When setting a target glycated haemoglobin (GHb):
- 9 • involve the person in decisions about their individual HbA1c target level, which may be
10 above that of 6.5 % set for people with Type 2 diabetes in general
 - 11 • encourage the person to maintain their individual target unless the resulting side effects
12 (including hypoglycaemia) or their efforts to achieve this impair their quality of life
 - 13 • offer therapy (lifestyle and medication) to help achieve and maintain the HbA1c target
14 level
 - 15 • inform a person with a higher HbA1c that any reduction in HbA1c towards the agreed
16 target is advantageous to future health
 - 17 • avoid pursuing highly intensive management to levels of less than 6.5 %.
- 18 Offer self-monitoring of plasma glucose to a person newly diagnosed with Type 2 diabetes
19 only as an integral part of his or her self-management education. Discuss its purpose and
20 agree how it should be interpreted and acted upon.
- 21 When starting insulin therapy, use a structured programme employing active insulin dose
22 titration that encompasses:
- 23 • structured education
 - 24 • continuing telephone support
 - 25 • frequent self-monitoring
 - 26 • dose titration to target
 - 27 • dietary understanding
 - 28 • management of hypoglycaemia
 - 29 • management of acute changes in plasma glucose control
 - 30 • support from an appropriately trained and experienced healthcare professional.

3.2 Algorithms

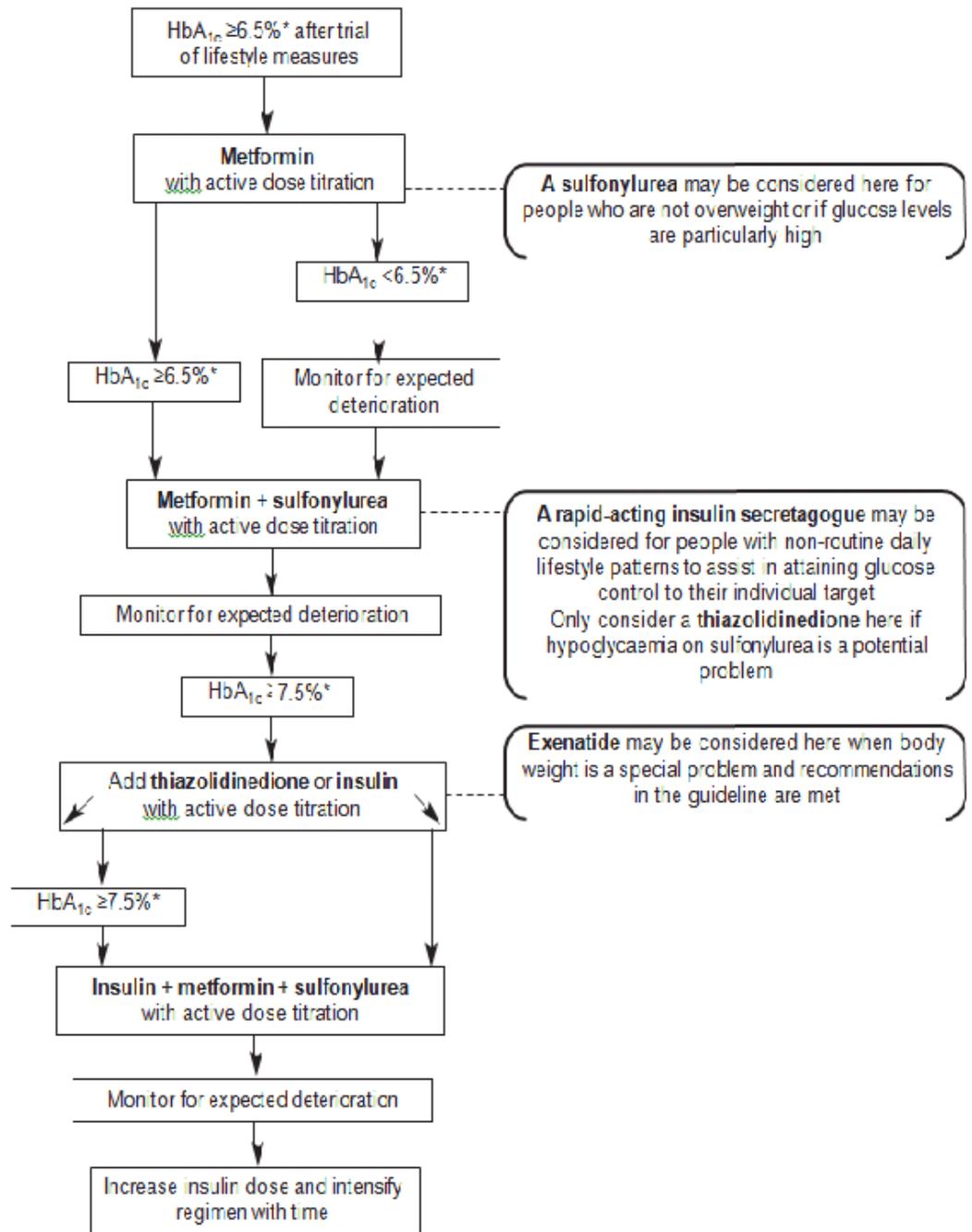


Figure 3.1 Scheme for the pharmacotherapy of glucose lowering in people with Type 2 diabetes. For details see recommendations on glucose lowering targets, clinical monitoring, use of oral agents, and use of insulin.

* or as individually agreed

2
3

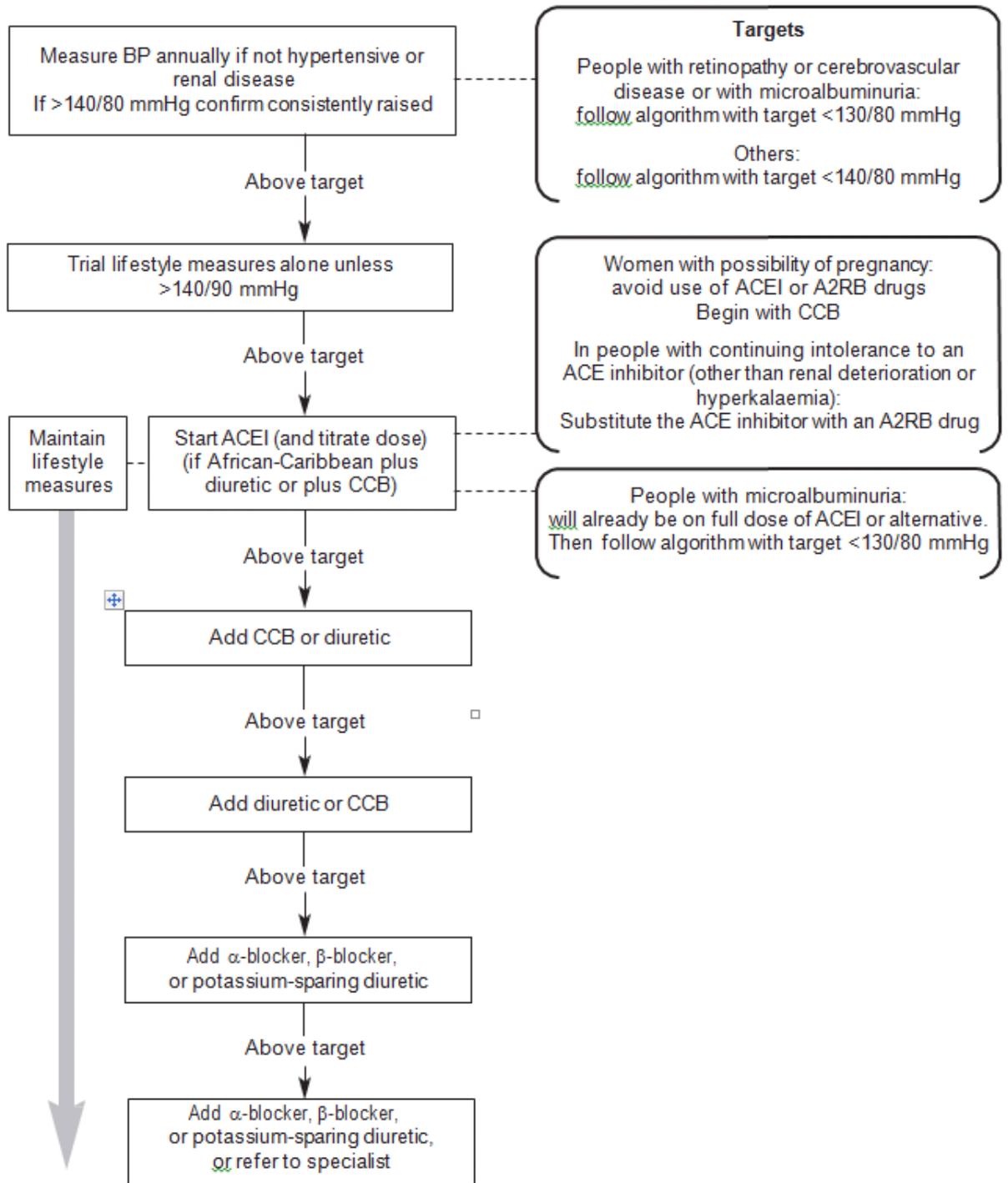


Figure 3.2 Scheme for the management of blood pressure (BP) for people with Type 2 diabetes
ACEI, angiotensin-converting enzyme inhibitor; A2RB, angiotensin 2 receptor blocker (sartan); CCB, calcium channel blocker

1

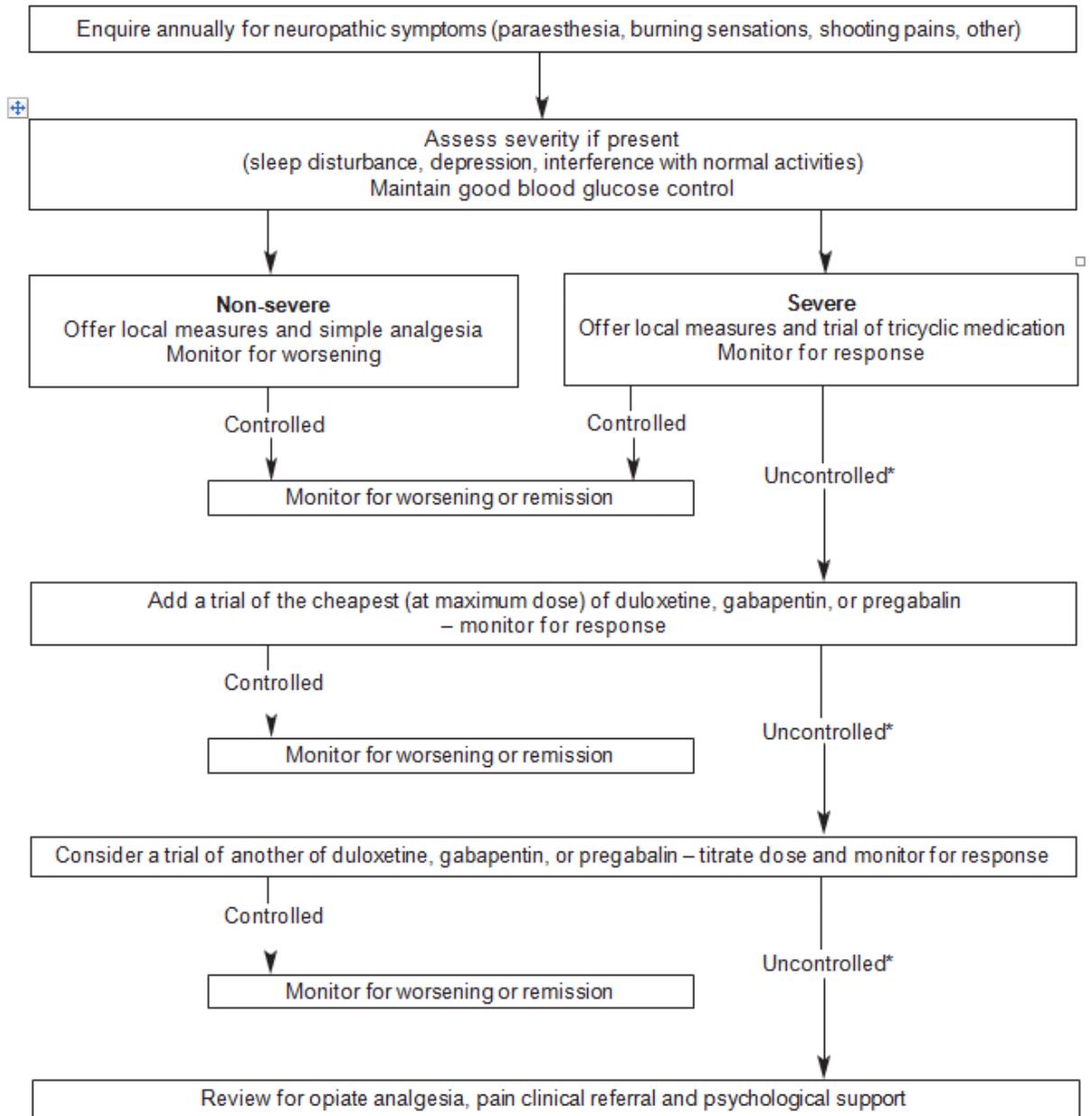


Figure 3.3 Diabetic symptomatic neuropathy management – a therapeutic summary

*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

1

4 Glossary and definitions

- 2 **ACEI** Angiotensin-converting enzyme inhibitor
- 3 **ACR** Albumin creatinine ratio
- 4 **ADA** American Diabetes Association
- 5 **AER** Albumin excretion rate – a measure of kidney damage due to diabetes (and other
6 conditions) and a risk factor for arterial disease.
- 7 **Albuminuria** The presence of albumin and other proteins in urine.
- 8 **Alpha-glucosidase inhibitors** Group of drugs which inhibit the digestion of complex carbohydrates
9 in the gut, and thus flatten the post-meal blood glucose excursion.
- 10 **BMI** Body mass index – a index of body weight corrected for height.
- 11 **Cohort study** A retrospective or prospective follow-up study. Groups of individuals to
12 be followed up are defined on the basis of presence or absence of exposure to a suspected
13 risk factor or intervention. A cohort study can be comparative, in which case two or more
14 groups are selected on the basis of differences in their exposure to the agent of interest.
- 15 **CKD** Chronic kidney disease
- 16 **Confidence interval (CI)** A range of values which contains the true value for the
17 population with a stated 'confidence' (conventionally 95%). The interval is calculated from
18 sample data, and generally straddles the sample estimate. The 95% confidence value means
19 that if the study, and the method used to calculate the interval, is repeated many times, then
20 95% of the calculated intervals will actually contain the true value for the whole population.
- 21 **Cochrane review** The Cochrane Library consists of a regularly updated collection of
22 evidence-based medicine databases including the Cochrane Database of Systematic
23 Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
- 24 **Concordance** Concordance is a concept reflecting the extent to which a course of
25 action agreed between clinicians and a person with diabetes is actually carried out; often but
26 not solely used in the sense of therapeutic interventions or behavioural changes.
- 27 **Cost-effectiveness analysis** An economic study design in which consequences
28 of different interventions are measured using a single outcome, usually in natural units
29 (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected).
30 Alternative interventions are then compared in terms of cost per unit of effectiveness.
- 31 **Cost-utility analysis** A form of cost-effectiveness analysis in which the units of
32 effectiveness are quality adjusted life years.
- 33 **DCCT** Diabetes Control and Complications Trial – a landmark study of the effects of
34 intensification of diabetes care on development of microvascular complications.
- 35 **Diabetes centre** A generic term for a source of a unified multidisciplinary diabetes
36 service.
- 37 **Diabetes mellitus** Chronic condition characterised by elevated blood glucose levels.
38 Diabetes is of diverse aetiology and pathogenesis, and should not be regarded as a single
39 disease. Predominant types are Type 1 diabetes and Type 2 diabetes, diabetes secondary to
40 other pancreatic disease or other endocrine disease, and diabetes of onset in pregnancy.

- 1 **Diabetes UK** Self-help charity for people with diabetes in the UK, and a professional
2 organisation for diabetes care.
- 3 **Education** In the context of this guideline, patient education in self- management
4 of everyday diabetes issues like insulin therapy, dietary changes, self-monitoring of glucose
5 level, physical exercise, coping with concurrent illness, how to avoid hypoglycaemia,
6 complications, arterial risk control, jobs, travel, etc.
- 7 **FBG** Fasting blood glucose level or concentration
- 8 **FPG** Fasting plasma glucose level or concentration
- 9 **Framingham equation** A widely known and used calculation of arterial risk, derived from a
10 long-term study in Framingham, Massachusetts. Not valid in people with Type 1 or Type 2
11 diabetes.
- 12 **GDG** Guideline Development Group
- 13 **Glucose excursions** Change in blood glucose levels especially after meals.
- 14 **GFR** Glomerular filtration rate – a measure of kidney function.
- 15 **GHb** Glycated haemoglobin – see HbA1c.
- 16 **GI** Gastrointestinal
- 17 **HbA1c** The predominant form of glycated haemoglobin, present in red blood cells, and
18 formed when the normal haemoglobin A reacts non-enzymatically with glucose. As the
19 reaction is slow and only concentration dependent, the amount of HbA1c formed is
20 proportional only to the concentration of HbA and glucose. As HbA remains in the circulation
21 for around 3 months, the amount of HbA1c present, expressed as a percentage of HbA, is
22 proportional to the glucose concentration over that time.
- 23 **HTA** Health Technology Assessment, funded by the NHS Research and Development
24 Directorate.
- 25 **IDF** International Diabetes Federation – a global federation of diabetes associations.
- 26 **Incremental cost** The cost of one alternative less the cost of another.
- 27 **Incremental cost effectiveness ratio** The ratio of the difference in costs between two
28 alternatives to the difference in effectiveness between the same two alternatives. (ICER)
- 29 **Insulin analogues** A derivative of human insulin in which change of the amino-acid
30 sequence alters duration of action after injection.
- 31 **Insulin regimen** A therapeutic combination of different insulin preparations, including
32 time of injection and frequency during a day.
- 33 **IHD** Ischaemic heart disease
- 34 **Meta-analysis** A statistical technique for combining (pooling) the results of a number of
35 studies that address the same question and report on the same outcomes to produce a
36 summary result.
- 37 **Metabolic syndrome** Overweight (abdominal adiposity), insulin insensitivity, higher blood
38 pressure, abnormal blood fat profile.
- 39 **Methodological limitations** Features of the design or reporting of a clinical study
40 which are limitations known to be associated with risk of bias or lack of validity. Where a
41 study is reported in this guideline as having significant methodological limitations,
42 a recommendation has not been directly derived from it.

- 1 **MI** Myocardial infarction
- 2 **Microalbuminuria** A low but clinically significant level of albumin and other proteins in
3 the urine.
- 4 **NCC-CC** The National Collaborating Centre for Chronic Conditions, set up in 2000 to
5 undertake commissions from the NICE to develop clinical guidelines for the NHS.
- 6 **NHS** National Health Service – this guideline is written for the NHS in England and Wales.
- 7 **NICE** National Institute for Health and Clinical Excellence – a special health authority set up
8 within the NHS to develop appropriate and consistent advice on healthcare technologies, and
9 to commission evidence-based guidelines.
- 10 **NPH insulin** Neutral protamine Hagedorn insulin – a basal insulin, named after the
11 Danish researcher Hans Christian Hagedorn, and developed in the 1940s. Synonymous with
12 isophane insulin.
- 13 **NS** Not significant (at the 5% level unless stated otherwise).
- 14 **NSC** National Screening Committee (UK)
- 15 **NSF** National Service Framework – a nationwide initiative designed to improve delivery of
16 care for a related group of conditions.
- 17 **Observational study** Retrospective or prospective study in which the investigator
18 observes the natural course of events with or without control groups, for example cohort
19 studies and case-control studies.
- 20 **Odds ratio** A measure of relative treatment effectiveness. An odds ratio of 1 means
21 equality between the comparisons in the study, and higher numbers mean greater
22 differences. The odds of an event happening in the intervention group, divided by the odds of
23 it happening in the control group.
- 24 **PDE5 inhibitors** Phosphodiesterase type 5 inhibitors, a class of drugs developed in
25 recent years to treat erectile dysfunction.
- 26 **PROCAM** Prospective Cardiovascular Münster Heart Study – an epidemiological
27 study performed in Germany.
- 28 **Proteinuria** The presence of protein in the urine.
- 29 **p-values** The probability that an observed difference could have occurred by
30 chance. A p-value of less than 0.05 is conventionally considered to be ‘statistically
31 significant’.
- 32 **Quality of life** A term used to describe an individual’s level of satisfaction with their
33 life and general sense of well-being. It is often measured as physical, psychological and
34 social well-being.
- 35 **Quality of life-adjusted** A measure of health outcome which assigns to each period of
36 time year (QALY) a weight, ranging from 0 to 1, corresponding to the health-related
37 quality of life during that period, where a weight of 1 corresponds to optimal health, and a
38 weight of 0 corresponds to a health state judged equivalent to death; these are then
39 aggregated across time periods.
- 40 **RCT** Randomised controlled trial. A trial in which people are randomly assigned to two
41 (or more) groups – one (the experimental group) receiving the treatment that is being tested,
42 and the other (the comparison or control group) receiving an alternative treatment, a placebo
43 (dummy treatment) or no treatment. The two groups are followed up to compare differences

- 1 in outcomes to see how effective the experimental treatment was. Such trial designs help
2 minimise experimental bias.
- 3 **RR** Relative risk
- 4 **Sensitivity analysis** A measure of the extent to which small changes in parameters and
5 variables affect a result calculated from them. In this guideline, sensitivity analysis is used in
6 health economic modelling.
- 7 **Short-form 36 (SF-36)** The SF-36 assesses functioning and well-being in chronic disease.
8 Thirty-six items in eight domains are included, which cover functional status, well-being, and
9 overall evaluation of health.
- 10 **Specialist** A clinician whose practice is limited to a particular branch of medicine or
11 surgery, especially one who is certified by a higher medical educational organisation.
- 12 **Stakeholder** Any national organisation, including patient and carers' groups,
13 healthcare professionals and commercial companies with an interest in the guideline under
14 development.
- 15 **Statistical significance** ...A result is deemed statistically significant if the probability of the
16 result occurring by chance is less than 1 in 20 ($p < 0.05$).
- 17 **Systematic review** Research that summarises the evidence on a clearly formulated
18 question according to a pre-defined protocol using systematic and explicit methods to
19 identify, select and appraise relevant studies, and to extract, collate and report their findings.
20 It may or may not use statistical meta-analysis.
- 21 **Technology appraisal** Formal ascertainment and review of the evidence surrounding a
22 health technology, restricted in the current document to appraisals undertaken by NICE.
- 23 **Thiazolidinediones** A group of drugs which improve insulin sensitivity in people with
24 reduced sensitivity to their own or injected insulin; presently the licensed drugs are both of
25 the chemical group known as trivially 'glitazones' or PPAR- α agonists.
- 26 **Type 1 diabetes** Insulin-deficiency disease, developing predominantly in childhood,
27 characterised by hyperglycaemia if untreated, and with a consequent high risk of vascular
28 damage usually developing over a period of decades.
- 29 **Type 2 diabetes** Diabetes generally of slow onset mainly found in adults and in
30 association with features of the metabolic syndrome. Carries a very high risk of vascular
31 disease. While not insulin dependent many people with the condition eventually require
32 insulin therapy for optimal blood glucose control.
- 33 **UAER** Urinary albumin excretion rate
- 34 **UKPDS** United Kingdom Prospective Diabetes Study – a landmark study of the effect
35 of different diabetes therapies on vascular complications in people with Type 2 diabetes.
- 36 **WHO** World Health Organization

5 Glucose control levels

5.1 Clinical monitoring of blood glucose levels

5.1.1 Clinical introduction

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

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

5.1.2 Methodological introduction

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

25 Published results from the UKPDS were included in this review if they specifically reported
 26 results on the relationship between HbA1c and microvascular and/or macrovascular
 27 complications. One prospective observational study²⁸ was identified which analysed the
 28 UKPDS glucose control results in terms of both macrovascular and microvascular
 29 complications.

30 A meta-analysis²⁹ was also identified which assessed the association between glycosylated
 31 haemoglobin and cardiovascular (CV) disease in people with diabetes. This included an
 32 analysis of 10 studies specifically of people with Type 2 diabetes. As some of the cohorts
 33 included in this analysis were participants in the UKPDS study, it is necessary to be alert to
 34 double-counting.

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

5.1.3 Health economic methodological introduction

39 One paper was identified which was excluded from further consideration as it was not
 40 possible to compare the costs between patients with good or poor control because the well-
 41 controlled patients were probably earlier in the course of the disease³² Two evaluations
 42 based on the UKPDS were identified that were considered to be of good quality³³

5.1.4 Evidence statements

- 2 • The risk of each of the microvascular and macrovascular complications of Type 2 diabetes
- 3 and cataract extraction was strongly associated with hyperglycaemia as measured by
- 4 updated mean HbA1c.
- 5 • There was no indication of a threshold for any complication below which risk no longer
- 6 decreased, nor a level above which risk no longer increased.
- 7 •

Table 7.1 UKPDS study^{28¶}
 N=3,642 included in the analysis of relative risk¶
Level of evidence 2++^α

¶	→	1% reduction in updated mean HbA _{1c} was associated with reductions in risk of ^α
Microvascular/macrovascular complications or mortality →		21%, 95% CI 17% to 24% (p<0.0001)
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) ^α		
For deaths related to diabetes (MI, sudden death, stroke, lower extremity amputation or fatal peripheral vascular disease, renal disease, hyperglycaemia or hypoglycaemia) ^α	→	21%, 95% CI 15% to 27% (p<0.0001)
All cause mortality →		14%, 95% CI 9% to 19% (p<0.0001) ^α
MI (fatal MI, non-fatal MI, and sudden death) →		14%, 95% CI 8% to 21% (p<0.0001) ^α
Stroke (fatal and non-fatal stroke) →		12%, 95% CI 1% to 21% (p=0.035) ^α
Peripheral vascular disease (lower extremity amputation or death from peripheral vascular disease) ^α	→	43%, 95% CI 31% to 53% (p<0.0001)
Microvascular complications (retinopathy requiring photocoagulation, vitreous haemorrhage, and fatal or¶ non-fatal renal failure) ^α	→	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) ^α
Cataract extraction →		19%, 95% CI 11% to 26% (p<0.0001) ^α
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%. ^α		
* 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 ^α		

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- 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

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- 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 levels

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

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- 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 registry³¹
 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 [□]	

1

5.1.5 Health economic evidence statements

3 The UKPDS included an analysis of intensive blood glucose control with metformin for
 4 overweight patients compared to conventional treatment primarily with diet. The study
 5 included 753 overweight (>120% ideal body weight) patients with newly diagnosed Type 2
 6 diabetes from 15 hospital-based clinics in England, Scotland and Northern Ireland. Of these
 7 patients 342 were allocated to an intensive blood glucose control policy with metformin and
 8 411 were allocated to conventional treatment, primarily with diet alone. The study was
 9 conducted from 1977 to 1991. The median follow-up period was 10.4 years.

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

16 In the 2001 cost-effectiveness analysis, intensive treatment with metformin cost on average
 17 £258 less than conventional treatment, and resulted in a longer life expectancy of 0.4
 18 years.³⁴

19 In the 2005 cost-utility analysis the discounted cost (6% discount rate) of an intensive blood
 20 glucose control policy with insulin or sulphonylureas was on average £884 more per patient
 21 and the discounted benefits gained were 0.15 quality of life-adjusted year (QALY), a cost per
 22 QALY gained of £6,028.³³

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

5.1.6 From evidence to recommendations

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

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

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

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

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

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

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

28 with higher CV risk and longer duration of diabetes, mostly on multiple insulin injection
29 therapy³⁵

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

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

5.4.7 Recommendations

43 **R16** When setting a target glycosylated haemoglobin HbA1c:

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

- 1 • encourage the person to maintain their individual target unless the resulting side effects
2 (including hypoglycaemia) or their efforts to achieve this impair their quality of life
3 • offer therapy (lifestyle and medication) to help achieve and maintain the HbA1c target
4 level
5 • inform a person with a higher HbA1c that any reduction in HbA1c towards the agreed
6 target is advantageous to future health
7 • avoid pursuing highly intensive management to levels of less than 6.5 %.
8
9 **R18** If HbA1c levels remain above target levels, but pre-meal self-monitoring levels remain
10 well controlled (<7.0 mmol/l), consider self-monitoring to detect postprandial hyperglycaemia
11 (>8.5 mmol/l), and manage to below this level if detected
12
13 **R19** Measure HbA1c using high-precision methods and report results in units aligned with
14 those used in DCCT Trial (or as recommended by national agreement after publication of this
15 guideline).

6 Self-monitoring of plasma glucose

6.121 Clinical introduction

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

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

6.122 Methodological introduction

15 Three recent systematic reviews^{36–38} were identified which compared self-monitoring of blood
16 glucose (SMBG) with usual care and/or with self-monitoring of urine glucose (SMUG) in
17 patients with Type 2 diabetes not using insulin. One was a Cochrane review³⁸ of six RCTs
18 without a meta-analysis. The same authors also published a second review³⁷ with the same
19 studies including a meta-analysis. The third review was a meta-analysis of eight RCTs.³⁶
20 Although all of these reviews were of high methodological quality, this was not true of the
21 studies included within them. In two reviews,^{37,38} four out of six studies were found to be of
22 low quality and in the other review,³⁶ five of the eight studies were judged to be of moderate
23 risk of bias and three to be of high risk of bias. A further systematic review and meta-analysis
24 included Type 2 diabetic patients that were on insulin treatment and used Bayesian methods
25 to conduct a mixed treatment comparison.³⁹

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

32 The meta-analysis by Jansen³⁹ scored the included studies for internal validity and adjusted
33 for this in sensitivity analysis. This was also the only new study that compared the effects of
34 urine versus blood self-monitoring on glycaemic control, albeit in an indirect comparison.

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

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

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

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

3 One cross-sectional study⁴⁷ and one case-series⁴⁸ were also identified.

4 The GDG requested for a separate qualitative search to be conducted on this topic. This
5 search identified two papers which considered self-monitoring from a patient perspective.^{49,50}
6 The papers reported results from the same qualitative Scottish study although the papers
7 had slightly different aims. One explored the respective merits of urine testing and SMBG
8 from the perspective of newly diagnosed patients with Type 2 diabetes⁴⁹ whilst the other
9 explored the pros and cons of self-blood glucose monitoring from the patients' perspective.⁵⁰

6.1.3 Health economics methodological introduction

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

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

6.2.4 Evidence statements

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

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

28 The other review³⁶ concluded that, 'in the short term, and when integrated with educational
29 advice, self-monitoring of blood glucose as an adjunct to standard therapy, may contribute to
30 improving glycaemic control among non-insulin requiring Type 2 diabetes patients'. **Level 1+**

31 In an indirect analysis, Jansen³⁹ found a non-significant reduction in HbA1c of 0.3% when
32 interventions with SMBG were compared with those associated with SMUG.

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

39 An RCT looking at the effects of an education manual⁴¹ on blood glucose monitoring found
40 that the greatest reduction in HbA1c occurred in the education manual group ($-0.13 \pm 1.28\%$)
41 compared with both the SMBG ($-0.04 \pm 1.31\%$) and standard care ($0.04 \pm 1.10\%$) groups. The
42 authors did not report whether there was a significant difference between groups. **Level 1+**

43 A second multicentre RCT⁴² found a significantly greater reduction in HbA1c in the SMBG
44 compared to the non-SMBG group ($p=0.0086$). **Level 1+**

- 1 A retrospective cohort study performed in the USA (N=976) found that duration of SMBG (0–
2 3 years) was not a significant predictor of HbA1c values in those with Type 2 diabetes on oral
3 medication.⁴⁵ **Level 2+**
- 4 In a German retrospective cohort study of 1,609 patients with Type 2 diabetes, hazard ratios
5 indicated that SMBG was associated with a 32% reduction in morbidity for combined
6 macrovascular (MI and stroke) and microvascular (foot amputation, blindness or end-stage
7 renal failure) non-fatal endpoints (HR=0.68, 95% CI 0.51–0.91, p=0.009). This was despite
8 an increase of microvascular events, and a 51% reduction in mortality over the observation
9 period (HR=0.49, 95% CI 0.31–0.78, p=0.003) where mean follow-up was 6.5 years. In those
10 not receiving insulin, SMBG was associated with a 28% reduction in combined non-fatal
11 endpoints (HR=0.72, 95% CI 0.52–0.99, p=0.0496) and a 42% reduction in mortality over the
12 observation period (HR=0.58, 95% CI 0.35–0.96, p=0.035).⁴⁴ **Level 2+**
- 13 A retrospective cohort study of people with diabetes in a US medical care programme⁴³ found
14 greater SMBG practice frequency among new users, which was associated with a graded
15 decrease in HbA1c (relative to non-users) regardless of diabetes therapy (p<0.001).
16 Changes in SMBG frequency among prevalent users were associated with an inverse
17 graded change in HbA1c but only among pharmacologically-treated patients (p<0.0001).
18 **Level 2+**
- 19 A study including patients from the Fremantle Diabetes Study (FDS) cohort⁴⁶ over 5 years of
20 follow-up did not find any difference in HbA1c or in fasting plasma glucose, either overall or
21 within treatment groups in patients who used SMBG than those who did not (p≥0.05). There
22 were also no differences in HbA1c or FPG between SMBG adherent and non-adherent users
23 by treatment group (p≥0.09). **Level 2+**
- 24 In a qualitative study performed in Scotland of newly diagnosed Type 2 diabetics, ‘patients
25 reported strongly negative views of urine testing, particularly when they compared it with self-
26 monitoring of blood glucose. Patients perceived urine testing as less convenient, hygienic
27 and accurate than self-monitoring of blood glucose. Most patients assumed that blood
28 glucose meters were given to those with a more advanced or serious form of diabetes.
29 Patients often interpreted negative urine results as indicating that they did not have
30 diabetes.⁴⁹
- 31 A Scottish qualitative study sought newly diagnosed Type 2 diabetes patients’ perspectives
32 on the pros and cons of SMBG.
- 33 Pros of self-monitoring:
- 34 • provides a heightened awareness of, and evidence of, the condition
- 35 • when readings are within advised guidelines and fluctuations are easily interpretable,
36 patients emphasise the positive role that monitoring has in their diabetes management.
37 Low readings are a high point giving personal gratification
- 38 • cultivates independence from health services and enhances self-regulation.
- 39
- 40 Cons of self-monitoring:
- 41 • potentially, self-monitoring can raise anxiety about readings
- 42 • blood glucose parameters were found to be problematic by patients when they felt they
43 were receiving contradictory information about upper thresholds or no guidance about
44 ideal parameters
- 45 • lack of awareness as to how to manage hyperglycaemia
- 46 • increased self-responsibility accompanied by increased self-blame and negative
47 emotional reactions to high glucose readings
- 48 • counter-intuitive readings could be sources of distress and anxiety, in some cases
49 adversely effecting adherence to diabetic regimens by promoting nihilistic attitudes

- 1 • healthcare professionals were not interested in readings.⁵⁰
- 2

6.1.5 From evidence to recommendations

4 The newer meta-analyses did not add significantly to the views expressed in the previous
5 Type 2 diabetes guideline. The findings of the ROSSO study⁴⁴ and the data from the large
6 Kaiser Permanente cohorts⁴³ added considerable confidence to the view that SMBG was an
7 integral part of effective patient education packages and enabled the effective use of many
8 other therapies and lifestyle interventions. The view in the previous guideline that self-
9 monitoring of plasma glucose is not a stand-alone intervention was endorsed.

10 Concern was expressed over a number of issues surrounding the successful use of self-
11 monitoring, and recognised that its cost meant that it had to be effectively deployed. It should
12 only be supported in the context of a provision of a package of care, including structured
13 education, from a primary or secondary diabetes care team. The initial education should be
14 provided by a properly trained and skilled professional with understanding of the problems of
15 the technology. Also, the skills of people with diabetes in using the technology should be the
16 subject of regular quality assurance (together with the devices) perhaps as part of the regular
17 annual review process. Devices should be calibrated to plasma glucose levels in line with
18 2006 WHO recommendations.

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

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

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

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

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

6.4.6 Recommendations

42

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

1 **R23 Self-monitoring of plasma glucose should be available:**

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

9

10 **R25 If self-monitoring is appropriate but blood glucose monitoring is unacceptable to**

11 **the individual, discuss the use of urine glucose monitoring.**

12

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

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

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

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

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

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

7.2.2 Health economic methodological introduction

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

7.2.3 Evidence statements

27 Mortality and morbidity

28 In terms of mortality and morbidity, a Cochrane review⁵⁶ looked at the events listed in the
29 Clinical Endpoint Analyses from the UKPDS^b (UKPDS-34 1998). The systematic review
30 found five studies providing data on mortality and/or morbidity outcomes (four RCTs in
31 addition to the UKPDS).

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

38 In the same vein, the UKPDS found that overweight participants assigned to intensive blood
39 glucose control with metformin (N=342) showed a greater benefit than overweight patients on
40 conventional treatment (non-intensive blood glucose control, mainly with diet), (N=411), for
41 any diabetes-related outcomes, diabetes-related death, all-cause mortality, and MI. For the
42 rest of the outcomes such as stroke, peripheral vascular disease and microvascular, there
43 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.

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

Table 9.1 Metformin mortality and morbidity studies ^a		
Study/comparison ^a	Outcome ^a	Effect-size (RR) ^a
UKPDS: metformin vs sulfonylureas or insulin ^a	Any diabetes-related outcomes ^a	0.78 (95% CI 0.65 to 0.94) p=0.009 ^a
	All-cause mortality ^a	0.73 (95% CI 0.55 to 0.97) p=0.03 ^a
	Diabetes-related death ^a	NS ^a
	Myocardial infarction ^a	NS ^a
	Stroke ^a	NS ^a
	Peripheral vascular disease ^a	NS ^a
	Microvascular ^a	NS ^a
UKPDS: metformin vs conventional (non-intensive blood glucose control, ^a mainly with diet) ^a	Any diabetes-related outcomes ^a	0.74 (95% CI 0.60 to 0.90) p=0.004 ^a
	Diabetes-related death ^a	0.61 (95% CI 0.40 to 0.94) p=0.03 ^a
	All-cause mortality ^a	0.68 (95% CI 0.49 to 0.93) p=0.01 ^a
	Myocardial infarction ^a	0.64 (95% CI 0.45 to 0.92) p=0.02 ^a
	Stroke ^a	NS ^a
	Peripheral vascular disease ^a	NS ^a
	Microvascular ^a	NS ^a
Non-UKPDS trials: metformin vs ^a comparison ^a	All-cause mortality ^a	NS ^a
	Ischaemic heart disease ^a	NS ^a

4

5 Glucose control

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

1 Body weight/ body mass index

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

9 Lipid profile

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

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

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

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

18 In a comparison of metformin against insulin, significant benefits for metformin were found in
19 terms of total and LDL-C levels but not high-density lipoprotein cholesterol (HDL-C).⁵⁶ **Level**
20 **1++**

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

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

28 Where MIR was compared with MXR treatment, lipid profiles were similar between groups
29 (statistical significance not reported) except for triglycerides where the mean change from
30 baseline in the immediate-release group was 1 mg/dL; but was 34 mg/dl in the MXR 1,000
31 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 ⁶⁶ 12 studies N=1,387	SMD -0.97 (95% CI -1.25 to -0.69)	SMD -0.07 (95% CI -1.15 to -0.01)	NE	NS	—	NS Four studies N=906	NS Four studies N=415	NS Three studies N=374	NS Four studies N=415
Metformin vs diet	Cochrane systematic review ⁶⁶ Three studies N=814	SMD -1.06 (95% CI -1.89 to -0.22)	NS	NE	NS	—	SMD -0.59 (91% 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 ⁶⁶ 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 One study N=62
Metformin vs sulfonylureas	Cochrane systematic review ⁶⁶ 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 ⁶⁶ 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

1

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 ⁶⁶ 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 ⁶⁸ N=1,198	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 +0.05 mmol/l metformin p=0.001
Metformin vs insulin	Cochrane systematic review ⁶⁶ Two studies N=811	NS	NS	NE	SMD -0.01 (95% CI -1.44 to -0.37)	—	SMD -0.77 (91% CI -1.29 to -0.24) One study N=60	SMD -0.63 (95% CI -1.35 to -0.30) One study N=60	NS One study N=60	SMD 0.85 (95% CI 0.13 to 1.17) One study N=60

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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 ⁶² 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 and –1 mg/dL, MXR 1,500*
Rosiglitazone/metformin (FDC) vs metformin	One study ⁶³ N=569	Treatment difference: –0.22% (95% CI –0.36 to –0.09%, p=0.007)	–18.5 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 (+3 (0.22) kg) and a mean decrease in the ME 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*	–6.5% change from baseline for MET vs +2.2% RSG/MET*	–1.3% change from baseline for MET vs 4.1% RSG/MET*

Continued

1

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 ⁶⁴ 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	0.3 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	0.30%, p=0.007	NE	PPBG NS	NE	NS	NE	NE	NS	NS

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

2

3

1 **Adverse events**

2 Adverse events

3 The main differences across all the different treatment groups were:

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

10 **Level 1+**

11 In the only RCT⁶⁵ directly comparing MIR and MXR, more diarrhoea, flatulence and
12 abdominal pain were experienced in the extended-release group whilst more or equivalent
13 proportions of patients, experienced nausea/vomiting, headache and dyspepsia/heartburn in
14 immediate-release group (significance tests not performed). In placebo-controlled studies,
15 patients on MXR always experienced more GI AEs than those on placebo.⁶⁶ **Level 1+**

16 A retrospective chart review⁶⁷ found a significantly reduced frequency of GI AE in a cohort of
17 patients when they were switched from MIR to MXR. A cohort of patients taking metformin
18 for the first time also experienced less GI AEs if they were commenced on MXR rather than
19 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

20

Table 9.3 Metformin adverse events – <i>continued</i>		
Comparison	Study	Size effect
Head-to-head comparisons – <i>continued</i>		
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

1

Table 9.3 Metformin adverse events – *continued*

Comparison	Study	Size effect
Head-to-head comparisons – <i>continued</i>		
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		

1

2 Lactic acidosis

3 A Cochrane review⁵⁷ looked at the risk of lactic acidosis in patients treated with metformin.
4 There were no cases of fatal or non-fatal lactic acidosis reported. **Level 1+**

5 In addition, one RCT⁵⁸ did not find a significant difference in plasma lactate levels between
6 metformin-treated patients and patients treated with other antidiabetic agents. **Level 1+**

7.2.4 Health economics evidence statements

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

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

- 1 Resource use was routinely collected as part of the study. Non-inpatient resource use data
 2 was collected using a questionnaire distributed between January 1996 and September 1997.
 3 The incremental costs reported in the analysis have the study protocol driven costs removed.
 4 These were replaced with a pattern of clinic visits reflecting general practitioner and
 5 specialist clinical opinion on the implementation of intensive policy.
- 6 Where a patient was still alive at the end of the follow-up, a simulation model was used to
 7 estimate the time from end of follow-up to death. It was assumed that there would be no
 8 continuation of benefit of therapy beyond the trial period in both evaluations.
- 9 The data was used in a cost-effectiveness analysis³⁴ and a cost-utility analysis.³³ Both
 10 evaluations showed intensive blood glucose control with metformin for overweight patients to
 11 be cost-saving compared to conventional treatment.
- 12 In the cost-utility analysis, within trial costs and projected costs were included. In the cost-
 13 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	
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)

- 14
 15
 16

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)

1

2 In the cost-effectiveness model with costs and effects discounted at a 6% rate, there was a
3 71% probability that metformin would prove to be cost-saving compared with a conventional
4 policy.³⁴

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

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

7.3 Insulin secretagogues

7.3.1 Methodological introduction

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

20 Twenty-one studies were identified, four of which were excluded due to methodological
21 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

1

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

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

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

7.3.2 Health economic methodological introduction

10 Thirteen papers were identified in the literature search. Of these, three were considered of
11 good quality and relevant to the guideline. Two UKPDS papers were identified; a cost-utility
12 analysis³³ and a cost-effectiveness⁹⁸ analysis of intensive blood glucose control.

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

7.3.3 Evidence statements

2 Metiglinides (repaglinide and nateglinide) vs placebo

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

Table 9.9 Nateglinide (120 mg) vs placebo

1 study⁸¹ N=47

Level of evidence 1+

HbA _{1c}	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			

6

Table 9.10 Nateglinide (30, 60, 120 mg) vs placebo

1 study⁸⁰ 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	<p>Hypoglycaemia</p> <p>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</p> <table border="1"> <thead> <tr> <th></th> <th>Symptomatic</th> <th>Confirmed</th> </tr> </thead> <tbody> <tr> <td>Placebo</td> <td>4.9%</td> <td>(1.2%)</td> </tr> <tr> <td>30 mg nateglinide</td> <td>12%</td> <td>(2.4%)</td> </tr> <tr> <td>60 mg nateglinide</td> <td>11.4%</td> <td>(4.0%)</td> </tr> <tr> <td>120 mg nateglinide</td> <td>22.8%</td> <td>(5.3%)</td> </tr> </tbody> </table>					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%)
	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%)																	

7

Table 9.11 Repaglinide vs placebo1 study⁸² 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)			

1

2 Repaglinide vs nateglinide

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

- 5 • repaglinide and nateglinide had similar postprandial glycaemic effects. However,
6 repaglinide was more effective than nateglinide in reducing HbA_{1c} and FPG values
7 • a greater weight gain (p=0.04) was seen in repaglinide-treated patients when compared to
8 • nateglinide-treated patients
9 • hypoglycaemic events were more frequently reported by patients receiving repaglinide
10 (non-significant difference between the two groups).
11

Table 9.12 Repaglinide vs nateglinide1 study⁸³ 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			

1

2

3 Meglitinides vs sulfonylureas

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

Table 9.13 Repaglinide vs glimepiride1 study⁸⁴ 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			

7

Table 9.14 Repaglinide vs glipizide1 study⁸⁵ 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)			

1

Table 9.15 Repaglinide vs glibenclamide1 study⁸⁶ 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				

2

1 Gliclazide modified release vs gliclazide

- 2 When a modified-release version of gliclazide was compared with the immediate-release
3 version of gliclazide in people with Type 2 diabetes who had been on diet control or on
4 treatment with oral hypoglycaemic agents:
- 5 • both versions were associated with significant reductions in HbA1c (non-significant
6 difference between the two groups). FPG decreased significantly on gliclazide MR but not
7 on gliclazide (non-significant difference between the two groups)
 - 8 • no clinically significant changes were seen in terms of lipid profile (non-significant
9 difference between the two groups)
 - 10 • hypoglycaemic events were only reported by patients receiving gliclazide MR (9%) (non-
11 significant difference was reported between the two groups).
- 12

Table 9.16 Gliclazide MR vs gliclazide

1 study⁹⁴ N=63

Level of evidence 1+

HbA1c	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	<p>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%)</p> <p>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</p>			

13

14 Gliclazide MR vs glimepiride

- 15 When a modified-release version of gliclazide was compared with glimepiride in people with
16 Type 2 diabetes being treated with diet alone or with either metformin or alpha-glucosidase
17 inhibitors:
- 18 • both interventions were equally effective in terms of glycaemic control (alone or in
19 combination with metformin or alpha-glucosidase inhibitors)
 - 20 • gliclazide MR had a better safety profile than glimepiride.

Table 9.17 Gliclazide MR vs glimepiride1 study⁹³

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 mmol/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 ratio of 2.5 (95% CI, 1.4 to 4.7)			
* Indicates statistical significance tests between groups were not reported/performed				

1

2 Insulin lispro vs glibenclamide

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

- 5 • both regimes produced comparable effects in the control of glycaemia with respect to
6 HbA_{1c}. However, treatment with insulin lispro resulted in smaller postprandial blood
7 glucose excursions compared to oral treatment with glibenclamide
- 8 • no significant differences were observed between the treatment groups regarding
9 hypoglycaemic episodes and other AEs.

10

Table 9.18 Insulin lispro vs glibenclamide1 study⁹⁶ 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			

11

1 **Bedtime NPH + repaglinide vs bedtime NPH + gliclazide**

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

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

9

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			

10

11

12 **Nateglinide + metformin vs gliclazide + metformin**

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

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

17

Table 9.20 Nateglinide + metformin vs gliclazide + metformin				
1 study⁹¹ 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			

1
2

3 **Glimepiride + metformin vs glimepiride vs metformin**

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

- 6 • combination treatment was more effective than either drug alone in terms of glycaemic
7 control
- 8 • combination therapy was more effective than either drug in reducing TC levels
- 9 • metformin alone resulted in a significantly lower BMI than either glimepiride alone, or the
10 combination
- 11 • the incidence of hypoglycaemic episodes was significantly higher in the combination
12 treatment group than in either of the monotherapy groups.
13

Table 9.21 Glimepiride vs metformin vs glimepiride + metformin
 1 study⁹⁵ 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 <table border="1"> <thead> <tr> <th></th> <th>N</th> <th>(%)</th> </tr> </thead> <tbody> <tr> <td>Metformin</td> <td>22</td> <td>(29%)</td> </tr> <tr> <td>Glimepiride</td> <td>38</td> <td>(25%)</td> </tr> <tr> <td>G + M</td> <td>45</td> <td>(31%)</td> </tr> </tbody> </table> 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)					N	(%)	Metformin	22	(29%)	Glimepiride	38	(25%)	G + M	45	(31%)
	N	(%)														
Metformin	22	(29%)														
Glimepiride	38	(25%)														
G + M	45	(31%)														

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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:

- 1 • nateglinide, metformin and combination therapy (nateglinide + metformin), were
 2 associated with significant reductions in HbA_{1c}, FPG and PPGE (an additive effect was
 3 seen with combination therapy)
 4 • the incidence of GI AEs was higher in patients receiving combination therapy and
 5 metformin than in those receiving placebo and nateglinide
 6 • the incidence of hypoglycaemic episodes was higher in the combination treatment group
 7 than in either of the monotherapy groups.

Table 9.22 Nateglinide vs metformin vs nateglinide + metformin
 1 study⁹¹ 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	<p>No serious AEs judged to be related to study medication</p> <p>GI</p> <p>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)</p> <p>Incidence of symptomatic hypoglycaemia in patients receiving combination therapy=29%</p> <p>Incidence of confirmed hypoglycaemia in drug naive patients receiving combination therapy 3.4% (with all considered to be mild)</p>				

8
 9
 10

1 **Nateglinide + insulin glargine vs placebo + insulin glargine**

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

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

7

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.			
		Difference in mmol/l		
	Time	(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			

8
9

10 **Diet vs sulphonylurea vs insulin**

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

1

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			
		Grades 1–4 hypoglycaemia	Grades 2–4 hypoglycaemia	
	Therapy			
	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				

2

7.34 Health economic evidence statements

4 Sulphonylurea monotherapy

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

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

13 Combination therapy

14 Metformin monotherapy (1,500 mg/day) was compared with nateglinide (360 mg/day) plus
15 metformin (1,500 mg/day) in a UK setting. A hypothetical population based on US data was
16 used. The mean baseline HbA_{1c} level was 8.4%. The duration of diabetes was not stated,
17 although a pre-model period of 7 years was included. The resulting cost per QALY was
18 £8,058 (1999 cost year, 3% discount rate).⁷⁴

7.4 Acarbose

7.4.21 Methodological introduction

3 A Cochrane review⁹⁹ and eight RCTs^{100–107} compared monotherapy acarbose or other
4 combination OAD drugs, with other OAD drug regimens or placebo. Studies were excluded
5 unless they were of at least 12-weeks duration. Two of the RCTs^{100,107} were excluded due to
6 methodological limitations.

7 The Cochrane review⁹⁹ identified 30 RCTs in a search performed in April 2003 which
8 compared acarbose monotherapy with placebo, sulfonylureas, metformin or nateglinide. The
9 additional six RCTs included in this analysis compared acarbose with placebo when both
10 groups were also treated with metformin,¹⁰⁴ with sulphonylureas,^{105,106} or with insulin,¹⁰³ and
11 there were also comparisons between acarbose and pioglitazone¹⁰¹ and acarbose and
12 sulfonylurea.¹⁰²

13 Although a substantial amount of evidence has been found in this area, several different drug
14 combinations and comparisons, differing dosing and titration regimens and the differing
15 populations included in the studies, limit direct comparison between studies. Additionally,
16 some study results may not be generalisable to a UK population of people with Type 2
17 diabetes. For example, the study by Lin¹⁰⁶ was undertaken in a Chinese population with a
18 mean BMI of 25 kg/m².

7.4.22 Health economic methodological introduction

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

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

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

7.4.23 Evidence statements

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

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

38

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		

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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		

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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

1
2**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)

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continued

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

Comparison	Study	BMI (kg/m ²)	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

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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

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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

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7.5 Oral glucose control therapies; from evidence to recommendations

2

7.5.1 Metformin

4 None of the newer evidence altered the priority given to metformin cited in the previous
 5 guideline. Although the specific cardioprotective effects of metformin suggested by the
 6 UKPDS study were open to challenge from some of the very recent studies, this was not on
 7 the basis of strong outcome data. Large observational studies from Canada and Scotland
 8 ^{111,112} appeared to support the widespread advantage of metformin over sulfonylureas, but
 9 the A Diabetes Outcome Progression Trial (ADOPT) study did not. The cardioprotective
 10 gains shown in the UKPDS and in the Scottish study far outweighed the concerns over lactic
 11 acidosis (provided renal function was adequate) in people with mild to moderate hepatic and
 12 cardiac disease. Nearly all the data related to overweight people, and there was little to guide
 13 metformin use in the normal weight person without extrapolation of the evidence. However,
 14 the overwhelming majority of people with Type 2 diabetes are overweight; in making this
 15 judgement however attention has to be paid to differences between ethnic groups.

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

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

7.5.2 Insulin secretagogues

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

29 The evidence base for the insulin secretagogues was more extensive than ascertained for
 30 the parent guideline. However, in many of the papers in which they are compared to other
 31 drugs they were being used as the comparator therapy rather than the investigated therapy.
 32 New evidence did not lead to new conclusions about the role of these drugs in clinical
 33 management, either from the point of view of efficacy or safety. Sulfonylureas proved as
 34 efficacious as newer comparator therapies in reducing surrogate outcomes (principally
 35 HbA1c) highlighting that they still have a role in modern management of Type 2 diabetes. In
 36 the ADOPT study⁵⁴ the sulfonylurea glibenclamide controlled HbA1c as effectively as
 37 rosiglitazone or metformin as monotherapy for the first 3 years, but persistence of glucose
 38 control after this time was worse. Cardiovascular outcomes were, if anything, better with the
 39 sulfonylurea.

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

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

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

7.58 α -glucosidase inhibitors

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

17 ORAL GLUCOSE CONTROL THERAPIES; RECOMMENDATIONS

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

19 Metformin

- 20 1. **Start metformin treatment in a person who is overweight or obese (tailoring the**
21 **assessment of body weight associated risk according to ethnic group^{*c}) and**
22 **whose blood glucose is inadequately controlled (see recommendation 16) by**
23 **lifestyle interventions (nutrition and exercise) alone. (26)**
- 24 2. **Consider metformin as an option for first-line glucose-lowering therapy for a**
25 **person who is not overweight. (27)**
- 26 3. **Continue with metformin if blood glucose control remains or becomes inadequate**
27 **(see recommendation 16) and another oral glucose-lowering medication (usually a**
28 **sulfonylurea) is added. (28)**
- 29 4. **Step up metformin therapy gradually over weeks to minimise risk of**
30 **gastrointestinal side effects. Consider a trial of extended absorption metformin**
31 **tablets where gastrointestinal tolerability prevents continuation of metformin**
32 **therapy. (29)**
- 33 5. **The benefits of metformin therapy should be discussed with a person with mild to**
34 **moderate liver dysfunction or cardiac impairment so that:**
 - 35 5.1. **due consideration can be given to the cardiovascular-protective effects of**
36 **the drug**
 - 37 5.2. **an informed decision can be made on whether to continue or stop the**
38 **metformin.**

39 Insulin secretagogues

- 40 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.jsp?action=byID&ID=11000

- 1 **6.1. the person is not overweight**
- 2 **6.2. the person does not tolerate or is contraindicated**
- 3 **6.3. a rapid response to therapy is required because of hyperglycaemic**
4 **symptoms.**
- 5 **7. Add a sulfonylurea as second-line therapy when blood glucose control remains,**
6 **or becomes, inadequate (see recommendation 16) with metformin.**
- 7 **8. Continue with a sulfonylurea if blood glucose control remains, or becomes,**
8 **inadequate (see recommendation 16) and another oral glucose-lowering**
9 **medication is added. (34)**
- 10 **9. Prescribe a sulfonylurea with a low acquisition cost (but not glibenclamide) when**
11 **an insulin secretagogue is indicated (see recommendation 32 and 33).**
- 12 **10. When drug concordance is a problem, offer a once daily, long-acting sulfonylurea.**
- 13 **11. Educate a person being treated with an insulin secretagogue, particularly if renally**
14 **impaired, about the risk of hypoglycaemia.**
- 15 **Rapid-acting insulin secretagogues**
- 16 **12. Consider offering a rapid-acting insulin secretagogue to a person with an erratic**
17 **lifestyle. (38)**
- 18 **Acarbose**
- 19 **13. Consider acarbose for a person unable to use other oral glucose-lowering**
20 **medications. (39)**
- 21
- 22
- 23 **NEED TO RE-ADD IN DIAGRAM BELOW FROM PDF**

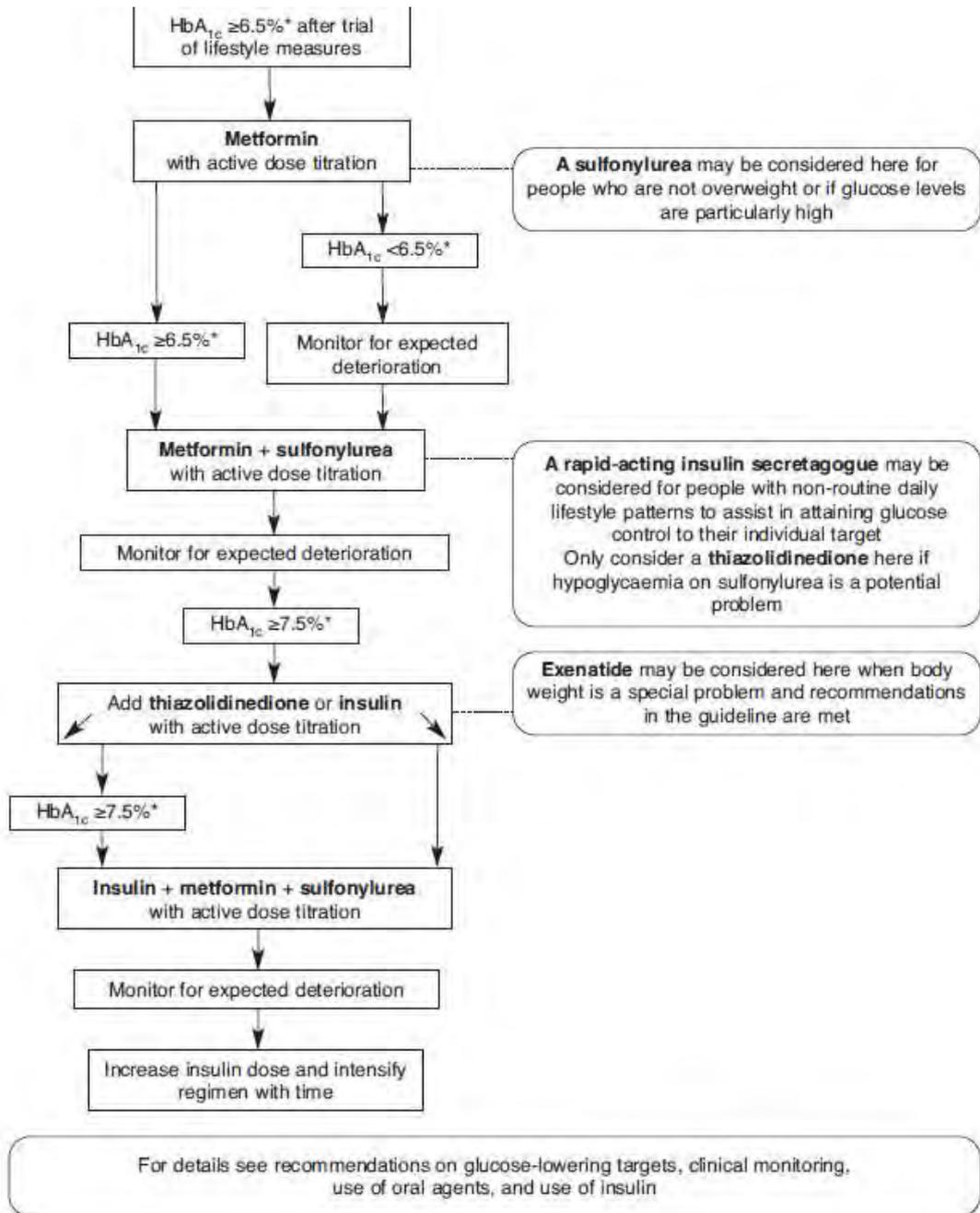


Figure 9.1 Scheme for the pharmacotherapy of glucose lowering in people with Type 2 diabetes
 For details see recommendations on glucose lowering targets, clinical monitoring, use of oral agents, and use of insulin
 * or as individually agreed

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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.’

1 Rosiglitazone

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

- 7 • as monotherapy in patients (particularly overweight patients) inadequately controlled by
8 diet and exercise for whom metformin is inappropriate because of contraindications or
9 intolerance
- 10 • as dual oral therapy in combination with:
 - 11 ○ metformin in patients (particularly overweight patients) with insufficient glycaemic
12 control despite maximal tolerated dose of monotherapy with metformin
 - 13 ○ a sulfonylurea, only in patients who show intolerance to metformin or for whom
14 metformin is contraindicated, with insufficient glycaemic control despite monotherapy
15 with a sulfonylurea
- 16 • as triple oral therapy in combination with metformin and a sulfonylurea, in patients
17 (particularly overweight patients) with insufficient glycaemic control despite dual oral
18 therapy.'
- 19 • Rosiglitazone is also available in two combination tablet formats (with metformin and also
20 with glimepiride).

21 Studies reporting cardiovascular outcomes

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

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

32 A further review of meta-analyses looking at the glitazones CV safety was undertaken in
33 order to clarify the concerns in relation to the apparent risk of MI in patients treated with
34 rosiglitazone. Five meta-analyses^{117–121} and one Cochrane systematic review¹²² were
35 identified. Among the five meta-analyses, three were looking at rosiglitazone,^{118,119,121} one at
36 pioglitazone¹¹⁷ and one at both glitazones agents.¹²⁰ EMA, US Food and Drug
37 Administration (FDA), and the Medicines and Healthcare products Regulatory Agency
38 (MHRA) statements on glitazones were also reviewed along with an independent FDA meta-
39 analysis on rosiglitazone presented at the FDA joint advisory committee on 30 July 2007.

d The European Medicines Agency (EMA) 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.

1 **Studies reporting surrogate outcomes**

2 Seventeen RCTs were identified which compared rosiglitazone as monotherapy or in
3 combination with other oral antidiabetic agents, with other oral antidiabetic agents and/or
4 placebo.^{54,61,62,123–136}

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

9 Two additional studies looking at the addition of insulin glargine or rosiglitazone to the
10 combination therapy of sulfonylurea plus metformin in insulin-naive patients were also
11 identified.^{139,140}

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

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

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

20 **Pioglitazone**

21 Pioglitazone is now licensed for use as monotherapy, combination therapy with metformin or
22 a sulfonylurea, as part of triple therapy with metformin and a sulfonylurea, or in combination
23 therapy with insulin. As from September 2007 the EMEA¹¹⁴ states that, 'pioglitazone is
24 indicated in the treatment of Type 2 diabetes mellitus:

- 25 • as monotherapy in patients (particularly overweight patients) inadequately controlled by
26 diet and exercise for whom metformin is inappropriate because of contraindications or
27 intolerance
- 28 • as dual oral therapy in combination with:
 - 29 ○ metformin in patients (particularly overweight patients) with insufficient glycaemic
30 control despite maximal tolerated dose of monotherapy with metformin
 - 31 ○ a sulfonylurea, only in patients who show intolerance to metformin or for whom
32 metformin is contraindicated, with insufficient glycaemic control despite maximal
33 tolerated dose of monotherapy with a sulfonylurea
- 34 • as triple oral therapy in combination with:
 - 35 ○ metformin and a sulfonylurea, in patients (particularly overweight patients) with
36 insufficient glycaemic control despite dual oral therapy
- 37 • pioglitazone is also indicated for combination with insulin in Type 2 diabetes mellitus
38 patients with insufficient glycaemic control on insulin for whom metformin is inappropriate
39 because of contraindications or intolerance.'

40 A Cochrane review¹⁴¹ was identified which searched for pioglitazone RCTs of at least 24-
41 weeks duration published up until August 2006. The review identified 22 studies including
42 comparisons of pioglitazone monotherapy with placebo, pioglitazone monotherapy with any
43 other OAD medication, and pioglitazone in combination with any other OAD medication or
44 insulin, compared with any other OAD medication or insulin.

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

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

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

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

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

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

23 As noted in the rosiglitazone section a further review of meta-analyses published up to
24 December 2007 looking at the glitazones CV safety was undertaken. In relation to
25 pioglitazone two meta-analyses were identified as relevant: a meta-analysis analysing
26 pioglitazone studies¹¹⁷ and one looking at both glitazones agents.¹²⁰

27 **Thiazolidinediones and the risk of oedema**

28 One meta-analysis¹⁵³ was identified assessing the overall risk for developing oedema
29 secondary to glitazones (rosiglitazone and pioglitazone).

8.2.2 **Health economic methodological introduction**

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

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

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

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

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

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

8.2.3 Evidence statements

8.2.3.1 Rosiglitazone

7 Cardiovascular outcomes

8 One meta-analysis¹¹⁵ concluded that rosiglitazone was associated with a significant increase
 9 in the risk of MI and a borderline significant finding for death from CV causes (see tables
 10 10.1 and 10.2).^e
 11

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

12
13

14 Findings from an interim report of the RECORD study^{f116} were inconclusive regarding the
 15 effect of rosiglitazone on the overall risk of hospitalisation or death from CV causes. The
 16 report concluded that rosiglitazone was associated with a significant increase in the risk of
 17 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				

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

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

8 None of the 18 rosiglitazone trials analysed by the Cochrane systematic review¹²² included
9 mortality or morbidity as a primary or secondary endpoint. The review stated that active
10 glucose-lowering agents like metformin, glibenclamide, or glimepiride resulted in similar
11 reductions of HbA1c compared to rosiglitazone treatment. The only outcome that could be
12 subjected to meta-analysis was oedema whose incidence was significantly raised in patients
13 receiving rosiglitazone (OR 2.27, 95% CI 1.83 to 2.81). The systematic review concluded that
14 new studies should focus on patient-oriented outcomes to clarify the benefit–risk ration of
15 rosiglitazone therapy.

16 Three of the four rosiglitazone meta-analyses reported a statistically significant increase in
17 the RR of myocardial ischaemic events among patients taking rosiglitazone (see table 10.4).
18 In addition, the meta-analysis by Singh¹¹⁹ concluded that among patients with Type 2
19 diabetes, rosiglitazone use for at least 12 months is associated with a significantly increased
20 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

21
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23 One additional meta-analysis on rosiglitazone¹¹⁸ reanalysed the data set of 42 trials
24 considered originally by Nissen and Wolski¹¹⁵ by using various modelling and weighting

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

5 A meta-analysis of 19 pioglitazone trials¹¹⁷ (with the PROactive study being the largest study
 6 included) reported that treatment with pioglitazone was associated with a significantly lower
 7 risk of death, MI, or stroke. Pioglitazone was also associated with a significantly higher risk of
 8 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

9
 10 A further meta-analysis¹²⁰ looking at the risk of CHF and CV death in patient with pre-
 11 diabetes and Type 2 diabetes treated with glitazones reported a significantly higher risk of
 12 developing heart failure in those treated with rosiglitazone or pioglitazone compared with
 13 controls (RR 1.72 95% CI 1.21 to 2.42, p=0.002). By contrast, the study reported that the risk
 14 of CV death was not increased with either of the two glitazones.

8.2.32 Glycaemic control

16 Head-to-head comparisons

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

22 Combination therapy

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

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

8.2.33 Triple therapy

31 Two studies^{139,140} compared the addition of rosiglitazone to the combination of sulfonylurea
 32 and metformin with the addition of insulin glargine. HbA1c improvements from baseline were
 33 similar in both groups with no significant difference between the groups. However, one
 34 study¹³⁹ found that when baseline HbA1c was more than 9.5%, the reduction of HbA1c with

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

3 **Fixed-dose combination**

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

8.2.34 **Rosiglitazone vs pioglitazone**

9 Only one study compared metformin used in combination with rosiglitazone with treatment
10 with metformin and pioglitazone. The study did not find significant differences between the
11 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

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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 (–1.86% 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 –0.38 to –0.09, p=0.001) in favour of the FDC
Rosiglitazone/metformin (FDC) vs metformin monotherapy	One study ¹³⁵ N=528	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 238.4 to 181.1 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)
<i>continued</i>		

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Table 10.7 Fasting plasma glucose/fasting blood glucose outcomes – <i>continued</i>		
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

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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

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2 Lipid profile

3 Overall, treatment with rosiglitazone (used as monotherapy, dual therapy, fixed-dose
4 combination or triple therapy) was associated with significantly larger increases in total
5 cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) compared to other
6 therapies.⁹ In addition, rosiglitazone was associated with a significantly greater use of lipid-
7 lowering therapy.

8 The study comparing rosiglitazone and pioglitazone showed that patients in the pioglitazone
9 add- on to metformin group experienced significant reductions (p≤0.05) in TC, low-density
10 lipoprotein (LDL) and triglyceride (TG) levels when compared to those receiving rosiglitazone
11 + metformin. High-density lipoprotein (HDL) levels were significantly higher (p≤0.05) in
12 patients treated with pioglitazone + metformin when compared to patients in the rosiglitazone
13 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	+8%	+9%	-8%	+7%
	1+	+1%	+1%	+4%	0%
	1+	+5%	+6%	-4%	+7%
Rosiglitazone vs glibenclamide	One study ¹²⁸ N=203	NE	+7.7 mg/dl	-2.8 mg/dl	+7.7 mg/dl
	1+		-8.9 mg/dl	-13.8 mg/dl	
	One study ¹²⁹ N=598	+0.7 mmol/l	+0.4 mmol/l	NS	+0.17 mmol/l
1+	-0.1 mmol/l	-0.1 mmol/l		-0.08 mmol/l	

14

continued

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

Table 10.8 Lipid profile outcomes* (changes from baseline) – <i>continued</i>					
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 up titration	One study ¹³² N=471	+8.8% +1.2%	+10.9% 0%	+7.7% +3.5%	+6.8% 0%
Rosiglitazone + glibenclamide vs glibenclamide up titration	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 up titrated	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= 528	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=488 1+	FDC -2.2% RSG +5.3% (p=0.0008 vs FDC) MET -9% (p=0.009 vs 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

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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

1 * Significance testing not performed

2 Body weight/body mass index

3 Across most of the studies treatment with rosiglitazone was associated with a significant
4 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

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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=528	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

1

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

1

2 Quality of life

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

8 Adverse events

9 Apart from the CV data described earlier in this chapter, the evidence appraised suggested
10 that patients treated with rosiglitazone experienced a significantly higher incidence of
11 oedema and anaemia. Similarly, rosiglitazone was associated with a significant risk of distal
12 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%)*

13

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 up titration	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 up titration	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 up titrated	One study ⁶² N=589 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=528	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 $-0.02 \pm 0.002\%$) compared with the MET group (Hb -0.34 ± 0.07 g/dl, Hct $-0.01 \pm 0.002\%$). The difference between the groups was significant for both parameters ($p < 0.0001$)
Rosiglitazone/metformin (FDC) vs rosiglitazone vs metformin	One study ¹³⁴ N=488 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 (8%) 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 (28.8 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=28; rosiglitazone, N=14, $p < 0.0185$) 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 ($p=0.0073$)

1

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		

2

8.2.3.15 Pioglitazone

2 Cardiovascular outcomes^h

3 The systematic review¹⁴¹ found only one study¹⁵⁸ evaluating mortality and morbidity as
4 endpoints outcomes. As the primary composite endpoint, the PROactive study explored the
5 incidence of the following outcomes from the time of randomisation.

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

12 The study concluded that for this composite endpoint there were no statistically significant
13 differences between the pioglitazone and placebo group: the hazard ratio (HR) was 0.90
14 (95% CI 0.80 to 1.02, p=0.095). In the same vein, the individual components of the primary
15 composite endpoint did not disclose statistically significant differences between intervention
16 and control groups. **Level 1++**

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

21 A subgroup analysisⁱ of the PROactive study¹⁵⁰ was identified by the re-runs. It analysed the
22 effect of pioglitazone on recurrent MI in 2,445 patients with Type 2 diabetes and previous MI.
23 The study found no significant differences in the primary or main secondary endpoints
24 defined in the main PROactive study,^j and the individual endpoints of the primary composite.
25 In addition, the subgroup analysis suggest that patients treated with pioglitazone had a
26 statistically significant beneficial effect on the pre-specified endpoint of fatal and non-fatal MI
27 (28% risk reduction (RR), p=0.045) and ACS (37% RR; p=0.035) compared to those treated
28 with placebo. **Level 1+**

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

33 Another subgroup analysis^k of the PROactive study¹⁵² was also identified by the re-runs. This
34 analysis evaluated outcomes stratified for patients who entered the study with (N=984) and
35 without previous stroke (N=4,254). In the patients with previous stroke, there were no
36 significant differences in the primary or main secondary endpoints as defined in the main
37 PROactive analysis, but there was a trend of benefit (HR 0.78, 95% CI 0.60 to 1.02,
38 p=0.0670) for the primary endpoint. In patients with no previous stroke, there were no
39 significant differences between pioglitazone and placebo for any of the endpoints defined in
40 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.

8.2.3.16 Surrogate outcomes

2 HbA1c

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

7 A head-to-head RCT¹⁵¹ comparing pioglitazone monotherapy with glimepiride monotherapy
8 reported no significant difference in the HbA1c values between the two treatment groups until
9 week 48. By the end of the study (week 72) there was an absolute difference between the
10 two treatment groups of 0.32% favouring pioglitazone-treated patients (p=0.002). **Level 1+**

11 A 2-year follow-up study¹⁴⁸ reported no significant differences in terms of HbA1c when
12 patients receiving metformin and pioglitazone were compared with those treated with
13 metformin + gliclazide. **Level 1+**

14 A study comparing the addition of different doses of pioglitazone (30 and 45 mg) to stable
15 insulin therapy in patients with poorly controlled Type 2 diabetes¹⁴⁶ found that mean HbA1c
16 levels decreased significantly from baseline to week 24 in both groups: 1.2 from 9.9% and
17 1.5 from 9.7% in the pioglitazone 30- and 45-mg groups respectively (p<0.0001 for each
18 relative to baseline; p=0.011, 30 vs 45 mg). **Level 1+**

19 One RCT comparing the currently licensed combination of pioglitazone and insulin with
20 insulin plus placebo¹⁴⁵ found that after 6 months there was a significantly higher decrease in
21 HbA1c levels in patients treated with insulin and pioglitazone (difference -0.55; p<0.002).¹
22 **Level 1+**

23 Fasting plasma glucose

24 A 2-year follow-up study¹⁴⁸ showed a statistically significant difference in FPG between the
25 pioglitazone add-on to metformin group and the gliclazide add-on to metformin group at week
26 104 (-1.8 vs -1.1 mmol/l, p<0.001). **Level 1+**

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

30 One RCT comparing the combination of pioglitazone and insulin with insulin plus placebo¹⁴⁵
31 reported at 6 months a significant difference in terms of FPG favouring the pioglitazone +
32 insulin combination (difference 1.80 mmol/l, p<0.002). **Level 1+**

33 Lipid profile

34 An RCT¹⁵¹ comparing pioglitazone monotherapy with glimepiride monotherapy reported that
35 by the end of the study (week 72) pioglitazone-treated patients showed significantly higher
36 HDL levels (difference 0.16 mmol/l, p<0.001).

37 A 2-year follow-up study¹⁴⁸ reported a statistically significant percentage difference between
38 the pioglitazone add-on to metformin group and the gliclazide add-on to metformin from
39 baseline to last value for TG (-23% vs -7%, p<0.001), HDL-C (22% vs 7%, p<0.001) and
40 LDL-C (2 vs -6%, p<0.001). **Level 1+**

¹ 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%).

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

4 The RCT comparing the combination of pioglitazone and insulin with insulin plus placebo did
5 not find significant differences in LDL and TG levels. However, after 6 months patients
6 receiving pioglitazone and insulin had significantly higher levels of HDL (difference 0.13,
7 $p < 0.002$).^{m 145} **Level 1+**

8 **Body weight**

9 According to the systematic review, 15 studies evaluated body weight and observed an
10 increase up to 3.9 kg after pioglitazone treatment, seven studies described a rise in BMI up
11 to 1.5 kg/m². (Due to heterogeneity this outcome could not be subjected to meta-analysis.)
12 **Level 1++**

13 A 2-year follow-up study¹⁴⁸ reported a mean increase from baseline of 2.5 kg in the
14 pioglitazone add-on to metformin group and 1.2 kg in the gliclazide add-on to metformin at
15 week 104. **Level 1+**

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

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

24 **Adverse events**

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

30 **Oedema**

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

35 **Hypoglycaemia**

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

40 The review highlighted that the biggest trial¹⁵⁸ which compared pioglitazone versus placebo
41 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).

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

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

4 **Other adverse events**

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

8 The 2-year follow-up study¹⁴⁸ reported that there were more symptoms of hypoglycaemia
9 (11.5% vs 2.2%) and GI disorders (5.1% vs 3.8%) in the gliclazide group but less aggravated
10 CHF (0.6% vs 1.6%) and oedema (3.5% vs 7.6%) than in the pioglitazone group. **Level 1+**

11 A study comparing the addition of different doses of pioglitazone (30 and 45 mg) to stable
12 insulin therapy reported that in both groups, hypoglycaemia was the most commonly
13 reported drug-related AE (37 and 43% of patients respectively), followed by lower limb
14 oedema (13 and 12%), weight gain (7 and 13%) and aggravated oedema in patients with
15 oedema at baseline (4 and 3%). Frequency of CV AEs related to study group was low and
16 comparable between groups (1.2 and 0.6% for the 30- and 45-mg groups respectively).
17 Drug-related CHF was reported for three patients receiving pioglitazone 30 mg (one possibly
18 related and two probably related) and one patient receiving 45 mg (possibly related).¹⁴⁶ **Level**
19 **1+**

20 A study comparing the combination of pioglitazone and insulin with insulin plus placebo¹⁴⁵
21 showed that there were 90 (63.4%) reported incidences of subjective hypoglycaemic
22 episodes for PIO + INS and 75 (51.0%) for PLB + INS (p<0.05). There was no difference
23 between the treatment groups for clinical hypoglycaemia. The study also reported 20 cases
24 of oedema with PIO + INS and five cases with PLB + INS. No CV events reported. **Level 1+**

25 **Glitazones and the risk of oedema**

26 A meta-analysis¹⁵³ revealed a twofold increase in the RR of oedema secondary to
27 thiazolidinedione therapy compared to placebo, oral antihyperglycaemic agents, or insulin.
28 The pooled odds ratio was 2.26 (95% CI 2.02 to 2.53, p<0.00001) the increased risk of
29 oedema was present in both monotherapy and combination therapy studies. **Level 1+**

30 The same meta-analysis suggested that rosiglitazone was associated with a more
31 pronounced risk for oedema than pioglitazone. The calculated adjusted indirect comparison
32 of rosiglitazone to pioglitazone based on all included studies yielded an approximate
33 threefold higher risk of oedema with rosiglitazone, (2.74 (2.33 to 3.14)). When only placebo
34 controlled studies of pioglitazone (1.18 (0.61 to 2.28), p<0.063) and rosiglitazone (3.58 (2.11
35 to 6.10), p<0.00001) were considered, the risk was still greater with rosiglitazone. The
36 calculated adjusted indirect comparison of rosiglitazone to pioglitazone using only placebo
37 controlled trials was 3.03 (2.15 to 3.91). The omission of all open-label trials also pointed
38 towards an increased risk with rosiglitazone (3.64 (2.56 to 5.17)), over pioglitazone (2.18
39 (1.72 to 2.75), p<0.00001). **Level 1+**

8.2.4 **Health economic evidence statements**

41 The submission for the TA¹⁵⁴ looked at adding rosiglitazone to sulfonylurea or metformin
42 compared with other CTs or changing to insulin. The efficacy data was unreported in the TA
43 because it was submitted as commercial in confidence.

44 For patients who failed on metformin monotherapy:

- 45 • metformin plus a sulfonylurea compared to metformin plus rosiglitazone, led to an ICER of
- 46 £9,972 per QALY

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

4 In the TA¹⁵⁴ sensitivity analysis was included that appears to have been conducted by the TA
5 group. The sensitivity analysis indicated that some of the scenarios were very sensitive to
6 changes in key effectiveness variables. Small changes in the effect of rosiglitazone on β -cell
7 function and insulin sensitivity induced large changes in the cost per QALY ratios. When the
8 impact of rosiglitazone on insulin sensitivity and β -cell function was varied, in the comparison
9 of metformin plus a sulfonylurea and metformin plus rosiglitazone, rosiglitazone was
10 dominated by the sulfonylurea in combination therapy (metformin plus sulfonylurea is more
11 effective and less expensive).

12 The NICE 2003 guidance¹¹³ found that in patients in whom monotherapy with either
13 metformin or a sulfonylurea had failed, the use of combination therapy with a glitazone and
14 either metformin or a sulfonylurea was not likely to be cost-effective when compared with the
15 combination of metformin and a sulfonylurea.

16 Metformin plus sulfonylurea was compared with metformin plus rosiglitazone in patients who
17 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

18

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

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

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

35 As a broad summary of our results:

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

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

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

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

8.4 Exenatide: GLP-1 mimetics

8.4.1 Methodological introduction

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

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

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

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

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

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

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

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

8.4.2 Health economic methodological introduction

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

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

8.4.3 Evidence statements

2 Exenatide 5 µg and 10 µg compared with placebo

3 Three studies, all multicentre and triple-blinded based in the US used this comparison, total
 4 N=1,446.¹⁵⁹⁻¹⁶¹ For participants treated with sulfonylureas (N=377), those treated with
 5 metformin (N=336), and those treated with both (N=733), exenatide caused significant
 6 reductions in HbA1c, FPG (at the higher 10 µg dose), postprandial glucose and body weight.
 7 **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

8
9

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)

1

8.4.321 Open-label extension phase

3 The three RCTs in the table above^{159–161} had a further open-label extension phase of 52
4 weeks, which was open to those participants who had been originally randomised to
5 exenatide, N=668, analysis completed on N=314.¹⁶² This study showed that at the end of 82
6 weeks that the reductions in HbA1c and in FPG which had been identified at the end of week
7 30 were maintained to week 82.

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

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

16 This phase II study compared four doses of exenatide with placebo in participants treated
17 either with diet modification and exercise alone or a stable dose of metformin, N=156.¹⁶³

1 HbA1c

2 There was a decrease in HbA1c compared with an increase with placebo ($0.1\pm 0.1\%$), for all
3 doses: $2.5\ \mu\text{g}$ ($-0.3\pm 0.1\%$), $5\ \mu\text{g}$ ($-0.4\pm 0.1\%$), $7.5\ \mu\text{g}$ ($-0.5\pm 0.1\%$), $10\ \mu\text{g}$ ($-0.5\pm 0.1\%$),
4 $p<0.01$.

5 Fasting blood glucose

6 There was a decrease in FBG compared with an increase with placebo ($6.8\pm 4.1\ \text{mg/dl}$), for
7 all doses: $2.5\ \mu\text{g}$ ($-20.1\pm 5.2\ \text{mg/dl}$), $5\ \mu\text{g}$ ($-21.2\pm 3.9\ \text{mg/dl}$), $7.5\ \mu\text{g}$ ($-17.7\pm 4.8\ \text{mg/dl}$), $10\ \mu\text{g}$
8 ($-17.3\pm 4.4\ \text{mg/dl}$), $p<0.01$.

9 Body weight

10 Reductions in body weight with exenatide were significant for the $7.5\ \mu\text{g}$ ($-1.4\pm 0.3\text{kg}$) and 10
11 μg ($-1.8\pm 0.3\ \text{kg}$) groups, $p<0.01$, compared with the placebo group who were weight neutral.

12 Subgroup analysis

13 This used data from the $5\ \mu\text{g}$ and $10\ \mu\text{g}$ groups and considered those treated with
14 diet/exercise compared with those treated with metformin. This found that the effects of
15 exenatide were similar in both groups for HbA1c, FPG and body weight.

16 Adverse events and discontinuation

17 40.7% of participants taking exenatide had nausea (6.5% severe nausea) compared with
18 12.1% of those taking the placebo (3.0% severe nausea). The nausea appeared to be dose
19 dependent as it had a higher occurrence in the higher dose groups; $2.5\ \mu\text{g}$ (23.3%), $5\ \mu\text{g}$
20 (25.8%), $7.5\ \mu\text{g}$ (61.3%) and $10\ \mu\text{g}$ (51.6%). **Level 1+**

8.4.3.13 Exenatide vs insulin glargine

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

25 HbA1c

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

30 Fasting plasma glucose

31 Those taking insulin glargine showed a greater reduction in FPG than those receiving
32 exenatide (-2.9 vs $-1.4\ \text{mmol/l}$), $p<0.001$. Significantly more of the insulin glargine group
33 (21.6%) achieved a FPG of less than $5.6\ \text{mmol/l}$ compared with 8.6% in the exenatide group
34 ($p<0.001$).

35 Self-monitored blood glucose

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

1 Adverse events and discontinuation

2 There were higher incidences of the most frequent AEs of nausea and vomiting in the
3 exenatide group (57.1% and 17.4% respectively) compared with insulin glargine (8.6% and
4 3.7%).

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

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

9 Level 1+

10 The second exenatide and insulin glargine study considered the treatments in respect to
11 patient reported health outcome measures, N=549.¹⁶⁵ Both treatment groups showed
12 baseline to endpoint improvements on several of the health outcome measures; these were
13 not significant between the groups. Glycaemic control results were not reported. **Level 1+**

14 Exenatide vs biphasic insulin aspart

15 This study reported that HbA1c reduction in exenatide-treated patients (N=253) was non-
16 inferior to that achieved with biphasic insulin aspart (N=248). In relation to body weight gain,
17 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		

18

19 Exenatide + glitazone vs placebo + glitazone

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

23 Overall, the RCT showed that exenatide in combination with a glitazone improved glycaemic
24 control in patients with Type 2 diabetes that is suboptimally controlled with a glitazone, either
25 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)		

1

8.4.24 Health economic evidence statements

3 The analysis by Ray et al. was based on a 26-week trial which found exenatide was
4 associated with a 0.99% reduction in HbA_{1c} compared to 1.07% with glargine. Exenatide
5 was found to improve BMI, SBP, TC and LDL-C compared to glargine. No cost for exenatide
6 in the UK was available as it had not been licensed at the time of publication so various
7 proportions of the US price were tested from 20% to 100%. Exenatide was found to have a
8 cost per QALY of £22,420 compared to glargine. The results were most sensitive to variation
9 in the disutility values applied for weight change and nausea. The cost per QALY increased
10 to £39,763 when disutility values for set levels of BMI were used rather than changes in
11 weight.¹⁶⁹

12 The health economic analysis of exenatide as a third-line agent in Type 2 diabetes is
13 described in appendix C available at www.rcplondon.ac.uk/pubs/brochure.aspx?e=247. In
14 the base-case analysis (see table 23) exenatide is shown to have an ICER of £280,495.
15 Recognising the difficulties of factoring in the potential benefits of weight loss with exenatide,
16 various sensitivity analyses were performed, but the ICER remained consistently high and in
17 only one case became cost-effective, (£29,865 per QALY gained when exenatide patients
18 were started with an initial BMI of 27 kg/m² compared to a 33 kg/m² for all other treatments
19 and a utility gain of 0.064 due to 3% weight loss on exenatide, no nausea, compared to
20 weight gain for other treatments). In this model therefore, human insulin is a consistently
21 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

2

8.5.31 Thiazolidinediones (glitazones)

4 This section updates both the previous NICE inherited guideline and the previous NICE TA
5 guidance on the use of glitazones for the treatment of Type 2 diabetes. NICE TA guidance
6 63 (2003).¹¹³

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

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

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

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

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

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

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

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

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

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

8.52 Exenatide

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

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

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

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

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

3 Furthermore, the more obese require much higher insulin doses, such that insulin costs
4 alone can easily exceed those of exenatide (depending on the mix of insulin types chosen for
5 comparator) though the benefit from insulin could be expected to be higher than in the trials
6 (for reasons of dose titration given above). In these circumstances a confident judgment of
7 costs and benefits to be gained from HbA1c and weight change, and side effects, could not
8 be made. However the GDG's judgment was that costs of insulin and exenatide by the end of
9 the first year would be equivalent on average for people with a starting BMI (before these
10 medications) of approximately $>33 \text{ kg/m}^2$, while in this obese group the small metabolic
11 advantage to insulin on HbA1c would easily be outweighed by the metabolic advantage of
12 4kg weight loss on exenatide. In this restricted circumstance, and particularly at higher BMI's,
13 the cost-effectiveness of exenatide would then be at least as good as that of insulin.

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

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

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

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

37 **ORAL GLUCOSE CONTROL THERAPIES (2): OTHER ORAL AGENTS AND EXENATIDE;** 38 **RECOMMENDATIONS**

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

40 **Thiazolidinediones (glitazones)ⁿ**

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

- 44 • the combination of metformin and a sulfonylurea where insulin would otherwise be
45 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.

- 1 o employment, social or recreational issues related to putative hypoglycaemia
2 o barriers arising from injection therapy or other personal issues such as adverse
3 experience of insulin in others
4 o those likely to need higher insulin doses or with barriers to insulin arising from
5 particular concerns over weight gain (namely those with obesity or abdominal
6 adiposity)
7 • a sulfonylurea if metformin is not tolerated
8 • metformin as an alternative to a sulfonylurea where the person's job or other issues make
9 the risk of hypoglycaemia with sulfonylureas particularly significant.
- 10 **R41** Warn a person prescribed a thiazolidinedione about the possibility of significant
11 oedema and advise on the action to take if it develops.
- 12 **R42** Do not commence or continue thiazolidinedione in people who have evidence of heart
13 failure, or who are at higher risk of fracture.
- 14 **R43** When selecting a thiazolidinedione for initiation and continuation of therapy, take into
15 account up-to-date advice from the relevant regulatory bodies (the European Medicines
16 Agency and the Medicines and Healthcare products Regulatory Agency), cost and safety
17 issues (note that only pioglitazone can be used in combination with insulin therapy, see
18 recommendation 49).^o
- 19 **Gliptins: GLP-1 enhancers**
- 20 No recommendations are made on the use of gliptins as these drugs are not covered in this
21 guideline.
- 22 **Exenatide: GLP-1 mimetics**
- 23 **R44** Exenatide is not recommended for routine use in Type 2 diabetes.*
- 24 **R45** Consider exenatide as an option only if all the following apply for the individual:
25 • a body mass index over 35.0 kg/m² in those of European descent, with appropriate
26 adjustment in tailoring this advice for other ethnic groups
27 • specific problems of a psychological, biochemical or physical nature arising from high
28 body weight
29 • inadequate blood glucose control (HbA1c ≥7.5 %) with conventional oral agents after a
30 trial of metformin and sulfonylurea
31 • other high-cost medication, such as a thiazolidinedione or insulin injection therapy, would
32 otherwise be started.
- 33 **R46** Continue exenatide therapy only if a beneficial metabolic response (at least 1.0 %
34 HbA1c reduction in 6 months and a weight loss of at least 5% at 1 year) occurs and is
35 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

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

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

9.1.2 Methodological introduction

13 Studies were identified which compared insulin in combination with oral hypoglycaemic
 14 agents (OHAs) with insulin monotherapy in insulin naive Type 2 diabetic patients. A
 15 Cochrane review¹⁷⁰ was identified which included 20 RCTs in a search performed in March
 16 2004. Ten additional RCTs were identified, five of which were excluded due to
 17 methodological limitations.^{171–175}

18 Of the remaining five RCTs the treatment comparisons were:

- 19 • insulin and metformin vs insulin and placebo (most patients in each group on pre-mixed
 20 twice daily insulin regimens)¹⁷⁶
- 21 • neutral protamine hagedorn (NPH) insulin (bedtime) and sulfonylurea and metformin vs
 22 NPH insulin 30/70 (twice daily)¹⁷⁷
- 23 • insulin glargine (once daily) and glimepiride and metformin vs NPH insulin 30/70 (twice
 24 daily)¹⁷⁸
- 25 • biphasic insulin aspart 30/70 (twice daily) and pioglitazone vs biphasic insulin aspart 30/70
 26 (twice daily)¹⁴⁷
- 27 • NPH insulin (bedtime) and glimepiride vs NPH insulin (twice daily) vs NPH insulin 30/70
 28 (twice daily)¹⁷⁹
- 29 • biphasic insulin vs biphasic insulin and metformin vs glibenclamide and metformin
 30 (although only the biphasic insulin vs biphasic insulin and metformin comparison will be
 31 considered here).⁶⁴

32 It should be noted that the number of different drug combinations and comparisons, dosing
 33 and titration regimens limit direct comparison between the studies. Furthermore, all of the
 34 studies with the exception of one¹⁷⁶ were open-label.

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

- 40 • mixed insulin (25% regular, 75% protamine insulin) plus glibenclamide vs mixed insulin
 41 (25% regular, 75% protamine insulin) and placebo (N=140, Cochrane methodological
 42 quality score 2/7) (Bachman 1988)

- 1 • mixed insulin (intermediate acting NPH plus regular insulin) twice daily and glibenclamide
2 vs mixed insulin (intermediate acting NPH plus regular insulin) twice daily and placebo
3 (N=20, Cochrane methodological quality score 2/7) (Gutniak 1987)
- 4 • insulin (combination of short and intermediate acting insulin) once or twice daily plus
5 glibenclamide vs insulin alone (combination of short and intermediate acting insulin) once
6 or twice daily (N=27, Cochrane methodological quality score 2/7) (Ravnik-Oblak 1995)
- 7 • mixed insulin (70% NPH, 30% soluble) at supertime plus glibenclamide vs mixed insulin
8 (70% NPH, 30% soluble) and placebo (N=21, Cochrane methodology score 7/7) (Riddle
9 1992)
- 10 • mixed insulin (70% NPH, 30% regular human insulin) at supertime plus glimepiride vs
11 mixed insulin (70% NPH, 30% regular human insulin) and placebo (N=145, Cochrane
12 methodology score 6/7) (Riddle 1998).
- 13 It is notable that some of these studies had small sample sizes and/or low methodological
14 quality scores.

9.13 Health economic methodological introduction

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

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

9.14 Evidence statements

26 Glycaemic control

27 Overall the data seems to suggest that patients receiving a combination treatment with
28 insulin (NPH or pre-mixes) and metformin or a sulfonylurea showed significantly lower HbA1c
29 levels when compared to those treated with insulin monotherapy. FPG values were not
30 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)

1 SD, standard deviation; SU, sulfonylurea

2 Insulin dose

3 A Cochrane review¹⁷⁰ reported that insulin–OHA combination therapy was associated with a
4 significantly lower insulin dose compared to insulin monotherapy. An RCT¹⁷⁶ reported the
5 same trend for the combination of insulin and metformin.

6 Well-being and quality of life

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

11 Hypoglycaemia

12 Non-significant differences in the incidence of hypoglycaemic events between insulin–OHA
13 and insulin monotherapy were reported across most of the studies identified. However, a
14 higher number of hypoglycaemic events were observed in patients receiving monotherapy
15 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+PIO 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) ⁸⁴	No major hypoglycaemic episodes during the trial, minor hypoglycaemic episodes were similar amongst treatment groups	NS

1

2 Weight gain

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

6 Only one study¹⁴⁷ comparing the combination of BIAsp 30 plus pioglitazone with BIAsp
7 monotherapy showed a greater weight gain in patients treated with the combination therapy.

1 Other adverse events

2 Overall, no significant differences in frequency or severity of AEs were found for patients
 3 receiving insulin alone or combination therapy regimens. However, one study¹⁴⁷ found that
 4 more patients experienced product-related AEs in the biphasic aspart 30/70 plus pioglitazone
 5 group (28%) compared with patients receiving biphasic insulin aspart 30/70 monotherapy
 6 (20%). The combination group was also associated with a higher proportion of patients
 7 experiencing peripheral edema (6%) compared with aspart monotherapy (0%).

9.165 From evidence to recommendation

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

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

25 RECOMMENDATIONS

26 **R47** When starting basal insulin therapy:

- 27 • continue with metformin and the sulfonylurea (and acarbose, if used)
- 28 • review the use of the sulfonylurea if hypoglycaemia occurs.
- 29 •

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

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

33

34 **R49** Consider combining pioglitazone with insulin therapy for:

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

9.2 Insulin therapy

9.201 Clinical introduction

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

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

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

9.2.2 Methodological introduction

10 Biphasic insulin preparations vs NPH

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

13 There were three relevant RCTs. One study¹⁸² compared biphasic insulin aspart 30/70 and
14 NPH insulin in a population of 403 patients with a follow-up of 16 weeks. The other study¹⁸³
15 compared the combination of insulin aspart 30/70 and metformin with the combination of
16 NPH insulin and metformin in a population of 140 patients with a follow-up of 12 weeks. The
17 third study, a cross-over trial, compared a preprandial and basal regimen with insulin lispro
18 and NPH, with a basal only regimen with twice daily NPH in 30 patients spending 12 weeks
19 in each arm before cross-over.¹⁸⁴

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

22 Biphasic human insulin preparations vs biphasic analogue preparations

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

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

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

33 The study by Boehm¹⁸⁷ was an extension RCT of Boehm¹⁸⁶ comparing the long-term efficacy
34 of these two formulations. An additional RCT compared three times daily biphasic insulin
35 analog formulation (insulin aspart containing 30% soluble insulin aspart and 70% insulin
36 aspart crystallised with protamine) with once daily human pre-mixed insulin (30% regular,
37 70% NPH insulin).¹⁸⁸ One RCT compared a three times daily biphasic insulin analog
38 formulation (50% insulin lispro and 50% neutral protamine lispro suspension) with once daily
39 human pre-mixed insulin (30% regular insulin and 70% NPH).¹⁸⁹

40 One RCT compared patients on metformin plus either once daily biphasic insulin analog
41 formulation (insulin aspart containing 30% soluble insulin aspart and 70% insulin aspart
42 crystallised with protamine), NPH insulin or human pre-mixed insulin (30% regular, 70% NPH
43 insulin).¹⁸³ Another RCT compared a biphasic insulin analogue (insulin aspart containing
44 30% soluble insulin aspart and 70% insulin aspart crystallised with protamine) with a daily
45 basal-bolus regimen with insulin aspart before meals and evening human isophane insulin

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

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

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

7 **Multiple analogue insulin injection regimens compared to basal insulin or biphasic** 8 **insulin regimens**

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

10 A cohort study relevant to the question¹⁹¹ conducted in India compared a multiple analogue
11 insulin regimen with a pre-mix regimen in a cohort of 145 participants with a follow-up of 12
12 weeks.

13 The cohort study had the following limitations.

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

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

27 This subgroup analysis should be interpreted with caution because:

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

31 **Long-acting insulin analogues (insulin glargine compared to NPH insulin, biphasic** 32 **insulins or multiple daily injections)**

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

37 Two meta-analyses^{194,195} and 14 further RCTs^{178,196–208} were identified which compared a
38 regimen containing insulin glargine with another insulin containing regimen in those with
39 Type 2 diabetes. One RCT compared morning and evening administration of insulin glargine.
40 ²⁰⁹ One RCT compared insulin glargine with an optimised oral diabetic agent treatment arm.
41 ²¹⁰

42 A recent meta-analysis by Horvath¹⁹⁵ compared the long-acting insulin analogues (insulin
43 glargine and insulin detemir) with NPH insulin. Only the results of the insulin glargine and
44 NPH comparison are considered here. In this meta-analysis six RCTs were included in the

- 1 glargine and NPH comparison.^{196,199,211–214} A further RCT by Yokohama was mentioned in the
2 study but not included in the meta-analysis.²⁰⁸
- 3 An older meta-analysis by Rosenstock¹⁹⁴ which contained some of the same studies as the
4 Horvath analysis combined four RCTs^{211–214} which compared insulin glargine once daily with
5 NPH insulin once or twice daily (in three studies NPH insulin was administered once daily,^{211–}
6 ²¹³ and in the other study it was administered once or twice daily).²¹⁴ Four further RCTs
7 compared once daily insulin glargine with once daily NPH insulin.^{196,199,200,206} One RCT was
8 excluded for methodological reasons.²⁰⁸
- 9 Eight RCTs compared insulin glargine with biphasic insulins.^{178,198,201–205,207} In two studies
10 ^{201,202} an insulin lispro mix 75/25 (75% insulin lispro protamine suspension and 25% insulin
11 lispro) administered twice daily was compared with bedtime insulin glargine. Two further
12 studies compared intensive mixed preprandial regimens with insulin lispro before each meal
13 compared to once daily insulin glargine.^{203,205} Another study¹⁷⁸ compared insulin glargine
14 once daily with human pre-mixed insulin (30% regular, 70% NPH insulin) twice daily,
15 however these groups were not directly comparable as metformin and glimepiride were given
16 with the insulin glargine and not with the pre-mixed insulin. Three studies^{198,204,207} compared
17 a once daily biphasic insulin analog formulation (insulin aspart containing 30% soluble insulin
18 aspart and 70% insulin aspart crystallised with protamine) with once daily insulin glargine,
19 although in one of these studies²⁰⁴ glimepiride was added to the glargine arm and metformin
20 to the biphasic arm.
- 21 The study that compared morning and evening administration of insulin glargine included
22 glimepiride in both arms.²⁰⁹
- 23 The review commissioned by NICE,^{197,215} on which previous appraisal recommendations
24 were based, noted that in studies where insulin glargine is demonstrated to be superior in
25 controlling nocturnal hypoglycaemia, this may only be apparent when compared with once
26 daily NPH and not twice daily NPH. It is thus notable that no new studies were identified
27 which compared insulin glargine with NPH insulin administered twice daily.
- 28 The range of definitions of hypoglycaemia used and differing populations may limit direct
29 comparison between studies.

9.2.3 Meta-analyses

- 31 Meta-analyses were conducted (using the Cochrane Collaboration's RevMan software) to
32 investigate the choice of third-line therapies where more than one study was available for a
33 comparison. Interventions considered were:
- 34 • human insulin – NPH or a pre-mix of unmodified NPH 30/70
 - 35 • biphasic analogues (either lispro or aspart) – twice daily
 - 36 • insulin glargine – once daily
 - 37 • glitazones (pioglitazone and rosiglitazone)
 - 38 • exenatide.
- 39 Because of the high acquisition costs of these third-line therapies, the pooled point estimates
40 and CI of efficacy were used in a health economic model comparing these treatment options
41 (see below. Full results are shown in appendix C available at [www.rcplondon.ac.uk/pubs/
42 brochure.aspx?e=247](http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=247)). The economic model was an adaptation of the UKPDS risk
43 calculations, and in order to supply the risk factors in UKPDS, the following outcomes were
44 sought:
- 45 • HbA1c
 - 46 • systolic blood pressure (SBP)
 - 47 • total high-density lipoprotein cholesterol (HDL-C)

- 1 • smoking status.

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

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

10 The following studies were pooled:

- 11 • biphasic analogue vs human insulin: six studies, total N=1,001^{182,183,186–189}
12 • glargine vs human insulin: two studies, total N=591^{196,199}
13 • biphasic analogue vs glargine: three studies, total N=435.^{198,201,202}

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

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

19 The comparison of biphasic analogue with glargine had a pooled weighted mean difference
20 of 0.43% HbA1c (95% CI 0.40 to 0.46) in favour of biphasic analogues. This analysis was
21 dominated by one large trial⁹⁸ but all three trials showed significant differences in the same
22 direction of effect, which supports the validity of the pooled result.

9.234 Health economic methodological introduction

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

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

9.235 Evidence statements

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

9.2361 Biphasic insulin preparations vs NPH

37 HbA1c

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

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

3 **Fasting blood glucose/fasting plasma glucose**

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

7 **Postprandial blood/plasma glucose**

8 One study¹⁸² reported that the mean prandial glucose increment over the three main meals
9 was significantly lower in the aspart 30/70 group than in the NPH group, (0.69 mmol/l lower;
10 $p < 0.0001$, between groups.) **Level 1+**

11 The other study¹⁸³ found no significant differences between the groups regarding the mean
12 values for the 8-point self-monitoring of blood glucose (SMBG) profile at week twelve. The
13 study reported that SMBG values for before breakfast and before lunch values tended to be
14 lower for the NPH insulin group, while after dinner and 10 pm, values tended to be higher for
15 the NPH insulin group as compared to the biphasic insulin aspart. **Level 1+**

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

9.2.52 **Body weight**

19 Two studies^{183,184} found non-significant differences in terms of body weight gain between the
20 biphasic insulins and NPH. **Level 1+**

9.2.53 **Adverse events**

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

25 One study¹⁸² found that in terms of incidence of hypoglycaemia, the RR was not statistically
26 significantly different between treatments (RR=1.21 (95% CI 0.77 to 1.90), $p = 0.40$). The
27 other study reported that there was no significant difference between regimens for either
28 overall or nocturnal hypoglycaemia.¹⁸⁴ **Level 1+**

29 The other study¹⁸³ found that nocturnal hypoglycaemia (midnight–6 am) was less frequently
30 reported for patients receiving biphasic insulin aspart (seven patients) as compared to
31 patients in the NPH insulin group (11 patients). No statistical analysis was reported. **Level 1+**

9.2.54 **Lipid profile**

33 One study¹⁸⁴ reported changes in lipid measures between groups and found a significantly
34 lower fasting low-density lipoprotein cholesterol (LDL-C) and LDL-C/HDL-C ratio in the
35 biphasic insulin (lispro) and NPH arm compared with twice daily NPH ($p = 0.035$). After a
36 standard meal both LDL-C ($p = 0.012$) and HDL-C ($p = 0.004$) were significantly higher in the
37 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

	RCT¹⁸⁸ Three times daily biphasic insulin aspart vs once daily human pre-mixed insulin N=177 Duration: 24 weeks	RCT¹⁸⁵ Twice daily biphasic insulin aspart vs once daily human pre-mixed insulin N=294 Duration: 12 weeks *Type 1 and 2 diabetes	RCT¹⁸⁷ Twice daily biphasic insulin aspart vs once daily human pre-mixed insulin N=125 Duration: 24 months	RCT¹⁸³ Metformin plus: once daily biphasic insulin aspart or NPH insulin or human pre-mixed insulin N=140 Duration: 12 weeks	RCT¹⁸⁹ Three times daily biphasic insulin aspart vs once daily human pre-mixed insulin N=40 Duration: 12 weeks	RCT¹⁹⁰ Three times daily biphasic insulin aspart vs a basal-bolus regimen 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

1

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 regimen 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

1

PPG, postprandial glucose

2 **HbA1c**

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

1 One RCT found three times daily biphasic insulin lispro (50/50) gave a significantly greater
2 reduction from baseline in mean HbA1c values compared with once daily pre-mixed human
3 insulin 30/70.¹⁸⁹ **Level 1+**

4 **Fasting blood glucose**

5 Two RCTs found no significant differences among the treatment groups on FBG.^{186,183} **Level**
6 **1+**

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

9 **Postprandial glucose**

10 In terms of PPG, three RCTs reported significant treatment differences in favour of biphasic
11 insulin aspart.^{188,186,189} **Level 1+**

12 **Bodyweight**

13 No studies reported any significant differences between treatment groups.^{186,187,183,190} **Level**
14 **1+**

15 **Adverse events**

16 Studies reported similar AEs profiles for biphasic analogue insulin and biphasic human
17 insulin.^{188,186,187,183,189,190} **Level 1+**

18 **Hypoglycaemia**

19 Overall, few major hypoglycaemic episodes were associated with either biphasic analogue or
20 human insulin.^{188,186,183,189,190} **Level 1+**

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

24 No study reported any significant differences between treatments on minor or nocturnal
25 hypoglycaemic episodes.^{188,186,183,190} **Level 1+**

9.2.86 **Multiple analogue insulin injection regimens compared to basal insulin or biphasic 27 insulin regimens**

28 **HbA1c**

29 For HbA1c levels the cohort study reported that both multiple insulin regimen and pre-mix
30 insulin regimen lowered HbA1c levels significantly compared to baseline values. Pre-mix
31 insulin analogue fared better than the basal-bolus analogue therapy in lowering HbA1c
32 (1.58% vs 1.16% respectively, $p < 0.05$). Also 41% more patients in the pre-mix group could
33 achieve target HbA1c of $< 7\%$ at the end of 12 weeks (45.61% vs 32.26%). **Level 2+**

34 **FPG/PPPG**

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

1 **Body weight**

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

3 **Hypoglycaemia events**

4 The percentage of patients experiencing minor hypoglycaemia was significantly lower in the
5 pre-mix group than in the basal-bolus group at 12 weeks (16.7% vs 58.06%, $p < 0.05$). **Level**
6 **2+**

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

9 **Subgroup analysis**

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

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

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

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

Table 11.4 Insulin glargine vs NPH insulin						
	Meta-analysis¹⁹⁵ Bedtime insulin glargine vs NPH once or twice daily N=3,151 Duration: 6–12 months	Meta- analysis¹⁹⁴ Bedtime insulin glargine vs NPH once or twice daily N=2,304 Duration: 24–28 weeks	RCT¹⁹⁶ Bedtime insulin glargine vs bedtime NPH N=110 Duration: 36 weeks	RCT²⁰⁰ Insulin glargine once daily vs once daily NPH N=204 Duration: 4 weeks	RCT¹⁹⁹ Bedtime insulin glargine vs bedtime NPH N=481 Duration: 24 weeks	RCT²⁰⁶ 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 5.98±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=0.0005). 48% 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). 59% 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

1
2
3

	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

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

11 Seven studies^{198,201–205,207} reported better HbA1c outcomes with the insulin mixes compared
12 to insulin glargine. The other study found significantly higher reductions in HbA1c with insulin
13 glargine from baseline, however insulin glargine was combined with OAD drugs which were
14 not received by the insulin mix group.¹⁷⁸ With respect to decreases in FBG from baseline
15 results, they were less consistent. Statistically significant decreases in FBG were reported in
16 insulin glargine groups compared to the insulin mix groups in four studies,^{178,201,202,205}
17 although three studies did not find a significant difference.^{203,204,207} Insulin doses were higher
18 in the insulin mix groups in all studies.^{178,198,201–205,207} In five studies the insulin mix groups
19 had significantly increased body weight from baseline compared with insulin
20 glargine.^{198,201,202,205,207} Two studies found no significant difference in body weight change
21 between the groups^{178,203} and the remaining study²⁰⁴ reported a greater weight increase in
22 the insulin glargine and glimepiride group than in the biphasic insulin analogue and
23 metformin group although they did not report if this was statistically significant. In terms of
24 hypoglycaemia, one study found no significant difference²⁰² in overall hypoglycaemia rates,
25 while the remaining studies^{178,198,201,203–205,207} found overall hypoglycaemia rates were better
26 with insulin glargine than insulin mixes. For nocturnal hypoglycaemia, two studies reported
27 no significant difference between the groups,^{201,203} another found higher rates in the glargine
28 group²⁰² and two others found significantly reduced rates in that group compared to the
29 insulin mix group.^{178,207} Only one study reported daytime hypoglycaemia rates and these
30 were found to be significantly higher in the insulin mix group.²⁰² No significant differences
31 between the groups were reported in terms of AEs.^{178,198,201,202,204,205,207} **Level 1+**

32 Morning vs evening administration of insulin glargine

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

39 Insulin glargine vs oral therapy

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

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

9.2.16 Health economic evidence statements

2 In the long-acting insulin TA¹⁹³ there was an estimated cost-effectiveness ratio of £33,000
3 compared to NPH insulin, using the price of a vial of glargine. Using cartridges or pens gave
4 higher cost-effectiveness ratios, £41,000 and £43,000 respectively. The results were most
5 sensitive to the assumption on utility gained from reducing fear of hypoglycaemia. If it was
6 assumed that there was no utility gain from this then the cost-effectiveness ratio rose to
7 approximately £10 million per QALY.

8 The second study²¹⁶ found a cost-effectiveness ratio of £13,000 per QALY gained compared
9 to NPH insulin. But it did not take into account the disutility associated with the side effects of
10 insulin glargine and no comparison was made with other third-line therapies.

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

9.2.17 From evidence to recommendations

16 Pre-mix insulin

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

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

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

43 Basal insulins including long-acting insulin analogues

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

- 1 understanding of insulin glargine, but more so, to the optimal use of insulin in people with
2 Type 2 diabetes, in particular for people starting insulin therapy.
- 3 Very little useful information was found to assist in advising on the optimal insulin regimen
4 once progression of islet B-cell failure had progressed further, for example in people 3–5
5 years or more after starting insulin therapy. The observational study from India was open to
6 bias in patient and provider selection, and the subgroup analysis from A Trial comparing
7 Lantus® Algorithms to achieve Normal blood glucose Targets in patients with Uncontrolled
8 blood Sugar (AT.LANTUS) was similarly open to bias and in small numbers of people. The
9 preferred view was that as islet B-cell deficiency progressed people tended to a state of
10 insulin deficiency closer to those with Type 1 diabetes, suggesting that prior NICE guidelines
11 advice for that group of patients could be applied.
- 12 The strongest of the new evidence for insulin starters appeared to relate to comparisons with
13 NPH insulin, and of these the data on comparison with once daily (bedtime) human NPH
14 insulin was the most novel. It was noted that these treat-to-target studies have the problem,
15 given their limited duration, of driving control in the compared groups towards the same
16 levels, and indeed pre-breakfast glucose levels and HbA1c were similar for insulin glargine
17 and NPH, at similar insulin doses. The differences in nocturnal hypoglycaemia were
18 convincing, if small
- 19 in absolute terms. Despite post hoc analyses of the relationship between HbA1c and
20 nocturnal hypoglycaemia showing convincing advantage of insulin glargine over NPH insulin,
21 it was impossible to determine what the balance of advantage between the two measures
22 would be in real clinical practice, where differences in hypoglycaemia tend to drive
23 differences in insulin dosage and thus overall blood glucose control (which would be to the
24 advantage of the long- acting analogue).
- 25 Although not the subject themselves of a randomised comparison, the approaches used in
26 the treat-to-target studies of active dose titration in the context of appropriate education, self-
27 monitoring and support were an important means of obtaining optimal blood glucose control
28 whatever insulin was employed.
- 29 An issue relates to the choice of insulin preparation for starting insulin in people with Type 2
30 diabetes. As noted above, and provided that insulin was started reasonably early in the
31 disease process before HbA1c had deteriorated too far, there was little justification for the
32 use of more intensive mealtime plus basal insulin regimens in this situation. The studies
33 comparing insulin glargine with pre-mix insulin regimens gave mixed results, with improved
34 HbA1c apparently resulting from an ability to titrate twice daily insulin dosage faster (in total)
35 than once daily injections, but at a cost of increased hypoglycaemia and weight gain. These
36 results and the absence of longer term data on performance of the two regimens, together
37 with complexities such as the possibility of using three injections of pre-mix, or of adding
38 mealtime insulin to basal glargine, meant that the GDG was unable to identify overall
39 advantage to one approach or the other.
- 40 The previous NICE guidance in relation to a single daily injection of insulin glargine not
41 having to be given at any precise time was noted to be useful for those whose injections are
42 given by others.
- 43 The GDG found the health economic modelling problematic in the area of insulin therapy.
44 Major problems seem to relate to the difficulties of including fear of hypoglycaemia and its
45 effect on everyday lifestyle, restrictions on lifestyle with insulin injections, and the present day
46 educational costs associated with intensive insulin dose adjustment to achieve good target
47 control. While some attempts had been made to incorporate some of these in sensitivity
48 analyses, it was not possible to be sure of their validity, though the face value results all
49 suggested that human insulin regimens were the only cost-effective approach.

1 **RECOMMENDATIONS**

- 2 **R50** When other measures no longer achieve adequate blood glucose control to HbA1c
 3 <7.5% or other higher level agreed with the individual, discuss the benefits and risks of
 4 insulin therapy. Start insulin therapy if the person agrees.
- 5 **R51** When starting insulin therapy, use a structured programme employing active insulin
 6 dose titration that encompasses:
- 7 • structured education
 - 8 • continuing telephone support
 - 9 • frequent self-monitoring
 - 10 • dose titration to target
 - 11 • dietary understanding
 - 12 • management of hypoglycaemia
 - 13 • management of acute changes in plasma glucose control
 - 14 • support from an appropriately trained and experienced healthcare professional.
- 15 **R52** Insulin therapy should be initiated from a choice of a number of insulin types and
 16 regimens.
- 17 • Preferably begin with human NPH insulin, taken at bedtime or twice daily according to
 18 need.
 - 19 • Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a
 20 person who falls into one of the following categories:
 - 21 ○ those who require assistance from a carer or healthcare professional to administer their
 22 insulin injections
 - 23 ○ those whose lifestyle is significantly restricted by recurrent symptomatic
 24 hypoglycaemic episodes
 - 25 ○ those who would otherwise need once daily basal insulin injections in combination with
 26 oral glucose-lowering medications.
 - 27 • Consider twice-daily biphasic human insulin (pre-mix) regimens in particular where
 28 HbA1c is elevated above 9.0 %. A once-daily regimen may be an option when initiating
 29 this therapy.
 - 30 • Consider pre-mixed preparations of insulin analogues rather than pre-mixed human
 31 insulin preparations when:
 - 32 ○ immediate injection before a meal is preferred, or
 - 33 ○ hypoglycaemia is a problem, or
 - 34 ○ there are marked postprandial blood glucose excursions.
- 35 **R53** Offer a trial of insulin glargine if a person who has started with NPH insulin
 36 experiences significant nocturnal hypoglycaemia.
- 37 **R54** Monitor a person using a basal insulin regimen (NPH or a long-acting insulin
 38 analogue (insulin glargine) for the need for mealtime insulin (or a pre-mixed insulin
 39 preparation)). If blood glucose control remains inadequate (not to agreed target levels
 40 without problematic hypoglycaemia), move to a more intensive, mealtime plus basal insulin
 41 regimen based on the option of human or analogue insulins.
- 42 **R55** Monitor a person using pre-mixed insulin once or twice daily for the need for a further
 43 preprandial injection or for an eventual change to a mealtime plus basal insulin regimen,
 44 based on human or analogue insulins, if blood glucose control remains inadequate.

9.3 Insulin detemir

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

9.4 Insulin delivery devices (CG66)

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

9.4.1 Clinical introduction

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

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

9.4.2 Methodological introduction

15 Six crossover RCTs were identified which compared insulin pens or other delivery systems
16 with conventional syringes.^{219–224} One study was excluded for methodological reasons.²²⁴
17 Two crossover RCTs were also identified which compared different types of insulin
18 pens.^{220,225}

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

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

9.4.3 Health economic methodological introduction

27 No health economic papers were identified for this question.

9.4.4 Evidence statements: syringes vs other insulin delivery systems

29

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

34

35 Two studies noted no significant difference in the incidence of hypoglycaemic episodes
36 between pens and syringe treatments.^{219,221} In other studies no AEs were considered by the
37 investigator to be related to study treatment²²³ or the safety profiles for pen and the
38 vial/syringe appeared similar.²²² **Level 1+**

1

2 Operational use

3 In 1 study patients starting insulin using a pen found the insulin injections easy (63%) or very
4 easy (33%) at the end of 12 weeks, whilst those who commenced insulin with conventional
5 syringes found it more difficult with only 24% finding it very easy by the end of 12 weeks and
6 51% finding it easy (p=0.0005).²²¹ **Level 1+**

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

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

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

20 Pre-selection of dose

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

24 Other studies (which did not report significance) reported that 86% of participants found that
25 pre-selection of insulin dose with a pen was easier than insulin withdrawal from a vial with a
26 conventional syringe²¹⁹ and that 85% of patients reported that they found it easier to read the
27 insulin dose scale with the pen than the vial/syringe (10% found reading the insulin dose
28 scale easier using the vial/syringe).²²² **Level 1+**

29 Pain

30 A study found that injection pain was significantly lower with a pen than with syringes and
31 vials (p=0.0018). Patients commencing on syringes reported a significantly lower level of
32 injection pain after the switch to using the pen (p=0.0003).²²¹ Another study reported
33 participants found insulin injections with the pen, compared to the conventional syringe, were
34 55% less painful, although 43% did not notice any difference.²¹⁹ **Level 1+**

35 Preference for a device

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

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

1 **Insulin delivery devices vs other insulin delivery devices**

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

3 Auditory confirmation of dose setting was heard by 100% of study participants for NovoPen®
4 3, 98% for FlexPen®, 90% for InnoLet®, 75% for HumaPen Ergo® and 63% for the Humalog
5 Pen®. This was significantly different between the NovoPen® 3 and the Humalog Pen®
6 ($p<0.001$), the HumaPen Ergo® ($p<0.001$), and InnoLet® ($p<0.01$), and the FlexPen® and
7 the Humalog Pen® ($p<0.001$), and HumaPen Ergo® ($p<0.01$).²²⁵ **Level 1+**

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

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

19 **InnoLet® vs Humulin Pen®**

20 In a group of visually impaired patients, the InnoLet® insulin device (easy-to-read dial, large
21 button for injection and audible clicks for units injected) was found to be significantly more
22 effective than the Humulin Pen® in terms of visual accuracy when reading the dose scale
23 (92% vs 45%, $p<0.001$). Additionally, significantly more patients using InnoLet® were able to
24 intuitively set and dispense a 20U insulin dose (84% vs 41%, $p<0.001$) and InnoLet® was
25 significantly preferred to the Humulin Pen® (87% vs 13%, $p<0.001$).²²⁰

26

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

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

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

39

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

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

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

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

5

1

10 Cardiovascular risk estimation

10.121 Clinical introduction

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

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

10.122 Methodological introduction

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

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

29 One observational study²⁷⁷ assessed differences between absolute CHD risks calculated by
 30 the Joint British Societies' (JBS) risk calculator chart and UKPDS risk engine. The study had
 31 a median follow-up of 4.2 years and compared the two methods on a cohort of diabetic
 32 populations from guideline 26 NHS-general practices.

33 One study²⁷⁵ assessed differences between absolute CHD risks calculated by the
 34 Framingham study risk equation and UKPDS risk engine. The study compared the two
 35 methods by using clinical records from UK diabetic patients.

36 One study²⁷⁶ compared the prognostic value of four methods to predict CVD and CHD risk
 37 (JBS risk calculator, the CardioRisk Manager, the Prospective Cardiovascular Münster
 38 (PROCAM) calculation and the UKPDS risk engine) using data from a UK clinical-based
 39 population database of diabetic patients.

40 One study²⁷⁸ assessed the prognostic value of three risk calculators for CVD and CHD
 41 (Framingham study risk equation, Systematic Coronary Risk Evaluation (SCORE) project risk
 42 score and Diabetes Epidemiology Collaborative Analysis of Diagnostic criteria in Europe
 43 (DECODE) risk equation) using UKPDS data.

44 One study²⁷⁴ reported 74 validation exercises involving 18 clinical trials for the Archimedes
 45 diabetes model. (No studies were found comparing the Archimedes diabetes model with
 46 other risk calculators.)

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

10.1.271 **Methods of risk prediction analysed**

8 **Framingham based risk assessments**

9 The Framingham CV risk function, which is widely employed to estimate CVD and CHD risk,
10 is a survival model based on the Weibull distribution and derived from the risk profiles of
11 5,573 CHD-free members of the Framingham cohort, aged 30–74 years and followed for 12
12 years, 6% of whom had diabetes (N=337). The JBS charts and the CardioRisk Manager
13 program make use of modified versions of the Framingham model.

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

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

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

25 **The UKPDS risk engine**

26 The UKPDS risk engine (computer-based) for determining CHD risk is based on data from
27 4,540 participants in the UKPDS study and includes diabetes specific covariates. The
28 UKPDS risk engine model utilises nine risk factors, these are: age at diagnosis, duration of
29 diabetes, sex, ethnicity, smoking status, SBP, HbA1c, total and HDL-C to calculate CHD risk.

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

36 **The UKPDS modified risk engine (stroke)**

37 There is a modified UKPDS engine used to calculate the risk of a first stroke. The equation is
38 based on data from 4,549 patients enrolled in the UKPDS. Variables included in the final
39 model were duration of diabetes, age, sex, smoking, systolic blood pressure (SBP), total
40 cholesterol (TC) to HDL ratio and presence of atrial fibrillation. Not included in the model
41 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.

1 PROCAM score system

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

10 SCORE risk charts

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

19 DECODE risk score

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

28 The Archimedes model

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

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

10.133 Health economic methodological introduction

39 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

10.1.4.21 UKPDS risk engine vs Framingham equation

3 One observational study was identified assessing the prognostic value of these two methods
4 in a cohort of patients newly diagnosed with Type 2 diabetes.²⁷⁷ In addition the sensitivity
5 and specificity of both models at a 15%, 10-year CHD risk threshold (NICE guidelines) was
6 compared with that of the ADA lipid threshold (LDL \geq 2.6 mmol/l or TG \geq 4.5 mmol/l). **Level**
7 **2++**

8 Overall

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

13 Gender/ hypertension treatment

14 The Framingham results suggested a tendency towards a greater degree of underestimation
15 of CHD events in men than women (41% vs 26%) and for pre-treated rather than untreated
16 BP (42 vs 31%). (See tables 13.1–13.3.)

17 Risk stratification

18 When using both risk calculation methods similar proportions were assigned, 10-year scores
19 less than 15% (Framingham 27.3% and UKPDS 25.7%). However, the UKPDS risk engine
20 assigned a 10-year score over 30% to 187 (43.7%) of the study participants as compared
21 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	*

1

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	*

2

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	*

3

10.1.4.2 Framingham and UKPDS risk engine vs ADA lipid threshold

5 The 15%, 10-year CHD risk threshold with both the Framingham and UKPDS risk engines
6 had similar sensitivity for primary CVD as the lipid level threshold 85.7 and 89.8% vs 93.9%
7 (p=0.21 and 0.34) and both had greater specificity 33.0 and 30.3% vs 12.1% (p<0.001 and
8 p<0.001).

10.1.413 UKPDS risk engine vs JBS risk chart

2 One study²⁷⁵ compared the prognostic value between these two risk calculators by using
3 data from NHS clinical databases. **Level 3**

4 Overall

5 Overall, the UKPDS risk engine was found to calculate a significantly higher mean 10-year
6 risk (UKPDS vs JBS, 21.5 vs 18.3%, $p < 0.0001$) with the mean difference of 3.2% (95% CI
7 2.7–3.8). However, both methods identified approximately 65% of patients with Type 2
8 diabetes who would require primary prevention intervention and therefore have comparable
9 accuracy in identifying these high-risk patients.

10 Gender differences

11 A bias towards men to have a much higher CHD risk with the UKPDS risk engine was
12 reported. The mean difference in risk score between men and woman was approximately
13 8.4% with the UKPDS risk engine in comparison with 1.7% with the JBS calculator. For men,
14 the UKPDS risk engine calculated CHD risk approximately 6% higher than the JBS
15 calculator.

16 Risk stratification

17 Both methods identified similar proportions of patients with CHD risk of at least 15% over 10
18 years. However, the main differential feature found between the two methods was the
19 tendency of the UKPDS risk engine to identify significantly more patients in the high-risk
20 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%

21

10.1.424 JBS risk calculator, the CardioRisk Manager, the PROCAM calculation and the UKPDS risk engine

24 One study²⁷⁶ assessed the prognostic value across four risk calculators. Analysis was
25 conducted by accessing medical records from a cohort of diabetic patients who had attended
26 a NHS clinic for a period of 10 years. **Level 3**

27 Overall, the study showed that all tests (except PROCAM) demonstrated acceptable
28 discrimination with respect to CHD/CVD, however all underestimated the risk of future
29 events.

Table 13.5 Discrimination 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)

1 CRM, Cardio Risk Manager

10.1.425 Framingham study risk equation, SCORE project risk score and DECODE risk equation

3
4 One study²⁷⁸ evaluated these three risk equations in patients with Type 2 diabetes using
5 UKPDS data. **Level 3**

6 **The 10-year fatal CVD event rate**

7 The 10-year fatal CVD event rate (95% CI) observed in UKPDS was 7.4% (6.5–8.3).
8 Framingham underestimated this by 32% with an AR of 5.0%, SCORE overestimated risk by
9 18% (AR 8.7%) whereas DECODE (AR 6.6%) yielded an acceptable estimate.

10 For males, only SCORE provided a reasonable estimate. In females, only Framingham
11 performed well.

12 For Caucasians (N=3,207), the 7.9% (6.7–9.0) observed event rate was underestimated by
13 34% using Framingham (AR 5.2%), overestimated by 19% using SCORE (AR 9.4%), and
14 estimated appropriately by DECODE (AR 7.1%).

15 **The 10-year fatal CHD event rate**

16 The 10-year fatal CHD event rate (95% CI) observed in UKPDS was 6.3% (5.5–7.1).
17 Framingham underestimated this (AR 4.3%) while SCORE provided a reasonable estimate
18 (AR 5.7%). Both equations provided reliable estimates for females but not males. For
19 Caucasians, the observed rate of 7.2% (6.3–8.1) was underestimated by both Framingham
20 (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

21

10.1.416 External validation of the Archimedes diabetes model

2 A study²⁷⁴ reported results from a total of 74 validation exercises which were conducted
3 involving different treatments and outcomes in 18 clinical trials (10 of which were not used to
4 build the model).^s **Level 3**

5 For 71 of the 74 exercises there were no statistically significant differences between the
6 results calculated by the model and the results observed in the trial. Overall, the correlation
7 coefficient for all 74 exercises is $r=0.99$.

8 If the outcomes in the control group and the absolute differences between the control and
9 treated groups are compared for model and trial, the correlation coefficient is $r=0.99$.
10 Focusing specifically on the absolute differences in the outcomes, which determines the
11 number needed to treat, the correlation coefficient is $r=0.97$. For the 10 trials that were not
12 used to build the model, the correlation coefficient is also $r=0.99$.

10.135 From evidence to recommendations

14 The UKPDS risk engine and to a lesser extent the older JBS-2 charts had some evidence of
15 validity in people with Type 2 diabetes, at least once over the age of 40 years. However, in
16 their latest revision JBS-2 charts for people with Type 2 diabetes are not available. Other
17 estimations based on the Framingham population were not reliable, and the reasons for this
18 were understood. No system included all the desirable variables, with the exception of
19 Archimedes, but this was not intended as a clinical tool.

20 It was noted that a wide range of epidemiological studies suggested that people with
21 diabetes were over twice as likely as the background population (age and sex matched) to
22 develop CVD, and that many had confounding factors (such as use of antihypertensive or
23 glucose-lowering medications) which prevented use of calculators. Studies such as the UK
24 validation analysis reported above were clearly not consistent epidemiologically with UK
25 populations at diagnosis, and furthermore excluded people already on therapy, and are
26 therefore not reliable as a means of estimating the size of the population justifying therapy
27 except for comparing tools. The group concluded that the normal approach, once age was
28 considered, of managing nearly all people with Type 2 diabetes as having risk $>20\%/10$ -
29 years was appropriate, particularly as outcome from MI is known to be worse for those with
30 diabetes, and preventative therapy therefore more cost effective.

31 Particular concerns were also expressed by the GDG over people with microalbuminuria,
32 those with more extreme family histories of CVD, and those with previous and recurrent CV
33 events. This and the age problem meant that it was recognised that any risk estimation had a
34 limited role. However, the GDG were also concerned that some people with Type 2 diabetes
35 do not have the classical phenotype of the disease with abdominal adiposity (or obesity) and
36 low HDL-C. It was concerned that such people should be recognised at diagnosis and
37 managed more conservatively.

10.136 Recommendations

39 **14. Consider a person to be at high premature cardiovascular risk for his or her age**
40 **unless he or she:**

41 **14.1. is not overweight, tailoring this with an assessment of body weight**
42 **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

- 1 **14.2. is normotensive (<140/80 mmHg in the absence of antihypertensive therapy)**
- 2 **14.3. does not have microalbuminuria**
- 3 **14.4. does not smoke**
- 4 **14.5. does not have a high-risk lipid profile**
- 5 **14.6. has no history of cardiovascular disease, and**
- 6 **14.7. has no family history of cardiovascular disease.**

- 7 **15. If the person is considered not to be at high cardiovascular risk, estimate**
- 8 **cardiovascular risk annually using the UK Prospective Diabetes Study (UKPDS)**
- 9 **risk engine.²⁷⁹**

- 10 **16. Consider using cardiovascular risk estimates from the UKPDS risk engine for**
- 11 **educational purposes when discussing cardiovascular complications with the**
- 12 **individual.²⁷⁹**

- 13 **17. Perform full lipid profile (including high-density lipoprotein cholesterol and**
- 14 **triglyceride estimations) when assessing cardiovascular risk annually, and before**
- 15 **starting lipid-modifying therapy.**

11 Management of blood lipid levels

11.1 Overall clinical introduction

3 Nearly all people with Type 2 diabetes are at high cardiovascular (CV) risk. Epidemiologically
4 that excess risk is independently associated with their hyperglycaemia together with high
5 blood pressure (BP) and dyslipidaemia, the last typically the low high-density lipoprotein
6 cholesterol (HDL-C) and raised triglyceride (TG) levels found as components of the
7 metabolic syndrome.²⁸⁰ Studies have suggested that people with Type 2 diabetes without
8 declared cardiovascular disease (CVD) are at as high a risk of a CVD event as someone
9 without diabetes with declared CVD.²⁷³ While this is disputed by other studies, it still leaves
10 individuals with Type 2 diabetes as nearly always in the high CVD risk category, and
11 accordingly it has been usual to manage them actively as if for secondary rather than primary
12 prevention of CVD. Nevertheless, in a few people with Type 2 diabetes the clinical phenotype
13 is not that associated with high CV risk, albeit these people being generally remarkable for
14 not being overweight nor having features of the metabolic syndrome, and being insulin
15 sensitive. More importantly people with Type 2 diabetes who have declared CVD are at
16 much higher risk (>1.5–2.6) of further events or CV death as people with CVD without
17 diabetes.²⁷³ Such extreme risk would appear to justify more intensive management than
18 usually offered to someone who has, for example, had a heart attack.

19 The management of CV risk through glucose lowering, BP lowering, and anti-platelet therapy
20 is dealt with elsewhere in this guideline. This chapter deals with lipid-lowering therapy;
21 dietary modification also being dealt with in a separate chapter. Paradoxically, although low-
22 density lipoprotein cholesterol (LDL-C) levels are not particularly raised in people with Type 2
23 diabetes compared to the background population, the opportunity to lower risk through lipid
24 management is currently greatest through drugs which lower LDL-C, principally the statins.
25 Nevertheless, a variety of other lipid modifying drugs are available and will be considered in
26 turn.

11.2 Targets and intervention levels

11.2.1 Clinical introduction

29 The principal aspects of the blood lipid profile recognised as risk factors for CVD include
30 LDL-C, HDL-C, and TGs. As the means of management of these is widely available (lifestyle
31 and drugs) it might seem logical to treat them as safe targets. Unfortunately there is no 'safe'
32 level, nor a level at which they do not contribute to vascular risk, a situation analogous with
33 blood glucose control and BP control. This leads to the question of the level of blood lipids
34 that should be acceptable without intensive therapy in people with diabetes, or whether
35 instead it is risk and not lipid levels that should be managed.

36 The clinical question is to what levels if any should LDL-C, HDL-C and serum TG be
37 managed in clinical practice.

11.2.2 Methodological introduction

39 There were three studies which were specifically relevant to target levels for lipid levels and
40 two meta-analysis studies.

41 The Cholesterol Treatment Trialists' (CTT) Collaborators completed a prospective meta-
42 analysis in 14 randomised trials of statins, published in 2005.²⁸¹ This analysis included data
43 from 90,056 (N=45,054 allocated a statin, N=45,002 controls) participants with diabetes. The
44 studies included were published over 10 years from 1994–2004.

1 A meta-analysis was completed which considered pharmacological lipid-lowering therapy in
 2 Type 2 diabetes. This analysis included 14 studies (total N=17,749), six primary prevention
 3 studies (N=11,025) and eight secondary prevention studies (N=6,724). The studies included
 4 were published from 1987–2003.²⁸²

11.2.3 Health economic methodological introduction

6 No health economic papers were identified.

7 The health economic analysis performed for statin therapy (appendix D, available at
 8 www.rcplondon.ac.uk/pubs/brochure.aspx?e=247) addressed the question of target levels in
 9 part. This is considered further in the section on statin therapy.

11.2.4 Evidence statements

11.2.4.1 Outcomes

12 CTT collaborators

13 The CTT collaborators meta-analysis identified that there is an approximately linear
 14 relationship between the absolute risk reductions in LDL-C found in the 14 studies and the
 15 proportional reductions in the incidence of coronary and other major vascular events.²⁸¹

16 The proportional reductions in major vascular event rates per mmol/l LDL-C reduction were
 17 very similar in all subgroups examined (i.e. including the diabetic subgroup), including not
 18 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	

19

20 Meta-analysis – lipid lowering therapy

21 The lipid-lowering therapy meta-analysis showed that the RR reductions were similar for both
 22 primary and secondary prevention.²⁸² However, the average absolute risk reduction was
 23 more than twice as high for those with coronary artery disease (secondary prevention) than
 24 for those without it (primary prevention).

25 Primary prevention trials – fixed effects analysis due to level of heterogeneity (p=0.18). The
 26 pooled RR for CV events with lipid-lowering therapy was 0.78 (0.67 to 0.89), with number
 27 needed to be treated (NNT) for benefit of 34.5 (for 4.3 years).

1 Secondary prevention analysis – random effects analysis as there was substantial between
2 study heterogeneity ($p=0.03$). The pooled RR for CV events with lipid-lowering therapy was
3 similar to that for primary prevention 0.76 (0.59 to 0.93), with NNT for benefit for of 13.8 (for
4 4.9 years).

5 The authors concluded that target cholesterol levels and the effectiveness of dose titration
6 (or the use of multiple agents) have not been rigorously examined. Most studies compared a
7 lipid- lowering drug with placebo but did not evaluate the effect of reaching specific
8 cholesterol levels. **Level 1++**

11.25 From evidence to recommendations

10 The GDG reviewed the evidence, and their clinical experience of trying to manage the
11 complexities of CV risk in clinical practice. They recognised the primacy of trying to control
12 risk cost effectively against treating-to-target, but also noted the practical utility of
13 measurements in assessing response to therapies and providing motivation to people with
14 diabetes. Ultimately the issue of cost effectiveness could only be resolved in the context of
15 the interventions being used to modify the lipid profile, and the evidence in this area was
16 therefore subsumed into the recommendations on the use of CV risk estimation, statins and
17 fibrates.

11.8 Statins and ezetimibe

11.39 Clinical introduction

20 Cholesterol lowering remained difficult, and indeed controversial, until the late 1980s when
21 statins became available. Subsequently these drugs became the mainstay of lipid-lowering
22 therapy, supported eventually by CV outcome studies. As discussed above, people with
23 Type 2 diabetes are at high CV risk, and most of their morbidity and increased mortality
24 comes from coronary, cerebral, and peripheral arterial disease. In earlier NICE technology
25 appraisals (TAs) and the prior Type 2 diabetes guideline, statins were recommended for all
26 people with extant CVD or at high risk thereof, states which include most people with Type 2
27 diabetes.²⁸³

28 Clinical questions which arise include whether more potent and more expensive statins
29 should ever be used (and if so when), the use of statins in younger people with Type 2
30 diabetes, whether any people should not be routinely given statins, and the use of
31 alternatives such as fibrates (addressed in the following fibrate section) and ezetimibe
32 addressed by a 2007 NICE TA.²⁸⁴

11.32 Methodological introduction

34 The issues around statins initiation therapy for the prevention of CV events have been
35 covered in a recently published NICE TA, 'Statins for the prevention of cardiovascular
36 events',²⁸³ which included RCTs conducted in people with Type 2 diabetes.

37 In addition, an ezetimibe TA²⁸⁴ was in development at the time of this review (ezetimibe for
38 the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia).
39 According to the scope, this TA is looking at the following clinical scenarios/comparisons.

- 40 • Patients (including Type 2 diabetes population) whose condition is not adequately
41 controlled with a statin alone.
 - 42 ○ Ezetimibe + statin vs statins monotherapy.
 - 43 ○ Ezetimibe + statin vs statins + other lipid-lowering agent.
- 44 • Patients (including Type 2 diabetes population) in whom a statin is considered
45 inappropriate, or is not tolerated.

- 1 o Ezetimibe monotherapy vs placebo.
- 2 o Ezetimibe vs other lipid-lowering agent.
- 3 • On these grounds, this review has excluded:
- 4 o all the studies that were included by the NICE TA 94 on statins
- 5 o any study that should be picked out by the ezetimibe TA.
- 6 Studies comparing statins with fibrates, (head-to-head comparisons or combination therapy)
- 7 since these are being analysed by the fibrate question. The purpose of this review is not to
- 8 repeat the statins or ezetimibe TAs, but to provide supplementary information about dose
- 9 escalation, sequencing of statins, and use of alternative agents (fibrates and nicotinic acid).
- 10 Seven RCTs were identified which reviewed the effectiveness and safety of statins.^{285–291}
- 11 One study was excluded due to major methodological limitations.²⁸⁵
- 12 Among the remaining six studies, three RCTs were conducted specifically on patients with
- 13 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)

- 14
- 15 The other three studies were post hoc analyses of large trials:^u Collaborative Atorvastatin
- 16 Diabetes Study (CARDS) (atorvastatin 10 mg vs placebo),²⁸⁹ Anglo-Scandinavian Cardiac
- 17 Outcomes Trial: Lipid lowering arm (ASCOT-LLA) (atorvastatin 10 mg vs placebo),²⁹⁰ and
- 18 Diabetes Atorvastatin Lipid Intervention (DALI) (atorvastatin 10 vs 80 mg).²⁸⁶
- 19 It should be noted that differing dosing and titration regimens, follow-up periods and the
- 20 differing populations included, may limit direct comparison between studies.

11.3.3 Health economic methodological introduction

- 22 No health economic papers were identified.
- 23 A health economic evaluation was developed by a health economist for the lipid modification
- 24 group which looked at different doses of statins. This was presented to the GDG for this
- 25 guideline as it was thought to be useful evidence.
- 26 The model was later further developed to consider specifically aspects of titration target and
- 27 titration strategy in people with diabetes, and is described in appendix D.
- 28 In summary this considered two uptitration levels (total or LDL-C: 5.0/3.0 and 4.0/2.0 mmol/l)
- 29 for people already started on simvastatin 40 mg/day, and either a one-step uptitration to 80
- 30 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

11.3.4.21 Cardiovascular outcomes

3 Studies conducted on Type 2 diabetes population

4 One RCT²⁹¹ found that over the 5 years of double-blind treatment, the incidence of a major
5 CV event^v was significantly lower in patients receiving atorvastatin 80 mg than in those
6 receiving atorvastatin 10 mg. This represented a 25% reduction in the risk of major CV
7 events in favour of the high-dose group ($p > 0.026$). This trend was observed across all
8 quintiles of patient age and duration of diabetes and in patients with HbA1c $\leq 7\%$ and A1C
9 $> 7\%$. **Level 1++**

10 The same RCT²⁹¹ reported significant differences between the groups, in favour of
11 atorvastatin 80 mg, for the secondary outcomes of time to cerebrovascular event ($p < 0.037$)
12 and time to CV event ($p < 0.044$). **Level 1++**

13 Post hoc sub-analysis

14 A post hoc analysis of the ASCOT-LLA study²⁹⁰ found a significantly lower incidence of CV
15 events in the subpopulation of people with Type 2 diabetes treated with atorvastatin –10 mg
16 when compared with those receiving placebo. (Hazard ratio 0.77, 95% CI 0.61 to 0.98,
17 $p < 0.036$.) **Level 1+**

18 A post hoc analysis of the DALI trial²⁸⁶ showed that both standard and aggressive therapy
19 with atorvastatin (10–80 mg) did not reverse endothelial dysfunction (as measure by the
20 surrogate marker of flow mediated vasodilatation). **Level 1+**

21 A post hoc analysis of the CARDS trial²⁸⁹ analysed the time between initiation of atorvastatin
22 10 mg and the appearance of significant differences in the incidence of CV events when
23 compared to placebo. The study demonstrated that by 1 year of follow-up the estimate of the
24 treatment effect of atorvastatin 10 mg on the primary endpoint of major CV events was
25 already at its final values of 37% reduction, and by 18 months the CI did not include unity.
26 **Level 1++**

11.3.4.22 Lipid levels

28 Studies conducted on the Type 2 diabetes population

29 An RCT²⁹¹ reported that end-of-treatment LDL-C levels increased by 3% to a mean of 98.6
30 mg/dl (2.5 mmol/l) in patients who continued atorvastatin 10 mg, while a further reduction of
31 19% to a mean of 77.0 mg/dl (2.0 mmol/l) was observed in those assigned to atorvastatin 80
32 mg ($p < 0.0001$). **Level 1++**

33 The same study²⁹¹ reported significant differences between the groups, in favour of
34 atorvastatin 80 mg, for total cholesterol (TC) levels and TG. **Level 1++**

35 One RCT²⁸⁷ reported that simvastatin 80 mg treatment resulted in significantly lower low-
36 density lipoprotein (LDL) levels compared with simvastatin 40 mg ($p < 0.001$). **Level 1+**

37 The same study²⁸⁷ showed that after a 6-week treatment, approximately 87% of patients
38 treated with simvastatin 80 mg, and 82% of patients treated with simvastatin 40 mg, had LDL
39 values that met or exceeded the National Cholesterol Education Program Adult Treatment
40 Panel III (NCEP ATP III) treatment goal of < 100 mg/dl (2.6 mmol/l), compared with only 14.3
41 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.

1 An RCT²⁸⁸ comparing treatment with rosuvastatin 10 mg vs atorvastatin 10 mg, reported that
2 at the end of the study rosuvastatin-treated patients had significantly lower LDL levels
3 compared with the atorvastatin group ($p < 0.0001$). The study also reported that at 16 weeks,
4 significantly more patients achieved their LDL goal with rosuvastatin compared with
5 atorvastatin (94% vs 88%, $p < 0.05$). **Level 1+**

6 **Post hoc sub-analysis**

7 The ASCOT-LLA post hoc study²⁹⁰ found that among diabetic participants in the atorvastatin
8 group, TC and LDL levels at year one of follow-up were lower than in the placebo group by
9 ~1.3 and 1.2 mmol/l respectively. By the end of the study, these differences were 0.9 and 0.9
10 mmol/l respectively. However, no statistical analysis was performed. **Level 1+**

11 In relation to lipid levels, the DALI post hoc analysis found that after 30 weeks, patients
12 receiving atorvastatin 80 mg had significantly lower LDL levels than those treated with only
13 10 mg of atorvastatin ($p < 0.01$).

11.3.4.3 **Safety issues**

15 **Studies conducted on Type 2 diabetes population**

16 An RCT²⁹¹ found no significant differences between the treatment groups (atorvastatin 10 mg
17 and 80 mg) in the rate of treatment related adverse events (AEs), including myalgia, or
18 persistent elevations in liver enzymes. No incidents of rhabdomyolysis were reported in
19 either treatment group. **Level 1++**

20 One RCT²⁸⁷ comparing different doses of simvastatin (simvastatin 40 and 80 mg) concluded
21 that no drug related serious clinical AEs were observed in the treatment groups. However,
22 the study reported that two patients on simvastatin 80 mg treatment had an Alanine
23 Transaminase (ALT) and Aspartate Transaminase (AST) level > 3 times the upper limit of
24 normal; one of these patients was discontinued because of these elevations (the liver
25 function tests returned to normal after discontinuation of the therapy). **Level 1+**

26 An RCT²⁸⁸ comparing treatment with rosuvastatin 10 mg vs atorvastatin 10 mg, reported that
27 both treatments were well tolerated, with overall incidences of AEs being similar between the
28 groups. According to the study ten patients discontinued because of AEs, three in the
29 rosuvastatin group and seven in the atorvastatin group. There were no cases of myopathy.
30 **Level 1+**

31 **Post hoc sub-analysis**

32 The model developed for this guideline suggested that one-step titration from simvastatin 40
33 mg to 80 mg daily was very cost-effective in those with no previous CV event or extant CVD
34 where TC still exceeded 4.0 mmol/l or LDL-C exceeded 2.0 mmol/l.

35 For those with already diagnosed CVD (or developing CVD) two-step titration (firstly to 80 mg
36 simvastatin and then if indicated to atorvastatin 80 mg daily) was found to be cost-effective in
37 those with already diagnosed CVD and whose TC still exceeded 4.0 mmol/l or LDL-C
38 exceeded 2.0 mmol/l.

11.3.5 **From evidence to recommendations**

40 The GDG were cognisant of the previous NICE statin appraisal, the prior Type 2 diabetes
41 guidelines, the ezetimibe appraisal, the deliberations of the NICE guidelines group on
42 management of CVD, and the health economic analysis. The evidence of effectiveness and
43 safety of generic statins, and in particular simvastatin seemed clear, and at current prices
44 probably cost- saving in the population with Type 2 diabetes over the age of 40 years

- 1 (irrespective of experience of CVD). There may be individuals in this group at lower CV risk
2 (discussed in section 13), but these people would be uncommon and easily identified by the
3 absence of CV risk factors (see 13.1.6). In others statin therapy should usually be with
4 generic simvastatin at standard dosage (40 mg) in line with the prior TA²⁸³ and the Heart
5 Protection Study.
- 6 The group recognised that some people below the age of 40 years were also at high risk (10
7 year risk >20%, or 20 year risk >40%). It was considered that they would have to be
8 identified by conventional risk factors; presence of features of the metabolic syndrome,
9 strong family history, ethnic group, and evidence of microvascular damage such as
10 nephropathy. Such people would then be treated with a statin, particularly as their 10-year
11 risk horizon came to include 40 years of age or greater. However, the contraindication of the
12 use of statins in pregnancy was felt to be great enough to deserve special mention, for any
13 woman of childbearing potential.
- 14 The health economic analysis suggested titration to simvastatin 80 mg was highly cost-
15 effective in those whose lipid levels were not controlled to target levels of 4.0/2.0 mmol/l (T-
16 /LDL-C) irrespective of presence or absence of diagnosed CVD.
- 17 In those with CVD the health economic analysis suggested that uptitration from simvastatin
18 80 mg to a more efficacious statin (modelled as atorvastatin 80 mg daily) was cost-effective if
19 the titration targets were not met on the simvastatin.
- 20 The GDG noted the stronger evidence base for atorvastatin than other higher efficacy
21 statins. In regard of the use of ezetimibe (addition to simvastatin), they noted that guidance
22 was provided by the NICE ezetimibe TA.
- 23 Unfortunately there is no easy way of calculating CV risk in people already under
24 preventative management (which would be likely to include recent lifestyle change, aspirin,
25 renin-angiotensin blockers and perhaps other drugs, as well as statins themselves). The
26 alternative approach of using lipid levels was less attractive, but had the advantage of being
27 pragmatic, and allowing monitoring of response.

11.4 Fibrates

11.4.1 Clinical introduction

- 30 Fibrates have a long and controversial history as lipid-lowering agents, beginning with
31 clofibrate over 30 years ago and being implicated in the problems which led to withdrawal of
32 cerivastatin in the 1990s. However, bezafibrate, fenofibrate and ciprofibrate have shown
33 considerable staying power in the market. Statins have, however, eclipsed fibrates as
34 primary cholesterol-lowering agents, so the issues surrounding fibrates relate to specific lipid
35 abnormalities. In clinical practice these mostly concern hypertriglyceridaemia, itself strongly
36 associated with low HDL-C levels, this problem being particularly common in people with
37 Type 2 diabetes (more so than raised LDL-C levels).
- 38 The clinical question then relates to whether and when a fibrate should be initiated before
39 statin therapy, and the circumstances under which a fibrate should be added to, or
40 substituted for, statin therapy.

11.4.2 Methodological introduction

- 42 There were eleven studies identified which included fibrates and involved participants with
43 Type 2 diabetes. Nine studies were reviewed, two studies comparing fenofibrate and placebo
44 were excluded,^{292,293} as the Effects of long-term fenofibrate therapy on cardiovascular events
45 in 9,795 people with Type 2 diabetes mellitus (FIELD) study,²⁹⁴ which had N=9,795
46 participants across 63 centres, was included.

- 1 One study considered fluvastatin and fenofibrate with fenofibrate monotherapy.²⁹⁵
- 2 There were three studies which considered fenofibrate in comparison with statin
- 3 monotherapy and the combination of fenofibrate and a statin; atorvastatin,²⁹⁶ rosuvastatin,²⁹⁷
- 4 and simvastatin.²⁹⁸
- 5 The remaining four studies included gemfibrozil in comparison with placebo,²⁹⁹ in comparison
- 6 with statin monotherapy; simvastatin³⁰⁰ and statin monotherapy and the combination of
- 7 gemfibrozil and a statin; pravastatin,³⁰¹ and atorvastatin.³⁰²

11.4.3 Health economic methodological introduction

- 9 Two evaluations were identified one conducted in the UK and in one the US. In both studies
- 10 no clinical evidence was found for fenofibrate and so it was assumed to be equally effective
- 11 as gemfibrozil. Both studies used a 5-year time horizon. The US study was excluded as it
- 12 was not generalisable to the UK setting.

11.4.4 Evidence statements

11.4.4.1 Outcomes – fenofibrate

15 Fenofibrate vs placebo

- 16 The double-blind, multicentre FIELD study with N=9,795 participants compared fenofibrate
- 17 200 mg/day with a placebo in a Type 2 diabetes population, over a 5-year duration.²⁹⁴

11.4.4.2 Lipids

- 19 At 4 months, 1 year, 2 years and at completion of the study there were significant decreases
- 20 in TC, LDL-C and TG levels and increases in HDL-C levels with fenofibrate compared with
- 21 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%)

- 22
- 23 For study participants who started other lipid-lowering therapy during the study (total
- 24 N=2,720, N=944 placebo group and N=1,776 fenofibrate group) they showed smaller
- 25 changes in lipid levels, but the significance between the groups remained p<0.05 at 2 years.
- 26 At study close the changes remained significant for TC and TGs between the groups;
- 27 however, the changes in LDL-C and HDL-C were NS.

11.4.4.3 Adverse events

- 29 There were small percentages (0.5 with placebo and 0.8% with fenofibrate) of possible
- 30 serious adverse drug reactions. Four participants had rhabdomyolysis which fully resolved

1 (N=3 with fenofibrate and N=1 with placebo). Rates of new cancer diagnosis were similar
2 between groups.

3 GI events were the most frequently reported event, these were noted with N=975 (20%) of
4 the fenofibrate and N=927 (19%) of the placebo group. **Level 1++**

5 **Fenofibrate vs simvastatin**

6 This single centre, double-blind study compared fenofibrate 160 mg/day with simvastatin 20
7 mg/day and both monotherapies with the combination of fenofibrate and simvastatin, with
8 N=300 participants.²⁹⁸

9 Fenofibrate was found to have significantly greater reductions in TC and for LDL-C than
10 simvastatin and than the combination of the drugs, differences between simvastatin and the
11 combined group were NS.

12 The fenofibrate and combined groups had significantly higher decreases in TGs than
13 simvastatin (NS between fenofibrate and combined treatments).

11.4.44 **Adverse events**

15 There were no serious drug related AEs. **Level 1++**

16 **Fenofibrate vs atorvastatin**

17 This study compared fenofibrate 200 mg/day and atorvastatin 20 mg/day monotherapies
18 compared with the combination of fenofibrate and atorvastatin, with N=120 participants.²⁹⁶

11.4.45 **Treatment goals**

20 The treatment goals for LDL-C (2.4 mmol/l), TGs (2.6 mmol/l) and HDL-C (1.2 mmol/l) were
21 reached in significantly more (reached by 97.5%, 100% and 60% respectively, p<0.05)
22 participants for the combination of fenofibrate and atorvastatin than the monotherapies. The
23 fenofibrate group compared with the atorvastatin group reached the treatment goals in a
24 significantly higher percentage for HDL-C (30% vs 17.5%) and TGs (92.5% vs 75%), while
25 the reverse was true for LDL-C with 80% of the atorvastatin reaching the treatment goal
26 compared with 5% of the fenofibrate group.

11.4.46 **Lipids**

28 The combination treatment reduced the TC, TGs and LDL-C significantly more than the
29 atorvastatin or the fenofibrate as monotherapies. This combination also significantly
30 increased HDL-C compared with atorvastatin monotherapy but not compared with
31 fenofibrate.

11.4.47 **Adverse events**

33 There were no significant AEs reported in this study. **Level 1+**

34 **Fenofibrate vs fluvastatin**

35 This double-blind study over 12 months compared the combination of extended-release
36 fluvastatin 80 mg and fenofibrate 200 mg and the monotherapy of fenofibrate 20 mg, N=48
37 participants.²⁹⁵

38 At 6 months the combination showed a significantly higher reduction in LDL-C compared with
39 fenofibrate monotherapy. For the 12-month point significantly there were greater reductions

1 in LDL-C and TG levels and increases in HDL-C with the combination group compared with
2 the monotherapy.

11.4.438 Adverse events

4 No serious AEs were reported, N=3 discontinued in the study due to myalgia. **Level 1++**

5 Fenofibrate vs rosuvastatin

6 This multicentre study incorporated both a double-blind, fixed-dose phase and an open-label
7 titrating dose phase, N=216.²⁹⁷

8 Fixed dose: the 6-week fixed-dose phase had placebo, rosuvastatin 5 mg and rosuvastatin
9 10 mg groups.

10 There were significant decreases for both rosuvastatin 5 mg and 10 mg groups compared
11 with increases with placebo in TC (–36.6%, –31.4% vs 1.1%, p<0.001) and TGs (–24.5%, –
12 29.5% vs 4.7%, p<0.001) and compared with decreases in LDL-C levels with placebo (–
13 40.7%, –45.8% vs –0.6%, p<0.001). At week 6, 77.4% of those in the rosuvastatin 10 mg
14 group had reached the LDL-C goal of <100 mg/dl, compared with 8.3% of those receiving
15 placebo.

11.4.439 Titrating dose

17 This 18-week phase used sequential dose increases at 6-week intervals provided the LDL-C
18 level remained >50 mg/dl (>1.3 mmol/l).

19 The groups were:

- 20 • placebo in fixed dose – rosuvastatin 10 mg (with possible increases to 20 and 40 mg)
- 21 • placebo in fixed dose – fenofibrate 67 mg once daily (with possible increases to BD and
22 TID fenofibrate)
- 23 • rosuvastatin 5 mg in fixed dose – rosuvastatin 5 mg and fenofibrate 67 mg once daily
24 (with possible increases to BD and TID fenofibrate)
- 25 • rosuvastatin 10 mg in fixed dose – rosuvastatin 10 mg and fenofibrate 67 mg once daily
26 (with possible increases to BD and TID fenofibrate).

27 By the final stage of the dose-titration phase a smaller proportion of those on the groups
28 which received rosuvastatin 10 mg required dose titration than in the other two groups.

11.4.420 Lipids

30 There was a significant decrease in LDL-C with placebo/rosuvastatin compared with a slight
31 increase with placebo/fenofibrate. This reduction in LDL-C was also significantly greater than
32 that found with rosuvastatin 5 mg/fenofibrate, but was NS compared with rosuvastatin 10
33 mg/fenofibrate.

34 The reductions in TG levels between the groups which had placebo in the fixed-dose phase
35 were NS. The decrease in TG levels with rosuvastatin 10 mg/fenofibrate were significantly
36 greater than those with placebo/rosuvastatin.

37 For each group those who reached the goal of LDL-C <100 mg/dl at the end of both the
38 fixed- dose and the titrating-dose phase were; rosuvastatin 40 mg (86.0%, N=50),
39 rosuvastatin 10 mg and fenofibrate 67 mg TID (75.5%, N=53), rosuvastatin 5 mg and
40 fenofibrate 67 mg TID (75.0%, N=60), and fenofibrate 67 mg TID (4.1%, N=49).

11.4.4.11 Adverse events

- 2 The most frequently reported AEs in a small number of participants were GI related, myalgia
3 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

4

11.4.4.12 Outcomes – gemfibrozil**6 Gemfibrozil vs placebo**

- 7 This study compared gemfibrozil 1,200 mg and a matched placebo in the Veterans Affairs
8 High Density Lipoprotein Intervention Trial (VA-HIT) and included a subgroup diabetic,
9 N=627.²⁹⁹
- 10 This study considered major CV events and identified in the diabetes group a significant
11 reduction in the risk of major CV events of 32%, of CHD death 41%, and of stroke 40%,
12 compared with placebo.
- 13 The lipid level analysis was not analysed by diabetic subgroup. **Level 1+**

1 **Gemfibrozil vs simvastatin**

2 This study compared gemfibrozil 1,200 mg compared with simvastatin 20 mg, N=70.³⁰⁰

3 This study did not complete comparisons between the groups, both treatments significantly
4 decreased TC and TG levels, and increased HDL-C compared with the baseline. There were
5 significant decreases in LDL-C with simvastatin compared with baseline but not with
6 gemfibrozil.

7 There were small numbers of incidents of GI events with gemfibrozil and generalised
8 weakness and muscle pain with simvastatin. **Level 1+**

9 **Gemfibrozil vs pravastatin**

10 This double-blind, multicentre study with N=268 participants compared gemfibrozil 1,200 mg
11 and pravastatin matched placebo with pravastatin 40 mg and gemfibrozil matched
12 placebo.³⁰¹

11.4.413 Lipids

14 There were significantly greater reductions in TC and LDL-C with pravastatin than with
15 gemfibrozil. Conversely there was a significantly greater reduction in TG levels with
16 gemfibrozil than with pravastatin $p < 0.001$. Changes in HDL-C were NS between the groups.

11.4.414 Adverse events

18 The AEs reported were considered not severe and the most frequent were GI related (N=28
19 gemfibrozil and N=24 pravastatin). **Level 1++**

20 **Gemfibrozil vs atorvastatin**

21 This open-label, crossover study compared gemfibrozil and atorvastatin and a combination of
22 both drugs, in a titrating dose study, N=44.³⁰²

11.4.425 Lipids

24 The atorvastatin and combination groups had significantly greater reductions in LDL-C than
25 the gemfibrozil group (reductions NS for atorvastatin vs combination). For TG levels the
26 gemfibrozil and combination groups had significantly greater reductions than the atorvastatin
27 group (reductions NS for gemfibrozil vs combination). There were NS differences between
28 the monotherapies and the combination treatment for HDL-C levels.

11.4.426 Adverse events

30 GI related (abdominal discomfort, constipation, loose stools, nausea) were reported by N=6
31 (atorvastatin), N=11 (gemfibrozil) and N=8 (combination). **Level 1+**

		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)

1

11.4.5 Health economic evidence statements

3 Feher et al.³⁰³ was a very simple analysis although it was unclear how the costs in the
 4 treated groups were calculated. Only costs of the drugs and a cost per CHD event were
 5 included. The costs used are now out of date and assuming the same risk reduction for
 6 statins and fenofibrate would result in statins being cost saving.

11.4.6 From evidence to recommendations

8 While the evidence was not as strong as for the statins, there was convincing evidence of the
 9 effectiveness of fibrates in CV protection in people with Type 2 diabetes. Some of the trials
 10 (e.g. FIELD) in which this evidence was found included people with TG levels down to the
 11 upper end of the normal range (~1.8 mmol/l). However, while the price of fibrates was
 12 considerably above that of generic statins, the more effective fibrates as judged by TG
 13 lowering were about half the price of proprietary statins when both are used at standard
 14 doses.

15 Hypertriglyceridaemia is a complex condition with both a genetic basis and often being
 16 secondary to other medical conditions, including poor blood glucose control. The GDG
 17 recognised it was not writing a guideline on management of hypertriglyceridaemia in people
 18 with Type 2 diabetes, but because of the interaction with blood glucose control and other
 19 medical conditions often associated with Type 2 diabetes (including renal impairment and
 20 liver disease), it could not avoid some general guidance in the area.

21 In drawing up the recommendations the GDG was also cognisant of the need to be aware of:

- 22 • the likely combination with statin therapy (given its recommendations on statins) and the
 23 higher rate of side effects of combined usage
- 24 • the more immediate risks of pancreatitis with higher levels of TGs
- 25 • the difficulty of assessing LDL-C levels when TG levels were above 4.5 mmol/l. A useful
 26 pragmatic compromise was felt to be to base recommendations around cut-off levels of
 27 2.3 and 4.5 mmol/l.

28 There is evidence of differences between fibrates: gemfibrozil had greater interactions with
 29 other drugs commonly used in diabetes care; bezafibrate was cheaper and less effective in
 30 TG lowering and with a poorer CV evidence base than fenofibrate; and ciprofibrate was more
 31 poorly investigated. Therefore recommendations were based around fenofibrate, though with
 32 a role for bezafibrate where CV risk was less pronounced, and ciprofibrate as an alternative.

- 1 Further information on fibrate statin combinations might become available when the
2 ACCORD trial reports.³⁵

11.5 Nicotinic acid and derivatives

11.5.1 Clinical introduction

5 Abnormalities of blood lipid profiles, including serum HDL-C and TGs, are recognised CV risk
6 factors, and are particularly likely to be abnormal in people with Type 2 diabetes. Nicotinic
7 acid preparations are one approach to improving lipid profiles. Nicotinic acid administration is
8 associated with side effects due to vasodilatation, and derivatives (acipimox) and modified-
9 release preparations have been made available to try and reduce the problem. The clinical
10 question is then what role nicotinic acid derivatives might have in the management of Type 2
11 diabetes.

11.5.2 Methodological introduction

13 There were four studies identified in this area. Two of the studies were multicentre, double-
14 blind RCTs, one of which considered immediate-release nicotinic acid against placebo,
15 N=125,³⁰⁴ the other study compared different doses of an extended-release nicotinic acid
16 with placebo, N=148.³⁰⁵

17 There were also two single centre studies identified, one crossover, non-blinded study which
18 considered nicotinic acid compared with no therapy, N=13.³⁰⁶ There was only one study
19 which considered nicotinic acid with any other drug and this was, nicotinic acid compared
20 with pravastatin, N=44.³⁰⁷

21 It should be noted that two of these studies used samples which were combinations of
22 diabetic and non-diabetic participants, one study represented the outcomes entirely
23 separately³⁰⁴ and therefore the N=543 non-diabetic participants are not reported here, solely
24 the N=125 diabetic participants. The other study gave combined results for the drug efficacy
25 results but separate results for the glycaemic effects, with a total sample of N=44 but a Type
26 2 diabetic sample of N=11, therefore the results are reported pooled with the other
27 participants for the efficacy section.³⁰⁷

11.5.3 Health economic methodological introduction

29 Two papers were identified. Armstrong et al.³⁰⁸ was given a negative rating because the time
30 horizon was very short and would not capture all the benefits of treatment.

31 Olson et al.³⁰⁹ was excluded as it was not a diabetic population and did not present results
32 according to risk.

33 An additional paper was suggested in the consultation comments, Roze et al.³¹⁰ The base-
34 case analysis excluded people with diabetes, but a sensitivity analysis was conducted for a
35 diabetic population. All patients received the same statin treatment with additional prolonged-
36 release nicotinic acid compared to no additional treatment. This paper was excluded as this
37 was not considered a suitable comparison for people with diabetes who have failed on statin
38 monotherapy.³¹⁰

11.5.4 Evidence statements

2 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, $p = 0.0006$

3

4 Overall nicotinic acid was found to show reduction in LDL, TGs and the TC/HDL ratio and
5 increases in HDL, compared with placebo in all three studies with more significant changes
6 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, $p = 0.016$

7

8 Nicotinic acid showed some glycaemic effects compared with placebo, one study identified
9 that HbA_{1c} remained stable with nicotinic acid but had a significant decrease with placebo,
10 this study included a downtitration of nicotinic acid if HbA_{1c} exceeded 10%, this occurred in
11 N=10 of the nicotinic acid group and N=8 of the placebo group.³⁰⁴

12 Two studies identified an increase in HbA_{1c} with doses of 1,500 mg/d, compared with
13 placebo for both immediate-release and extended-release formulations.^{305,306} **Level 1+**

1 Adverse events

2 Increases in uric acid were identified in two of the studies, for one this was from 339 to 386
3 $\mu\text{mol/l}$ and was significant compared with placebo, $p < 0.001$.³⁰⁴ The second study noted that
4 $N=2$ participants had very high uric acid levels of 684 and 761 $\mu\text{mol/l}$.³⁰⁶ The third (extended-
5 release) study found no significant differences in uric acid levels.³⁰⁵

6 Flushing was considered a minor complaint in one study, numbers not reported.³⁰⁶ Two thirds
7 of those taking the extended-release nicotinic acid formulation reported flushing at some
8 point during the trial, approximately 10% of those taking placebo reported it.³⁰⁵ **Level 1+**

9 Nicotinic acid vs pravastatin

10 One study considered nicotinic acid 1,500 mg/day compared with pravastatin 40 mg/day,
11 followed by a combination therapy phase of nicotinic acid 1,000 mg/day with pravastatin 20
12 mg/day. This study included both diabetic and non-diabetic participants ($N=11$, Type 2
13 diabetes).³⁰⁷ This study considered the results for lipid profiles for the combined diabetic and
14 non-diabetic participants. The glycaemic effect results were considered separately for
15 diabetic and non-diabetic participants.

16 Lipid profiles

17 Nicotinic acid was not found to be more effective than pravastatin as the later showed
18 significant reductions in LDL and TC levels compared with nicotinic acid. Combination
19 therapy showed significant decreases in LDL, TC and TG levels compared with nicotinic acid
20 and significant increases in HDL and decreases in TG levels compared with pravastatin.
21 **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 \pm 4.1 vs 18.4 \pm 5.8, $p < 0.001$)
LDL	Pravastatin showed reductions in LDL compared with nicotinic acid (-32.1 \pm 3.0 vs -18.9 \pm 3.3, $p < 0.01$)	Decreased with combination compared with nicotinic acid (-35.7 \pm 3.3 vs -16.9 \pm 3.3, $p < 0.01$)	NS
TC	Pravastatin showed reductions in TC compared with nicotinic acid (-24.9 \pm 2.0 vs -9.8 \pm 2.9, $p < 0.001$)	Decreased with combination compared with nicotinic acid (-23.8 \pm 2.9 vs -9.8 \pm 2.9, $p < 0.001$)	NS
TG	NS	Decreased with combination compared with nicotinic acid (-39.4 \pm 6.7 vs -31.8 \pm 6.8, $p = 0.03$)	Decreased with combination compared with pravastatin (-39.3 \pm 5.4 vs -28.0 \pm 5.1, $p = 0.01$)
Lipoprotein(a)	NS	NS	NS

22

23 Glycaemic effects

24 Diabetic participants: nicotinic acid monotherapy showed an increase in HbA1c by
25 approximately 8% ($p = 0.03$), pravastatin showed no change in HbA1c level and the increase
26 seen with combination therapy was non-significant. Nicotinic acid monotherapy increased
27 FPG by approximately 26% ($p = 0.02$), there were no changes with pravastatin or combination
28 therapy.

1 Non-diabetic participants: nicotinic acid monotherapy showed an increase in HbA1c by
 2 approximately 4% ($p=0.02$), combination therapy showed an increase of approximately 6%
 3 ($p<0.01$), pravastatin showed no change. None of the treatments showed changes in FPG.
 4 Level 1+

5 **Adverse events**

6 All of the participants in the nicotinic acid group complained of flushing, this generally lasted
 7 from 10 to 15 minutes and was ameliorated with aspirin. Nine participants (21%) withdrew
 8 from this study with significant flushing or nausea with nicotinic acid, one participant withdrew
 9 with nausea from the pravastatin group. **Level 1+**

11.55 **From evidence to recommendations**

11 This group of drugs was not considered in the previous guideline (2002).⁴¹⁴ The limited
 12 number of studies presented suggested that nicotinic acid can have some advantageous
 13 effect on serum HDL-C and lipids, but also that it has some negative effects on blood
 14 glucose control. In the absence of outcome trials in people with Type 2 diabetes, and given
 15 also the problems of using the current preparations (notably flushing despite prophylactic
 16 aspirin, dose titration and use of modified-release preparations), no general recommendation
 17 could be given for use of nicotinic acid. The group were aware of some possible special
 18 indications in people with extreme hypertriglyceridaemia, but felt this to be outside the remit
 19 of the current guideline.

11.6 **Omega 3 fish oils**

11.6.1 **Clinical introduction**

22 The concept of beneficial and harmful dietary fats has come to the fore in recent years.
 23 Some evidence does exist for the use of omega 3 fish oils in certain circumstances such as
 24 post-MI. The clinical question then was what role these oils might have in the management of
 25 people with Type 2 diabetes.

11.6.2 **Methodological introduction**

27 There were seven studies identified for participants with Type 2 diabetes. A Cochrane
 28 systematic review, for which the last search had been completed in September 2000,³¹¹
 29 included studies that were 2–24 weeks in duration.

30 A second systematic review and meta-analysis³¹² investigated the haematological and
 31 thrombogenic effects of omega 3 fatty acids and did not report on glycaemic and lipid control
 32 outcomes. Included studies were of 4–24 weeks duration.

33 There were five RCTs identified. Four of the studies compared; fish oil, eicosapentaenoic
 34 acid (EPA), docosahexaenoic acid (DHA), and placebo,³¹³ fish oil (one group taking EPA and
 35 one taking DHA) compared with olive oil³¹⁴ and fish oil (EPA and DHA) compared with corn
 36 oil,^{315,316} all of these studies used capsules of the oils. Two of the studies were conducted in
 37 the same centre using a virtually identical patient group and research method.^{315,316}

38 The final study compared the effects of a daily fish meal and light or moderate exercise, with
 39 no fish and light or moderate exercise.³¹⁷ These studies were of 6–8 weeks duration.

40 It should be noted that a systematic review including studies conducted in the general
 41 population (search performed up to February 2002) was also identified.³¹⁸ This review
 42 concluded that there was no evidence of a clear benefit of omega 3 fats on health.

- 1 Participants in these studies were often requested to follow dietary guidelines and their
- 2 compliance with these may have affected the findings.

11.63 Health economic methodological introduction

- 4 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: 0.24 mmol/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

2

3 Cochrane review and RCTs

4 The table above details the evidence from the RCTs comparing omega 3 and placebo, or
5 corn oil or fish oil.

1 All studies (Cochrane review and the five RCTs) found that treatment with omega 3
 2 significantly reduced TGs compared to placebo. **Level 1+**

3 The only other area where the Cochrane review identified significant changes was in LDL-C
 4 where omega 3 were associated with a significant increase compared with placebo. **Level**
 5 **1++**

6 **Subgroup analysis – Cochrane review**

7 A subgroup analysis was undertaken with the hypertriglyceridaemic participants, doses of
 8 fish oil and trial duration.

9 **Hypertriglyceridaemic participants (control TGs >4 mmol/l)**

10 An increased reduction in TGs was identified in trials (N=3) with only hypertriglyceridaemic
 11 participants; -1.45 mmol/l (-2.89 to -0.01 , $p=0.05$), compared with studies with non-
 12 hypertriglyceridaemic participants (N=11) -0.40 mmol/l (-0.61 to -0.19 , $p=0.0002$).

13 Increases in LDL-C levels were significant in the hypertriglyceridaemic groups (N=2 trials),
 14 0.6 mmol/l (0.16 to 1.04 , $p=0.008$), but they were NS in the non-hypertriglyceridaemic groups
 15 (N=9 trials).

16 **Dose of fish oil**

17 Trials with high doses of fish oil (>2 g EPA, N=4) showed a significant increase in LDL-C
 18 0.51 mmol/l (0.18 to 0.84 , $p=0.003$), this was NS for lower doses (<2 g EPA, N=7).

19 Levels of TGs in the high-dose groups decreased by 1.11 mmol/l (-2.21 to -0.10 , $p=0.03$),
 20 but in the low-dose group this was less at 0.54 mmol/l (-0.69 to -0.38 , $p<0.00001$).

21 **Trial duration**

22 In trials of longer than 2 months LDL-C levels increased by 0.33 mmol/l (0.00 to 0.65 ,
 23 $p=0.05$), the increases were NS in trials shorter than 2 months.

24 TG levels were reduced by 0.81 mmol/l (-1.21 to -0.41 , $p=0.00008$) in the longer trials and
 25 by less than 0.36 (-0.58 to -0.13 , $p=0.002$) in the shorter ones. **Level 1++**

11.6.261 **Daily fish meal and exercise comparison study**

27 **Triglycerides**

28 The study which included fish meals found that compared with the control (no fish meals,
 29 light exercise) the inclusion of a daily fish meal significantly reduced TGs, -0.9 ± 1.3 mmol/l,
 30 $p=0.0001$, with fish/moderate exercise reducing by 1.21 ± 0.3 mmol/l and fish/light exercise by
 31 1.22 ± 0.3 mmol/l $p=0.0001$. The addition of exercise without the fish also showed a significant
 32 decrease in TGs -0.7 ± 0.3 mmol/l, $p=0.03$, compared with the control.³¹⁷

33 **HDL-C (subgroups)**

34 The study which included fish meals found that high-density lipoprotein 2 cholesterol (HDL2-
 35 C) was significantly increased, 0.06 mmol/l, $p=0.01$ and high-density lipoprotein 3 cholesterol
 36 (HDL3-C) significantly reduced by the inclusion of fish compared with the low-fat control
 37 group, -0.05 mmol/l, $p=0.01$.³¹⁷ **Level 1+**

1 **Cardiovascular effects**

2 A meta-analysis found that participants who took omega 3 fatty acids had a significant
 3 reduction in diastolic BP of 1.79 mmHg (95% CI, -3.56, -0.02; p=0.05) and a non-significant
 4 reduction in systolic BP (p=0.32). There was also a non-significant reduction in heart rate
 5 (p=0.52).³¹² **Level 1++**

6 **Thrombogenic factors**

7 The pooled analysis of the data of two studies, showed a significant increase in factor VII of
 8 24.86% (95% CI, 7.17, 42.56; p=0.006).³¹² **Level 1++**

11.65 From evidence to recommendations

10 From the evidence available fish oils as a homogeneous therapeutic concept is problematic,
 11 as the evidence included showed a variation in the fish oil dosage used. Clinical experience
 12 confirmed that large total doses of oils used to get an adequate dose of omega 3 fish oils in
 13 some preparations can cause adverse effects. From the evidence available omega 3 fish oil
 14 preparations could help lower TG levels, but overall showed minimal improvement in lipid
 15 profiles in people who had not had a MI. The GDG agreed there were financial
 16 consequences in prescribing omega 3 supplements when the evidence showed no clear
 17 benefit.

18 It was recognised that the recommendations made must be understood as only applying for
 19 omega 3 fish oil supplementation, and not to recommendations on sources of dietary fats.

11.66 Recommendations

21 **R76 Review cardiovascular risk status annually by assessment of cardiovascular**
 22 **risk factors, including features of the metabolic syndrome and waist**
 23 **circumference, and change in personal or family cardiovascular history.**

24 **Statins and esetimibe**

25 **R77 Once a person has been started on cholesterol-lowering therapy, assess his**
 26 **or her lipid profile (together with other modifiable risk factors and any new**
 27 **diagnosis of cardiovascular disease) 1–3 months after starting treatment, and**
 28 **annually thereafter. In those not on cholesterol- lowering therapy, reassess**
 29 **cardiovascular risk annually, and consider initiating a statin (see**
 30 **recommendations 77 and 78).**

31 **Fibrates**

32 **R83 If there is a history of elevated serum triglycerides, perform a full fasting lipid**
 33 **profile (including high-density lipoprotein cholesterol and triglyceride estimations)**
 34 **when assessing cardiovascular risk annually.**

35 **R84 Assess possible secondary causes of high serum triglyceride levels,**
 36 **including poor blood glucose control (others include hypothyroidism, renal**
 37 **impairment and liver inflammation, particularly from alcohol). If a secondary cause**
 38 **is identified, manage according to need.**

12 Antithrombotic therapy

12.1 Antiplatelet therapy

12.1.1 Clinical introduction

4 Antiplatelet therapy now has an established role in the management of people at high risk of
5 cardiovascular (CV) events. People with Type 2 diabetes are known to have CV risk higher
6 than matched populations after allowance for other CV risk factors, and in some studies as
7 high as those without diabetes who have declared cardiovascular disease (CVD).²⁷³ National
8 guidelines and the previous NICE (inherited) Type 2 diabetes guideline recommend use of
9 aspirin in people at high CV risk.^{319,320} Other antiplatelet agents (clopidogrel and dipyridamole
10 modified release (MR)) have been the subject of a NICE technology appraisal (TA) but
11 without specific calculation for the higher CV event rate or the specific risk reduction in
12 people with Type 2 diabetes.³²¹ The increasing occurrence of Type 2 diabetes in younger
13 people raises the additional question of the use of antiplatelet therapy in those who CV risk
14 may be not be very high.

15 The guidelines are not concerned with the use of antiplatelet therapy after acute cardiological
16 events or cardiac interventions, or after acute cerebrovascular events.

17 The clinical question then is whether antiplatelet medications should be used in people with
18 Type 2 diabetes, or in which subgroups of such people, and if so which agents and in what
19 doses.

12.1.2 Methodological introduction

21 Aspirin

22 There were only two studies which were reviewed that considered aspirin and CVD in people
23 with Type 2 diabetes from 2001 onwards. There were a number of large trials completed
24 which evaluated aspirin in populations which had a diabetic subgroup included. A review
25 which included the Early Treatment of Diabetic Retinopathy Study 1992 (ETDRS),
26 Thrombosis Prevention Trial 1998 (TPT), Hypertension Optimal Treatment trial 1998 (HOT),
27 and Primary Prevention Project 2001 (PPP), the efficacy of low- and high-dose aspirin has
28 been evaluated and reductions on CV endpoints in high-risk patients demonstrated.
29 However, this review also noted that these trials had small numbers of participants with
30 diabetes and that no head-to-head comparison of low- versus high-dose therapy has been
31 conducted in diabetics.

32 The two studies reviewed comprised one RCT involving participants with Type 2 diabetic
33 nephropathy and compared aspirin with dipyridamole, a combination of aspirin and
34 dipyridamole with placebo. The authors stated that they believed this study to be the first
35 clinical trial of aspirin in Type 2 diabetic nephropathy.³²²

36 The second study was an open-label RCT which compared aspirin with vitamin E with 4,495
37 participants of whom 1,031 were diabetic. This study had been planned with a 5-year follow-
38 up but was terminated early (at 3.7 years) on the advice of the independent Data Safety and
39 Monitoring Board (DSMB) when newly available evidence on the benefit of aspirin in primary
40 prevention was available.³²³

41 There was also a multicentre RCT with a Type 2 diabetic sample (N=1,209),³²⁴ however, this
42 study compared aspirin with picotamide, which is unlicensed and therefore the study was
43 excluded.

1 Clopidogrel vs aspirin

2 Six large RCTs were identified, all of which had long follow-up periods, allowing assessment
3 of the long-term CV event risk.^{325–330} The studies were conducted in the general population
4 but included subgroup analysis of those with diabetes, none of the studies discriminated
5 between those with Type 1 or with Type 2 diabetes.

6 One RCT, a post hoc sub-analysis from the Clopidogrel vs Aspirin in Patients at Risk of
7 Ischemic Events (CAPRIE)^w study (N=3,866 with diabetes) compared aspirin monotherapy
8 with clopidogrel monotherapy.³²⁶

9 Four RCTs compared the combination of aspirin plus clopidogrel with aspirin plus placebo.

- 10 • The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management
11 and Avoidance study (CHARISMA)³²⁸ with a median follow-up of 28 months compared
12 the combination of clopidogrel 75 mg/day plus a low dose of aspirin with a low dose of
13 aspirin alone, in those with either clinically evident CVD (secondary prevention) or multiple
14 vascular risk factors (primary prevention) (N=6,556 for those with diabetes, 42% of the
15 total sample).
- 16 • The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial³²⁷ included
17 those with unstable angina or non-Q wave MI within 24 hours of an acute event, mean
18 follow-up of 9 months. The principal objectives of this study were to compare the early and
19 long-term efficacy and safety of the use of clopidogrel vs placebo on top of standard
20 therapy with aspirin. 12,562 patients were given clopidogrel 300 mg bolus and then 75 mg
21 daily plus aspirin (75–325 mg daily) or placebo plus aspirin (N=2,840 for those with
22 diabetes, 22.6% of the total sample). The patients were followed for a maximum of 12
23 months (mean 9 months).
- 24 • The PCI-CURE³³⁰ which was a sub-analysis of 2,658 CURE study patients requiring
25 percutaneous coronary intervention (PCI). Diabetic patients represented 18.9% (N=504)
26 of the total sample.
- 27 • The Clopidogrel Reduction of Events During Extended Observation (CREDO)³²⁹ trial
28 evaluated the efficacy of continuing clopidogrel on top of standard therapy with aspirin for
29 1 year following PCI. Participants received either a clopidogrel loading dose (300 mg) or
30 placebo 3–24 hours before intervention. Patients in both treatments arms then received
31 clopidogrel 75 mg/day for 28 days. Between 4 weeks and 12 months, patients in the
32 loading-dose group received prolonged clopidogrel therapy, and those in the control group
33 received placebo. Both treatment groups received aspirin throughout the study. Diabetic
34 patients represented 26.4% (N=560) of the total sample.

35 Only one RCT, Management of ATherothrombosis with Clopidogrel in High-risk patients with
36 recent transient ischaemic stroke (MATCH), was identified comparing the combination of
37 clopidogrel plus aspirin with clopidogrel plus placebo.³²⁵ Patients with recent ischaemic
38 stroke or transient ischaemic attack and at least one additional vascular risk factor were
39 randomised to aspirin 75 mg plus clopidogrel 75 mg or clopidogrel 75 mg plus placebo for 18
40 months. (N=7,599 for those with diabetes, 68% of the sample.)

41 It should be noted that differing dosing and titration regimens and the differing populations
42 included in the studies, such as patients with no clinical evidence of CVD,³²⁸ to patients with
43 recent ischaemic stroke³²⁵ or patients undergoing a coronary surgery³³⁰ may limit direct
44 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

2 One study was identified looking at aspirin compared to standard care, but the main
3 outcomes for the trial were blood pressure (BP) targets and results of the addition of aspirin
4 were not given for the diabetes subgroup.³³¹

5 In the HTA clopidogrel used in combination with aspirin compared to aspirin alone in the
6 treatment of non-ST segment elevation acute coronary syndromes (ACS), diabetes was
7 considered as one of the risk factors contributing to high risk.³³²

8 In the study by Weintraub et al.³³³ clopidogrel was compared to aspirin in patients
9 hospitalised within 24 hours of onset of symptoms indicative of ACS who did not have
10 significant ST segment elevation. A subgroup analysis was performed for diabetics.³³³

11 In the studies by Ringborg et al.³³⁴ and Cowper et al.³³⁵ the cost-effectiveness of clopidogrel
12 plus aspirin for 12 months was compared to only 1 month of therapy. In the Ringborg study
13 diabetes was not found to be a significant risk factor and the results for the whole population
14 are reported here.³³⁴ In the Cowper study diabetes was considered a high-risk factor.³³⁵

12.1.14 Evidence statements**16 Aspirin and dipyridamole**

17 This study found that there was a significant decrease in proteinuria with aspirin (–15.9%),
18 with dipyridamole (–14.8%) and with the combination of aspirin and dipyridamole (–37.3%)
19 compared with an increase in proteinuria found with placebo (1.9%), p=0.0007. Significant
20 decreases were also identified in the urinary protein/creatinine ratio with the three treatment
21 groups compared with the placebo.

22 There were no changes identified in BP, renal function tests and blood sugar. No adverse
23 events (AEs) were noted during this study. **Level 1+**

24 Aspirin and vitamin E

25 This study was terminated early (3.7 years) and in the diabetic subgroup there were no
26 significant changes identified with aspirin in incidence of major CV and cerebrovascular
27 events. **Level 1+**

12.1.15 Clopidogrel vs aspirin**29 CAPRIE: Post hoc sub-analysis**

30 This sub-analysis found a significantly lower incidence of CV events in diabetic patients
31 receiving clopidogrel compared to those treated with aspirin. Furthermore, the incidence of
32 rehospitalisation for any bleeding event was significantly lower with clopidogrel than with the
33 aspirin group (see table 15.1). **Level 1+**

Table 15.1 CAPRIE: Post hoc sub-analysis

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			

1

2 The authors acknowledged several limitations of this sub-analysis:

- 3 • compared with the original CAPRIE primary cluster endpoints this was a different endpoint
- 4 ('softer' according to the authors)
- 5 • the study was not sufficiently powered to allow identification of specific individual
- 6 endpoints
- 7 • the duration and severity of diabetes were unknown
- 8 • specific details regarding control of diabetes, such as glycosylated haemoglobin levels or
- 9 glycaemic control were not collected. **Level 1+**

12.1.402 Aspirin + clopidogrel vs aspirin + placebo

11 CHARISMA study

12 The CHARISMA study did not find a significant benefit associated with clopidogrel plus
13 aspirin as compared with placebo plus aspirin in reducing the incidence of the primary
14 endpoint of MI, stroke, or death from CV causes in patients with clinically evident CVD or at
15 high risk for such disease. **Level 1++**

16 The same study found a moderate, though significant, benefit associated with clopidogrel
17 plus aspirin as compared with placebo plus aspirin in reducing the secondary composite
18 endpoint of MI, stroke, or death from CV causes, or hospitalisation for unstable angina,
19 transient ischemic attack or revascularisation (see table 15.2). **Level 1++**

20 The CHARISMA study found no significant differences in the rate of severe bleeding
21 between the two groups. However, the combination of clopidogrel and aspirin was
22 associated with a significantly higher rate of moderate bleeding in comparison with treatment
23 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
1 TIA, transient ischaemic attack			

2 Subgroup analysis

- 3 A subgroup analysis suggested that in the population of patients with clinically evident CVD
4 (symptomatic) the combination of clopidogrel plus aspirin was significantly beneficial in
5 comparison with placebo plus aspirin with respect to the primary efficacy endpoint. (Among
6 the 12,153 symptomatic patients, there was a marginally significant reduction in the primary
7 endpoint with aspirin plus clopidogrel. See table 15.3.) **Level 1++**
- 8 The analysis suggested that there was a risk associated with dual antiplatelet therapy in the
9 asymptomatic group since among the 3,284 asymptomatic patients there was a 6.6% relative
10 increase in the rate of primary events with clopidogrel plus aspirin, compared to 5.5% with
11 placebo (see table 15.3). **Level 1++**
- 12 Furthermore, in the subgroup of asymptomatic patients, there was a significant increase in
13 the rate of death from all causes among the patients assigned to clopidogrel plus aspirin as
14 compared with those assigned to placebo plus aspirin, as well as a significant increase in the
15 rate of death from CV causes among those assigned to the combination therapy (see table
16 15.3). **Level 1++**
- 17 The rates of severe bleeding were higher, but not significant, among both the asymptomatic
18 and symptomatic patients receiving the combination therapy compared to those receiving
19 aspirin plus placebo (see table 15.3). **Level 1++**
- 20 Among asymptomatic patients, there was no significant difference in the rates of moderate
21 bleeding between the two groups. In contrast, the rates of moderate bleeding among
22 symptomatic patients were significantly higher in those treated with aspirin plus clopidogrel
23 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=12,133	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=3,204	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		

1

2 **CREDO study**

3 The CREDO study found that at 12 months long-term clopidogrel and aspirin treatment
4 significantly reduced the risk of death, MI or stroke in comparison with those treated with
5 clopidogrel and aspirin for 4 weeks and then aspirin plus placebo for 11 months. RR
6 reduction of 27%, 95% CI (3.9%–44.4%), p=0.02. Absolute reduction 3% (p=0.02). **Level**
7 **1++**

8 The study also showed that the clopidogrel pre-treatment loading dose did not significantly
9 reduce the combined risk of death, MI, or urgent target vessel revascularisation at 28 days.
10 **Level 1++**

11 There was no significant difference in the risk of major bleeding between the groups, though
12 there was a higher risk of major bleeding identified for those treated with long-term
13 clopidogrel and aspirin compared with those taking aspirin plus placebo. **Level 1++**

12.1.43 **Clopidogrel + aspirin vs clopidogrel + placebo**15 **MATCH study**

16 The study found that combination treatment with aspirin plus clopidogrel did not significantly
17 reduce the primary composite CV morbidity or mortality endpoint^x compared with clopidogrel
18 plus placebo. **Level 1++**

19 The secondary endpoint analysis (ischaemic stroke and/or vascular death, all-cause stroke,
20 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).

1 of aspirin to clopidogrel versus clopidogrel plus placebo, though rates were lower with aspirin
2 than with placebo, added to clopidogrel. **Level 1++**

3 In terms of AEs, the study concluded that adding aspirin to clopidogrel resulted in
4 significantly more bleeding complications than in the placebo and clopidogrel arm, doubling
5 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%)

6

7 There was no significant difference in overall mortality between the two treatment groups.
8 The most common type of haemorrhagic complication was GI bleeding. **Level 1++**

9 **Subgroup analysis**

10 Post hoc analysis found no significant difference among the 5,197 diabetic patients included
11 in the MATCH trial in terms of the incidence of primary endpoint. **Level 1++**

12.125 **Health economic evidence statements**

13 In the treatment of non-ST segment elevation ACS in high-risk patients the cost-
14 effectiveness of clopidogrel used in combination with aspirin compared to aspirin alone
15 £4,939 per QALY.³³²

16 A US study compared clopidogrel to aspirin in diabetic patients hospitalised within 24 hours
17 of onset of symptoms indicative of ACS, the cost-effectiveness was \$8,457–9,857 per life-
18 year gained.³³³ (In this analysis a cost-effectiveness ratio less than \$50,000 was considered
19 cost-effective.)

12.206 **From evidence to recommendations**

21 Little extra evidence of note on use of aspirin was available since the last review. However,
22 there is now better understanding of the extent of the CV risk faced by people with Type 2
23 diabetes. The rather poor direct evidence for people with Type 2 diabetes led to difficulties in
24 assessing the level of risk above which aspirin therapy should be advised. The GDG accepts
25 that its view that all people at, or over, the age of 50 years should be treated is somewhat
26 arbitrary. Primary prevention below that age would be by assessment of higher CV risk
27 (family history of premature vascular disease, abnormal lipid profile, marked abdominal
28 adiposity). While the group were aware of some discussions over the dose of aspirin to be
29 used in people with diabetes, they were not presented with any evidence that could lead to a
30 variation from the usual national recommendations of 75 mg.

31 NICE guidance for dipyridamole MR related only to people with cerebrovascular events.

1 The evidence for the use of clopidogrel was noted to relate to acute and non-acute
2 situations. The current guideline review was not concerned with acute vascular events or
3 interventions. The CHARISMA and MATCH trials suggested that the combination of aspirin
4 and clopidogrel carried a significant side-effect risk of a serious nature not balanced by
5 secure health gain, and therefore could not be generally recommended. NICE guidance for
6 secondary prevention of vascular events in people without diabetes was that clopidogrel
7 should not be used instead of aspirin except where intolerance or hypersensitivity to the
8 latter was present. The specific evidence for people with diabetes, mostly sub-analyses, did
9 not suggest that advice should be varied for people with Type 2 diabetes.

12.107 Recommendations

- 11 **18. Offer low-dose aspirin, 75 mg daily, to a person who is 50 years old or over if**
12 **blood pressure is below 145/90 mmHg.**
- 13 **19. Offer low-dose aspirin, 75 mg daily, to a person who is under 50 years old and has**
14 **significant other cardiovascular risk factors (features of the metabolic syndrome,**
15 **strong early family history of cardiovascular disease, smoking, hypertension,**
16 **extant cardiovascular disease, microalbuminuria).**
- 17 **20. Clopidogrel should be used instead of aspirin only in those with clear aspirin**
18 **intolerance (except in the context of acute cardiovascular events and procedures).**
19 **Follow the recommendations in the NICE TA ‘Clopidogrel and modified-release**
20 **dipyridamole in the prevention of occlusive vascular events’.³²¹**

21

13 Kidney damage

13.1 Diabetes kidney disease management

13.1.1 Clinical introduction

4 Kidney disease in people with Type 2 diabetes is becoming an ever larger health burden.³³⁶
 5 This reflects a number of trends including the increasing prevalence of people with diabetes,
 6 the better cardiovascular (CV) survival with modern management, and the better
 7 management of progression of kidney damage itself. The trend to younger onset of Type 2
 8 diabetes is also likely to see more kidney damage as these people are at lower CV risk, while
 9 in the elderly the condition is ever more complicated by comorbidities disease.

10 Primary prevention of kidney damage from diabetes centres around the prevention of
 11 microvascular (classical diabetic nephropathy) and arterial (and thus renovascular) damage
 12 discussed in other chapters of this guideline – the current section is concerned with detection
 13 and secondary prevention of kidney damage. For reasons of coherence some
 14 recommendations overlap with, or are reproduced from, other sections of the guideline.

15 The clinical questions addressed here include how often and by what means to detect and
 16 confirm the possibility of diabetic renal disease, and the means of monitoring its progression.
 17 In those with detected renal disease issues arise as to the means to reduce or stop such
 18 progression, and the point at which to engage specialist renal management.

13.1.2 Methodological introduction

20 Both methodologically and clinically this question attempts to cover a broad research area
 21 which encompasses different key issues relevant to the diagnosis and management of renal
 22 disease (e.g. monitoring of renal function (GFR, measurement of serum creatinine, renal
 23 ultrasound) and qualitative and quantitative measurements for albuminuria (screening tests).

24 A total of nine studies were identified as relevant to the question.^{337–345}

25 Given the diversity of studies the evidence has been divided into the following categories:

- 26 • studies comparing the accuracy of different equations used to estimated GFR
- 27 • studies looking at qualitative methods to detect microalbuminuria
- 28 • studies comparing several quantitative methods to assess renal disease such as renal
 29 ultrasound, serum creatinine, estimated glomerular filtration rate (eGFR) and tests for
 30 albuminuria (i.e. UAER, urinary albumin concentration (UAC), albumin:creatinine ratio
 31 (ACR).

13.1.2.1 Equations estimating GFR in Type 2 diabetes population

33 General background

- 34 • Although GFR can be measured directly using inulin, the classic method for measuring
 35 inulin clearance requires an intravenous infusion and timed urine collections over a period
 36 of several hours. Therefore, GFR is costly and cumbersome. Several other alternative
 37 measures have been devised; however, predictive equations have proven simpler.
- 38 • In adults the equations used are the Modification of Diet in Renal Disease (MDRD) study
 39 and the Cockcroft-Gault (CG) equations.
- 40 • Both the CG and the MDRD equations were developed in predominantly non-diabetic
 41 individuals.

- 1 • The CG equation has the advantage of being more widely known, easier to remember and
2 more extensively validated than the MDRD formula. However, the MDRD formula does
3 not require knowledge of the patient's weight (making it far more suitable for automated
4 laboratory reporting), and does not need correction for body surface (and therefore does
5 not require knowledge of the patient's height).
- 6 • The MDRD study equation has not been validated in children (aged under 18 years),
7 pregnant women, the elderly (aged over 70), racial or ethnic subgroups other than
8 Caucasians and African-Americans, in individuals with normal kidney function who are at
9 increased risk for CKD or in normal individuals.

10 **Studies included**

11 No RCTs were identified comparing the performance of different equations estimating GFR
12 in a Type 2 diabetes population.

13 Two cross-sectional studies^{344,345} were identified as looking at the performance of the
14 estimating equations in patients with diabetes and CKD.

15 One study³⁴⁴ compared the abbreviated MDRD equation with the CG in 249 CKD patients
16 with diabetes. The study used data from the renal function laboratory at the Cleveland Clinic
17 Foundation which performed approximately 9,000 measurements of GFR by 125 I-
18 iothalamate renal clearance from 1982 to 2002 and maintained a database with demographic
19 and laboratory variables.

20 The other study³⁴⁵ compared the performance of three equations (CG, MDRD and a
21 simplified CG).^y Data for the study was taken from 200 adult diabetic patients with CKD
22 attending a hospital in Pessac, France. GFR was evaluated by clearance of the radionuclide
23 marker was measured after intravenous injection of 51Cr-EDTA.

24 Studies in which serum creatinine assays were not adjusted (calibrated) to mimic that of the
25 MDRD study laboratory were excluded^z (it should be noted that the same exclusion criteria
26 has been adopted by the NICE CKD guideline – due to be published in September 2008). In
27 addition, studies were excluded if gold standards test were not used as the reference test or
28 if they had a small sample size (N<100).

13.1.22 **Qualitative methods to assess microalbuminuria**

30 **General background**

31 To be useful as screening tests, qualitative (or semiquantitative) tests must have high
32 detection rates for microalbuminuria (not only increased albumin concentrations in urine).
33 According to the US Laboratory Medicine Practice Guidelines the sensitivity of a clinically
34 useful qualitative test should be higher than 95%.

35 Dipstick tests are subject to false positives because of patient dehydration, hematuria,
36 exercise, infection, and extremely alkaline urine. Conversely, dipstick tests also are subject
37 to false negatives as a result of excessive hydration and urine proteins other than 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.

1 Studies included

2 No RCTs were identified addressing this issue.

3 Three cross-sectional studies^{339,340,343} were found evaluating the performance of a qualitative
4 method (Micral-Test II) with other methods to assess microalbuminuria in Type 2 diabetes
5 populations.

6 One study³³⁹ compared the Micral-Test II with nephelometry in 166 patients with Type 2
7 diabetes and essential hypertension.

8 Another study³⁴⁰ assesses the accuracy of the Micral-Test II, UAC, and ACR in a random
9 urine specimen in 278 diabetic patients.

10 One study³⁴³ compared the Micral-Test II with UAC by immunoturbidimetric.

11 Studies with a small sample (N<100) were excluded.

13.1.23 Studies comparing several quantitative methods to assess renal disease**13 General background**

- 14 • The most commonly used measure of overall kidney function in clinical practice is serum
15 creatinine concentration. Unfortunately, this measurement is affected by many factors
16 other than the level of kidney function and varies markedly with age, gender and muscle
17 mass. Moreover, as it was stated above, there is significant calibration issues associated
18 with the measurement of serum creatinine that lead to inter-laboratory variation.
- 19 • Consequently, many guidelines, including the Kidney Disease Outcomes Quality Initiative
20 (K/DOQI), British Renal Association and Kidney Disease Improving Global Outcomes
21 (KDIGO) guidelines have recommended that serum creatinine concentration alone should
22 not be used to assess the level of kidney function.
- 23 • UAC and ACR are alternative ways of estimating loss of glomerular permselectivity when
24 using single urine samples instead of timed urine collections (i.e. UAER in a 24-hour
25 sample). The amount of albumin lost in the urine will primarily depend on the degree of
26 damage to the glomerular membrane, whereas UAC, in addition, will depend on the extent
27 to which the urine has been concentrated in the tubular system.
- 28 • By dividing UAC by urinary creatinine concentrations (i.e. ACR), an attempt is made to
29 correct for inter- and intraindividual differences in daily urine volume.

30 Studies included

31 No RCTs were identified addressing this issue.

32 Four cross-sectional studies^{337,338,341,342} were found comparing different quantitative methods
33 to assess renal disease.

34 One study³³⁷ analysed the status of eGFR (by diethylene triamine pentaacetic acid (DTPA)
35 renal scan) vis-à-vis other non-invasive modes of assessment of renal involvement (UAER,
36 serum creatinine and ultrasound) in 100 diabetic patients.

37 One study³³⁸ determined the diagnostic performance of albuminuria (ACR) and a serum
38 creatinine >120 µmol to detect an eGFR <60 ml/min/1.73m² in a population of 4,303
39 diabetics.

40 Similarly, one study³⁴² examined the ability of ACR to detect clinically meaningful CKD (GFR
41 <60 ml/min 1.73 m²) compared with estimated GFR (by using the MDRD equation) in a
42 population of 7,596 diabetics.

1 Another study³⁴¹ analysed the association between GFR (by DTPA renal scan) and UAER
 2 (timed urine collection) in 301 Type 2 diabetes patients. In particular, the study determined
 3 the prevalence and characteristics of patients with impaired renal function (GFR <60 ml/min
 4 1.73 m²) and an AER within the normoalbuminuric range.

13.153 Health economic methodological introduction

6 No health economic papers were identified.

13.174 Evidence statements

13.1.481 Equations estimating GFR in Type 2 diabetes population

9 Bias

10 One study³⁴⁴ reported that in the whole CKD group (diabetics and non-diabetics N=828), the
 11 MDRD equation was superior to the CG equation in terms of bias. The MDRD equation
 12 slightly underestimated the measured eGFR while the CG equation significantly
 13 overestimated the eGFR (−0.5 vs 3.5 ml/min per 1.73 m² p<0.001). **Level 2+**

14 The study³⁴⁴ showed that the MDRD equation was also significantly less biased than the CG
 15 in the diabetic subgroup (N=249) and in people with a measured GFR <30 ml/min per
 16 1.73m² (N=546) p<0.001 in each group. **Level 2+**

17 The study³⁴⁴ concluded that the MDRD and CG equations were significantly more biased in
 18 people with GFR >60 ml/min per 1.73 m² (N=117). The MDRD equation underestimated the
 19 measured eGFR, while the CG equation significantly overestimated the GFR (−3.5 vs 7.9
 20 ml/min per 1.73 m², p<0.001). The equations were also biased, but to a lesser extent in
 21 patients with GFR 30–60 ml/min per 1.73 m². Level 2+

22 One study³⁴⁵ revealed a bias for the MDRD and MCG – the differences between the
 23 predicted and the measured GFR were correlated with their means (MDRD: r=0.054,
 24 p<0.0001; MCG: r=0.27, p<0.001). There was no such bias for CG.

25 Test correlation

26 In terms of test correlation, the study³⁴⁴ demonstrated that in the CKD population, both the
 27 MDRD (r=0.90) and CG equations (r=0.89) correlated highly with measured¹²⁵ I-iothalamate
 28 GFR. **Level 2+**

29 One study³⁴⁵ showed that over the whole population the mean isotopic GFR was 56.5±34.9
 30 ml/min/1.73 m², the mean CG 61.2±35.6 (p<0.01 vs isotopic), the mean MCG. 60.0±29.9
 31 (p<0.05 vs isotopic) and the mean MDRD, 51.0±24.3 (p<0.001 vs isotopic). The MCG was
 32 better correlated with isotopic GFR than was the CG (CG: r=0.75, MCG: r=0.83; p<0.05 vs
 33 CG, MDRD: r=0.82; p=0.068 vs CG). **Level 2+**

34 Accuracy

35 In relation to accuracy, the study³⁴⁴ showed that in the diabetic group, the MDRD equation
 36 was significantly more accurate (63%) than the CG equation (53%) p<0.05. **Level 2+**

37 One study³⁴⁵ stated that the receiver operating characteristic (ROC) curves showed that the
 38 MDRD and the MCG had a better maximal accuracy for the diagnosis of moderate (N=119;
 39 area under curve (AUC): 0.866 for CG, 0.920 for MDRD, 0.921 for MCG; both 0.891 vs CG)
 40 and severe (N=52; AUC: 0.891 for CG, 0.930 for MDRD, 0.942 for MCG; both p<0.05 vs CG)
 41 renal failure. **Level 2+**

1 The same study³⁴⁵ concluded that as the MCG was more accurate for high GFR, and the
2 MDRD was more accurate for low GFR, the MCG could be used at low serum creatine
3 values and the MDRD at high values.

13.1.42 Studies looking at qualitative methods to assess microalbuminuria

5 One study³³⁹ comparing the Micral-Test II with nephelometry demonstrated that the dipstick
6 had a sensitivity of 83% and a specificity of 96%. The correlation between nephelometry and
7 Micral Test II results was 0.81 ($p < 0.0001$). **Level 2+**

8 The same study³³⁹ showed that when the ROC curve for the Micral-Test II as a diagnostic
9 test for microalbuminuria was analysed, the calculated mean area under the ROC curve
10 (\pm SEM) was 0.91 ± 0.03 (CI 95% 0.85–0.96) and the corresponding best cut-off value was
11 30.5 mg/l. **Level 2+**

12 One study³⁴³ comparing the Micral-Test II with UAER (in a 24-hour timed urine collection)
13 reported a sensitivity 88% and a specificity 80%.

14 When performance was assessed by different concentrations readings the study found that
15 Micral-Test II strips performed reasonably well at 0.50 and 100 mg/l with a high percentage
16 of true negatives (93%, 0 mg/l), true positives (81%, 50 mg/l and 91%, 100 mg/l), low
17 percentages of false negatives (7%, 0 mg/l) and false positives (19%, 50 mg/l and 9%, 100
18 mg/l). However, at 20 mg/l Micral strips did not perform well (51% false positive). **Level 2+**

19 One study³⁴⁰ assessing the accuracy of the Micral-Test II, the UAC and the ACR in a random
20 urine specimen found the following test correlations:

- 21 • UAER vs UAC: 0.76 $p < 0.0001$
- 22 • UAER vs ACR: 0.74 $p < 0.0001$
- 23 • ACR vs UAC: 0.86 $p < 0.0001$

24 The study³⁴⁰ also reported that age and 24-hour creatinuria presented a negative correlation
25 (278 patients, $r = -0.19$, $p = 0.002$). No correlation was observed between age and UAER
26 ($r = 0.02$, $p = 0.74$), age and UAC ($r = 0.07$, $p = 0.22$) and age and UACR ($r = 0.11$, $p = 0.08$). **Level**
27 **2+**

28 The same study³⁴⁰ showed that the specificity of UAC and UACR was similar when
29 considering the 100% sensitivity cut-off points. The sensitivity and specificity of the Micral-
30 Test II strip for a 20 mg/l cut-off point (as indicated by manufacturer) on fresh urine samples
31 based on ROC curve analysis (N=130) were 90 and 46% respectively. **Level 2+**

32 In terms of accuracy, the study³⁴⁰ stated that the comparison among the areas under the
33 ROC curves for UAC, UACR and the Micral-Test II took into account the individual results,
34 for each single patient (N=130), of the three screening methods being tested and of the
35 reference test method (UAER). The study concluded that a similar area was observed under
36 the UAC (0.934 ± 0.032) and UACR (0.920 ± 0.035) curves ($p = 0.626$).

37 The area under the curve was smaller for the Micral-Test II (0.846 ± 0.047) than for UAC
38 ($p = 0.014$). **Level 2+**

13.1.43 Studies comparing several quantitative methods to assess renal disease

40 Ultrasound – serum creatinine – albuminuria – GFR

41 One study³³⁷ analysed the status of GFR (by DTPA renal scan) vis-à-vis other non-invasive
42 modes of assessment of renal involvement (UAER, serum creatinine and ultrasound) in 100
43 Type 2 diabetes patients. Patients were divided into three subgroups depending on the

1 duration of initial detection of Type 2 diabetes. Group A constituted patients with less than 5
2 years duration, group B 5–15 years and group C more than 15 years duration.

3 **Ultrasound**

4 The study³³⁷ reported that most of the patients in group A and B had a large kidney with
5 preserved corticomedullary (CM) differentiation (83.9% and 80%); only group C had a
6 significantly higher prevalence of large kidney with loss of CM differentiation (75.9%). **Level**
7 **2+**

8 **Serum creatinine**

9 The study³³⁷ concluded that there was no difference between group A and B as far as the
10 serum creatinine was concerned. High level of serum creatinine was only significantly
11 associated with group C (44.8%). **Level 2+**

12 **Albuminuria**

13 The study³³⁷ found that normoalbuminuria and microalbuminuria were significantly higher in
14 group A (25.8% and 74.2%). Macroalbuminuria was higher in both group B and C (80% and
15 69%).

16 For UAER group A had a significantly lower level compared to both B and C ($p < 0.01$),
17 however, there was no significant difference between group B and C with respect to the
18 amount of both micro- and macroalbuminuria. **Level 2+**

19 **Glomerular filtration rate**

20 The study³³⁷ showed that group A presented a significantly higher prevalence of normal and
21 raised GFR (25.8% and 61.3%). Group B had a significantly higher prevalence of low GFR,
22 while prevalence of very low GFR was highest in group C (37.9%).

23 The GFR had a progressively significant decrement from group A through group B to C
24 ($p < 0.01$). **Level 2+**

25 The study³³⁷ concluded that GFR estimation was the only renal parameter which could singly
26 provide a picture of the actual renal status of Type 2 diabetes patients at any duration
27 irrespective of the status of albuminuria, azotaemia or renal size and morphology as their
28 variability or progression is non-linear.

13.1.294 **Diagnostic performance of ACR >120 μmol to detect an eGFR <60 ml/min/1.73 m²** 30 **(MDRD)**

31 After ranking 4,303 diabetics based on their eGFR (>90, 90–60, 60–30 and <30 ml/min per
32 1.73 m²) one study³³⁸ showed that the proportion of individuals with abnormal serum
33 creatinine rose with progressive fall in eGFR (0%, 1%, 37% and 100% with creatinine >120
34 $\mu\text{mol/l}$ in eGFR >90, 90–60, 60–30 and <30 ml/min per 1.73 m² respectively), as did the
35 proportion with abnormal albuminuria (33%, 27%, 42% and 77% with ACR >3.5 mg/mmol).
36 **Level 2+**

37 The study³³⁸ found that of the 1,296 individuals with an eGFR <60, 539 (42%) had abnormal
38 serum creatinine, 579 (45%) had abnormal albuminuria and 798 (62%) had either abnormal
39 serum creatinine or urine ACR. Thus, a creatinine and ACR based strategy would have
40 missed the renal risk of 498 (38%) individuals since they had normal values of both despite
41 having a significantly impaired eGFR <60 ml/min per 1.73 m². **Level 2+**

42 The same study³³⁸ also demonstrated that the proportion missed by current markers was
43 more marked in women (N=757) where the prevalence of those with abnormal serum

1 creatinine, urine ACR and either were 20%, 38% and 47% respectively, compared with 72%,
2 54% and 83% observed in men (N=539). **Level 2+**

3 When the study analysed the data by ethnic origin, it was found that white people appeared
4 to benefit the most from eGFR, with a greater prevalence of normocreatinaemic and
5 normoalbuminuric renal insufficiency, whereas the majority of the African-Caribbean group
6 with low eGFR had either an abnormal creatinine or ACR 39%, 42% and 59% respectively,
7 with abnormal creatinine, ACR and either in white people (N=997); 62%, 69% and 80%
8 respectively, in African-Caribbeans (N=84); and 44%, 54% and 69% respectively in Indo-
9 Asians (N=210). **Level 2+**

10 The study did not find difference in performance when data was analysed by the type of
11 diabetes. **Level 2+**

12 The study³³⁸ concluded that GFR estimates may have a place in routine diabetes clinical
13 care, being a more sensitive marker of risk than serum creatinine or albuminuria. eGFR also
14 appears to eliminate the gender and ethnic bias observed with current markers and also
15 provides an opportunity to monitor longitudinal changes.

16 Another study³⁴² using data from 7,596 diabetics found that 27.5% (N=1,715) of the
17 population had an eGFR <60 ml/min/1.73 m²; of these 19.4% had normoalbuminuria; 20.4%
18 had albuminuria, the remainder not having had albuminuria determined.^{aa} The study also
19 reported that serum creatinine was normal (£120 mmol/l) in 54.7% of those with eGFR <60
20 ml/min/1.73 m² and £150 mmol/l in 82.2%. **Level 2+**

21 This study³⁴² found that the sensitivity of abnormal serum creatinine levels in identifying
22 eGFR <60 ml/min/1.73 m² is 45.3%, albuminuria is 51.2% and either an abnormal serum
23 creatinine or albuminuria is 82.4%. **Level 2+**

24 The same study also reported that unidentified CKD, defined as the presence of a GFR <60
25 ml/min/1.73 m² but without any evidence of an abnormal creatinine (i.e. serum creatinine
26 £120 mmol/l) was significantly greater in females compared with males adjusting for age,
27 type of diabetes and secondary care setting (OR 8.22, CI 6.56 to 10.29). Using albuminuria
28 as a screening test also failed to identify CKD in females (OR 2.22, CI 1.63 to 3.03). The
29 presence of abnormal serum creatinine and albuminuria to identify CKD continued to display
30 a significant bias against females (OR 7.58, CI 5.44 to 10.57). **Level 2+**

31 The study³⁴² concluded that current screening techniques based upon albuminuria and/or
32 abnormal serum creatinine would fail to detect a significant number of participants with an
33 eGFR <60 ml/min/1.73 m². Therefore, without eGFR reporting the clinician may not be
34 alerted to the presence of CKD and be falsely reassured that renal function is normal.

13.1.45 Association between GFR (by DTPA renal scan) and UAER (timed urine collection)

36 One study³⁴¹ divided 301 Type 2 diabetes patients on the basis of their GFR (i.e., < or ≥60
37 ml/min 1.73 m²) and albuminuria status (i.e., normo <20 µg/min, micro 20–200 µg/min,
38 macro >200 µg/min). The study found a significant correlation between a decreasing GFR
39 with increasing levels of AER (r=-0.29, p<0.0001). **Level 2+**

40 Glomerular filtration rate status

41 The study³⁴¹ reported that for the 109 patients with a GFR <60 l/min 1.73 m² the prevalence
42 of normo-, micro- and macroalbuminuria was 39%, 35% and 26% respectively. For the 192
43 patients with a GFR ≥60 ml/min 1.73 m² the prevalence of normo-, micro- and
44 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

1 UAER status

2 When the study³⁴¹ stratified the 301 patients according to their AER status regardless of their
3 GFR, 52% had normo-, 34% had micro-, and 14% had macroalbuminuria. For the 158
4 normoalbuminuric patients, 27% had a corresponding GFR <60 ml/min 1.73 m² and 73% had
5 a GFR ≥60 ml/min 1.73 m². **Level 2+**

6 The study also demonstrated that normoalbuminuric patients were significantly older
7 (p<0.01) and more commonly female (p<0.01) in comparison to those with
8 macroalbuminuria. There were no differences in the duration of diabetes, BMI, prevalence of
9 retinopathy, history of CVD, smoking history, HbA1c levels, systolic blood pressure, diastolic
10 blood pressure (DBP), total cholesterol, low-density lipoprotein, high-density lipoprotein and
11 triglyceride levels among patients with a GFR <60 ml/min 1.73 m² associated with normo-,
12 micro-, or macroalbuminuria.

13 Overall, the study did not find significant differences in the use of any antihypertensive agent
14 (specifically renin-angiotensin system inhibitors (RAS-inhibitors)) for patients with a GFR <60
15 ml/min 1.73 m² and normo-, micro- or macroalbuminuria. **Level 2+**

16 The study³⁴¹ calculated the prevalence of a GFR <60 ml/min 1.73 m² and normoalbuminuria
17 after excluding 23 of 43 patients whose normoalbuminuric status was possibly altered by the
18 use of RAS inhibitors. After this adjustment the prevalence of a <60 ml/min 1.73 m² and
19 normoalbuminuria was 20 of 86 (23%). **Level 2+**

13.26 From evidence to recommendations

21 The GDG noted the importance to health in delaying or preventing the progression of
22 diabetes renal damage, and the certainty of evidence that this could be done. Detection of
23 early diabetes kidney damage at a stage when therapy could be usefully intensified was now
24 nearly universally through urinary ACR – review of the evidence showed no reason to doubt
25 this was appropriate. This measure is also a CV risk factor, and accordingly features
26 elsewhere in **chapter 13**.

27 Some discussion of the logistics of collection of first-pass morning urine samples revealed
28 there was no single right answer to establishing a sound process for ensuring samples were
29 obtained annually. No changes in the process for confirming presence of microalbuminuria
30 were felt necessary.

31 It was noted that laboratory estimation of serum creatinine was now reported with an eGFR
32 result using the method abbreviated MDRD (4-variable) equation. The group recognised
33 some problems with these calculations (worse overall in people with diabetes than in the
34 general population) but could see no better alternative.

35 The management of diabetic nephropathy when confirmed was felt not to have changed from
36 that of the previous NICE guideline and that for Type 1 diabetes, centring around renin-
37 angiotensin system blockade, tight blood pressure control, and specialist referral. Non-
38 diabetic renal disease will also occur in people with diabetes and needs not to be confused
39 with diabetic nephropathy. The group noted that there were a series of markers which
40 suggested when renal disease in people with diabetes was not diabetic nephropathy.

41 The group noted that there is a NICE CKD clinical guideline which also considers people with
42 diabetes. This guideline is due to be published in September 2008.

13.46 Recommendations

44 **R93 Ask all people with or without detected nephropathy to bring in a first-pass**
45 **morning urine specimen once a year. In the absence of proteinuria/urinary tract**

- 1 infection (UTI), send this for laboratory estimation of albumin:creatinine ratio.
2 Request a specimen on a subsequent visit if UTI prevents analysis.
- 3 **R94** Make the measurement on a spot sample if a first-pass sample is not provided
4 (and repeat on a first-pass specimen if abnormal) or make a formal arrangement
5 for a first-pass specimen to be provided.
- 6 **R95** Measure serum creatinine and estimate the glomerular filtration rate (using
7 the method- abbreviated modification of diet in renal disease (MDRD) four-variable
8 equation) annually at the time of albumin:creatinine ratio estimation.
- 9 **R96** Repeat the test if an abnormal albumin:creatinine ratio is obtained (in the
10 absence of proteinuria/UTI) at each of the next two clinic visits but within a
11 maximum of 3–4 months. Take the result to be confirming microalbuminuria if a
12 further specimen (out of two more) is also abnormal (>2.5 mg/mmol for men, >3.5
13 mg/mmol for women).
- 14 **R97** Suspect renal disease, other than diabetic nephropathy and consider further
15 investigation or referral when the albumin:creatinine ratio (ACR) is raised and any
16 of the following apply:
- 17 • there is no significant or progressive retinopathy
 - 18 • blood pressure is particularly high or resistant to treatment
 - 19 • had a documented normal ACR and develops heavy proteinuria (ACR >100
20 mg/mmol)
 - 21 • significant haematuria is present
 - 22 • the glomerular filtration rate has worsened rapidly
 - 23 • the person is systemically ill.
- 24 **R98** Discuss the significance of a finding of abnormal albumin excretion rate, and
25 its trend over time, with the individual concerned.
- 26 **R99** Start ACE inhibitors with the usual precautions and titrate to full dose in all
27 individuals with confirmed raised albumin excretion rate (>2.5 mg/mmol for men,
28 >3.5 mg/mmol for women).
- 29 **R100** Have an informed discussion before starting an ACE inhibitor in a woman for
30 whom there is a possibility of pregnancy, assessing the relative risks and benefits
31 of the use of the ACE inhibitor.
- 32 **R101** Substitute an angiotensin II-receptor antagonist for an ACE inhibitor for a
33 person with an abnormal albumin:creatinine ratio if an ACE inhibitor is poorly
34 tolerated.
- 35 **R102** For a person with an abnormal albumin:creatinine ratio, maintain blood
36 pressure below 130/80 mmHg.
- 37 **R103** Agree referral criteria for specialist renal care between local diabetes
38 specialists and nephrologists.
39

14 Diabetic neuropathic pain management

14.121 Clinical introduction

3 Neuropathic pain is a troublesome symptom of chronic exposure to poor blood glucose
4 control that cannot be managed acutely by restoration of blood glucose control. It can take
5 many forms, and is often distressing and sometimes depressing, particularly if symptoms are
6 predominantly nocturnal and disturb sleep. People with diabetes may be reluctant to report
7 the symptoms to those with expertise in diabetes care, because of lack of awareness that the
8 problem is diabetes related. A number of drug and non-drug approaches to management are
9 available, this diversity reflecting that none of them are fully effective.

10 Clinically the issues are when to start specific drug therapy for neuropathic pain, which
11 medications to use, and in what order to try them.

14.122 Methodological introduction

13 Tricyclics

14 There were nine studies identified in this area. All five studies included were double-blind,
15 crossover studies. One study compared desipramine, amitriptyline and active placebo^{bb}
16 (benzotropine to mimic dry mouth).³⁴⁸ One study compared clomipramine with
17 desipramine.³⁴⁹ One study compared imipramine with mianserin (60 mg/day).³⁵⁰ One study
18 considered amitriptyline with gabapentin,³⁵¹ and the last study compared amitriptyline with
19 lamotrigine.³⁵² Four studies were excluded for methodological reasons.^{353,354,355,356}

20 One study specified the proportion of patients with Type 2 diabetes, 88%,³⁵¹ and a second
21 study was conducted only in patients with Type 2 diabetes.³⁵²

22 The different drug and dose comparisons prevented a direct comparison between the
23 studies.

24 Duloxetine

25 There were six RCTs and one meta-analysis identified in this area.^{357–363} The meta-analysis
26 was excluded for methodological reasons.³⁶⁰

27 Two double-blind studies compared patients on duloxetine 60 mg/day and duloxetine 60 mg
28 twice daily with placebo,^{358,362} and a further study compared patients on duloxetine 20
29 mg/day, 60 mg/day or 60 mg twice daily with placebo³⁵⁹ all over a 12-week study duration.
30 There were two open-label long-term efficacy studies of 52-weeks duration comparing
31 duloxetine 60 mg twice daily with routine care,^{357,363} although in one of these studies the dose
32 of duloxetine could be reduced to 60 mg/day in cases of poor tolerability. Additional
33 medications were allowed in both studies; including gabapentin, amitriptyline, venlafaxine
34 extended release and acetaminophene,³⁵⁷ and paracetamol, non-steroidal anti-inflammatory
35 drugs (NSAIDs) or opioids.³⁶³ The final study compared duloxetine 60 mg twice daily with
36 duloxetine 120 mg once daily in an open-label study over 28 weeks.³⁶¹

37 The majority of study participants had Type 2 diabetes; between approximately 88–94% in all
38 studies.^{357–359,361–363}

bb Based on the results of two studies amitriptyline compared with desipramine and fluoxetine compared with placebo (N=52).

1 **Gabapentin**

2 There were five studies identified in this area, four of these were RCTs and one was an
3 open-label study.³⁶⁴

4 One study³⁶⁵ was excluded for methodological reasons.

5 Two studies compare gabapentin with placebo,^{366,367} (the study by Simpson DA³⁶⁷ reported
6 on a three-phase study. Phases two and three included gabapentin compared with
7 venlafaxine and therefore only phase one, gabapentin compared with placebo, has been
8 included here). One study considered gabapentin and amitriptyline in a crossover study.³⁵¹

9 The open-label study considered a fixed dose of gabapentin compared with a titrating dose
10 which was titrated until it was perceived to have reached clinical effect – that was a ≥50%
11 reduction in pain.³⁶⁴

12 The majority of study participants had Type 2 diabetes; approximately 75%,³⁶⁶ 89%,³⁶⁴
13 88%,³⁵¹ and 82%.³⁶⁷

14 **Pregabalin**

15 There were three studies identified in this area, all were RCTs comparing varying doses of
16 pregabalin (75 mg/day to 600 mg/day) with placebo for those with both Type 1 and Type 2
17 diabetes, N=729.^{368–370}

18 The majority of the participants in each study were those with Type 2 diabetes; 90.1%,³⁶⁸
19 91%,³⁶⁹ and 87%.³⁷⁰

20 There were no studies which considered pregabalin in comparison with other treatments for
21 painful diabetic neuropathy. The included studies were all of short duration (6–9 weeks) and
22 there were no studies which considered longer-term effectiveness.

23 **Carbamazepine**

24 There were a limited number of studies identified in this area. It should be noted that studies
25 looking at oxcarbazepine, a new form of carbamazepine which has the same indications but
26 seems to be better tolerated, were also included. All the studies were conducted in diabetic
27 patients.

28 In relation to carbamazepine, we found three small RCTs with a crossover design. Two of
29 them compared carbamazepine against placebo.^{cc371,372} The third RCT³⁷³ compared
30 carbamazepine monotherapy with the combination of nortriptyline-fluphenazine.

31 There were some methodological quality issues with the two placebo-controlled studies^{371,372}
32 which often involved a short follow-up and the absence of a washout period.

33 Three RCTs were identified comparing oxcarbazepine with placebo using a parallel
34 design.^{374–376} One of these studies was excluded due to a high dropout rate.³⁷⁶

14.13 **Health economic methodological introduction**

36 Three papers were identified from the literature search. One paper was excluded because it
37 was a review and did not include economic evidence. The other two papers were excluded
38 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.

14.1.14 Evidence statements

14.1.421 Tricyclics

3 Outcomes

4 Pain related outcomes were measured using either a six-item neuropathy scale,^{349,350} or a
5 pain diary.³⁴⁸

6 Mean pain score

7 Overall, the results indicate that all of the drugs, with the exception of mianserin,³⁵⁰ produced
8 reduction in pain scores compared to placebo. However, there are no statistically significant
9 differences between the individuals.^{348,349,351} **Level 1+**

10 There was a significant reduction on the observer and the self-rating neuropathy scale in
11 favour of clomipramine ($p < 0.05$) and desipramine ($p < 0.05$ and $p < 0.01$) both compared to
12 placebo ($p < 0.05$). There were no statistically significant differences between the two
13 treatments. The median reduction as compared with placebo was on clomipramine 39%
14 (95% CI 27 to 79%) and desipramine 32% (0 to 46%).³⁴⁹ **Level 1+**

15 Desipramine and amitriptyline resulted in an equivalent reduction in mean pain scores and
16 pain intensity. Both treatments were superior to placebo on mean pain score (mean change
17 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,
18 $p < 0.05$, one-tailed Dunnett's test).³⁴⁸ **Level 1+**

19 There was a significant difference in favour of imipramine compared to placebo ($p = 0.03$) and
20 compared to mianserin ($p = 0.033$) on the observer-rated score but not the self-rated score.
21 There was no significant difference between mianserin and placebo.³⁵⁰ **Level 1+**

22 Although both gabapentin and amitriptyline showed significant reductions in pain intensity
23 scores there was no significant difference between the drugs, this was also found for global
24 pain score.³⁵¹ **Level 1+**

25 Both amitriptyline and lamotrigine resulted in improvements in pain relief on several pain
26 measures, although there was no significant difference between the treatments.³⁵² **Level 1+**

27 Adverse events and dropout rates

28 The total side-effect score was significantly higher for clomipramine (median 4.0) and
29 desipramine (median 4.5) than during placebo (median 0.02, $p < 0.05$ for both). There were
30 no statistically significant differences between clomipramine and desipramine. The most
31 common side effects were dry mouth, sweating, orthostatic dizziness and fatigue. Six
32 patients withdrew from the study all due to side effects (three each during clomipramine
33 and desipramine).³⁴⁹ **Level 1+**

34 The proportion of patients who experienced any side effects associated with amitriptyline,
35 desipramine or placebo treatments was 81%, 76% and 68% respectively. Seven patients
36 withdrew whilst on amitriptyline and seven whilst on desipramine, all due to drug-associated
37 side effects.³⁴⁸ **Level 1+**

38 The total adverse effect scores were significantly higher during mianserin (median 2.03,
39 $p = 0.0093$) and imipramine (median 4.00, $p = 0.0001$) than during placebo (median, 0.98) but
40 there were no significant differences between the two active treatments. The most common
41 side effects were dry mouth, orthostatic dizziness and fatigue. One patient withdrew due to
42 side effects whilst taking imipramine.³⁵⁰ **Level 1+**

dd The data has been extracted from a graphical representation of the results.

1 With the exception of weight gain with amitriptyline ($p < 0.03$) there was no significant
 2 difference in occurrence of adverse events (AEs) between amitriptyline and gabapentin.
 3 Adverse effects included sedation, dry mouth, dizziness, postural hypotension, weight gain,
 4 ataxia and lethargy. Two patients (one from each group) crossed over early due to AEs and
 5 completed the study.³⁵¹ **Level 1+**

6 Amitriptyline resulted in significantly more AEs overall than lamotrigine ($p < 0.001$), the major
 7 side effect being an increase in sleep. More patients discontinued treatment while on
 8 amitriptyline (19/46) than while on lamotrigine (8/46).³⁵² **Level 1+**

14.1.42 Duloxetine

10 Pain

11 Pain-related outcomes were measured throughout the papers using recognised and
 12 validated tools.

13 Overall, duloxetine 60 and 120 mg/day (delivered as 60 mg twice daily) were associated with
 14 significant reductions in measures of pain (24-hour average pain, brief pain inventory (BPI)
 15 and Short-form McGill Pain Questionnaire (SF-MPQ)) when compared with placebo.^{358,359,362}
 16 Two studies found greater improvements in all pain measures in the duloxetine 120 mg/day
 17 arm,^{359,362} while the other study found greater improvements in the duloxetine 120 mg daily
 18 arm in selected pain measures (BPI interference scores and SF-MPQ).³⁵⁸ **Level 1++ and**
 19 **level 1+**

20 One study found a significantly lower dose of concomitant analgesics (acetaminophen) used
 21 in the duloxetine 120 mg daily arm than either the duloxetine 60 mg daily arm ($p < 0.05$) or the
 22 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)^a

Measure ^a	Goldstein (2005) ¹⁴¹	Raskin (2005) ¹⁶¹	Wernicke (2006) ¹⁷¹
24-hour average pain ^a	Duloxetine 60-mg vs placebo ^a -1.17 (0.22) vs -1.84 (0.22) p<0.001 ^a Duloxetine 120-mg vs placebo ^a -1.45 (0.22) vs -2.13 (0.22) p<0.001 ^a	Duloxetine 60-mg vs placebo ^a -2.50 (0.18) vs -1.60 (0.18) p<0.001 ^a Duloxetine 120-mg vs placebo ^a -2.45 (0.18) vs -1.60 (0.18) p<0.001 ^a	Duloxetine 60-mg vs placebo ^a -2.72 (0.22) vs -1.39 (0.23) p<0.001 ^a Duloxetine 120-mg vs placebo ^a -2.84 (0.23) vs -1.39 (0.23) p<0.001 ^a
BPI ^a	Duloxetine 60-mg vs placebo ^a -2.81 (0.21) vs -2.40 (0.21) p<0.01 ^a Duloxetine 120-mg vs placebo ^a -3.07 (0.22) vs -2.40 (0.21) p<0.001 ^a	Duloxetine 60-mg vs placebo ^a -2.65 (0.19) vs -1.82 (0.19) p<0.01 ^a Duloxetine 120-mg vs placebo ^a -2.62 (0.19) vs -1.82 (0.19) p<0.01 ^a	Duloxetine 60-mg vs placebo ^a -2.66 (0.23) vs -1.48 (0.23) p<0.001 ^a Duloxetine 120-mg vs placebo ^a -3.05 (0.24) vs -1.48 (0.23) p<0.001 ^a
BPI: interference ^a	- ^a	Duloxetine 60-mg vs placebo ^a -2.43 (0.18) vs -1.56 (0.18) p<0.001 ^a Duloxetine 120-mg vs placebo ^a -2.54 (0.18) vs -1.56 (0.18) p<0.001 ^a	Duloxetine 60-mg vs placebo ^a -2.36 (0.19) vs -1.72 (0.19) p<0.05 ^a Duloxetine 120-mg vs placebo ^a -2.79 (0.19) vs -1.72 (0.19) p<0.001 ^a
SF-MPQ ^a	Duloxetine 20-mg vs placebo ^a -8.25 (0.65) vs -5.39 (0.66) p<0.05 ^a Duloxetine 60-mg vs placebo ^a -8.25 (0.65) vs -5.39 (0.66) p<0.001 ^a → Duloxetine 120-mg vs placebo ^a -9.18 (0.64) vs -5.39 (0.66) p<0.001 ^a	Duloxetine 60-mg vs placebo ^a -7.47 (0.61) vs -4.96 (0.60) p<0.01 ^a Duloxetine 120-mg vs placebo ^a -7.82 (0.61) vs -4.96 (0.60) p<0.001 ^a	Duloxetine 60-mg vs placebo ^a -7.23 (0.70) vs -4.18 (0.73) p<0.01 ^a Duloxetine 120-mg vs placebo ^a -7.98 (0.71) vs -4.18 (0.73) p<0.001 ^a
CGI – severity score ^a	Duloxetine 20-mg vs placebo ^a -1.28 (0.11) vs -0.83 (0.12) p<0.05 ^a Duloxetine 60-mg vs placebo ^a -1.42 (0.12) vs -0.83 (0.12) p<0.001 ^a → Duloxetine 120-mg vs placebo ^a -1.70 (0.12) vs -0.83 (0.12) p<0.001 ^a	Duloxetine 60-mg vs placebo ^a -1.42 (0.09) vs -0.3 (0.09) p<0.001 ^a Duloxetine 120-mg vs placebo ^a -1.40 (0.10) vs -0.3 (0.09) p<0.001 ^a	Duloxetine 60-mg vs placebo ^a -1.37 (0.11) vs -0.98 (0.12) p<0.05 ^a Duloxetine 120-mg vs placebo ^a -1.47 (0.12) vs -0.98 (0.12) p<0.01 ^a
PGI – improvement score ^a	Duloxetine 60-mg/d vs placebo ^a 2.21 (0.12) vs 2.91 (0.12) p<0.001 ^a Duloxetine 120-mg/d vs placebo ^a 2.24 (0.12) vs 2.91 (0.12) p<0.01 ^a	Duloxetine 60-mg vs placebo ^a 2.50 (0.10) vs 3.04 (0.10) p<0.001 ^a Duloxetine 120-mg vs placebo ^a 2.54 (0.10) vs 3.04 (0.10) p<0.001 ^a	Duloxetine 60-mg vs placebo ^a 2.61 (1.44) vs 3.17 (1.44) p<0.01 ^a Duloxetine 120-mg vs placebo ^a 2.40 (1.29) vs 3.17 (1.44) p<0.001 ^a
SF-36 ^a	Duloxetine 60-mg vs placebo ^a Bodily pain: 18.00 (1.89) vs 10.32 (1.89) p<0.01 ^a Mental health: 2.99 (1.65) vs -2.63 (1.69) p<0.05 ^a Duloxetine 120-mg/d vs placebo ^a Mental health: 1.84 (0.75) vs -1.09 (0.75) p<0.01 ^a Bodily pain: 18.32 (0.88) vs 10.32 (1.89) p<0.01 ^a General health perceptions: 9.56 (1.62) vs 2.03 (1.61) p<0.001 ^a Mental health: 5.14 (1.62) vs -2.63 (1.69) p<0.001 ^a	- ^a	Duloxetine 60-mg vs placebo ^a Physical functioning: 11.96 (1.81) vs 3.64 (1.90) p<0.01 ^a Vitality: 8.47 (1.73) vs 2.79 (1.78) p<0.05 ^a Physical component score: 6.85 (0.76) vs 3.67 (0.78) p<0.01 ^a Duloxetine 120-mg vs placebo ^a Physical functioning: 11.20 (1.86) vs 3.64 (1.90) p<0.01 ^a Physical component score: 7.46 (0.77) vs 3.67 (0.78) p<0.001 ^a Bodily pain: 20.59 (2.04) vs 12.17 (2.10) p<0.01 ^a General health perceptions: 7.73 (1.39) vs 2.39 (1.42) p<0.01 ^a Mental health: 3.82 (1.49) vs -0.31 (1.52) p<0.05 ^a
EQ-5D ^a	Duloxetine 60-mg and 120-mg vs placebo ^a 0.13 (0.02) vs 0.08 (0.02) p<0.05 ^a	- ^a	Duloxetine 60-mg and 120-mg vs placebo ^a 0.15 (0.02) vs 0.08 (0.02) p<0.05 ^a

CGI, clinical global impression; EQ-5D, EuroQol-5-Dimensional outcomes questionnaire; PGI, patient global impression; SF-36, short-form-36^a

1

2 **CGI, PGI and quality of life**

3 Overall, duloxetine 60 and 120 mg/day were associated with significant improvements on the
4 CGI and PGI compared with placebo-treated patients. **358,359,362 Level 1++ and level 1+**

5 Two studies reported a significant improvement in favour of duloxetine 60 and 120 mg/day
6 compared to placebo on the SF-36 and EQ-5D. **359,362 Level 1++ and level 1+**

1 One long-term efficacy study reported no significant differences between duloxetine and
 2 routine care on the SF-36 or EQ-5D.³⁵⁷ The other study found significant differences between
 3 duloxetine and routine care arms in SF-36 bodily pain ($p=0.021$) and in the EQ-5D
 4 ($p=0.001$).³⁶³ **Level 1+**

5 A 28-week open-label study comparing duloxetine 60 mg twice daily with 120 mg once daily
 6 found that both treatment groups showed improvement from baseline to endpoint on all
 7 subscales of the BPI and clinical global impression of change score (CGIC-S) ($p<0.001$ for
 8 both). (Results taken from graph.)³⁶¹ **Level 1+**

9 **Adverse events**

10 Three studies reported higher treatment-related AEs and discontinuation rate due to AEs, in
 11 duloxetine dose treatment arms compared with placebo or routine care.^{358,359,362} Two studies
 12 reported higher AEs in the routine care or placebo arms, which was significant in one of the
 13 studies,³⁵⁷ although both these studies also reported higher discontinuation due to AEs in the
 14 duloxetine arm.^{357,363} **Level 1++ and level 1+**

15 Three studies reported significant differences in treatment-emergent AEs in duloxetine
 16 groups compared with placebo.^{358,359,362} In these studies the following treatment-emergent
 17 AEs were reported to occur significantly more in one or both duloxetine groups (60 mg daily
 18 or 60 mg twice daily); nausea, somnolence, increased sweating, dizziness, constipation,
 19 fatigue, insomnia, vomiting, dry mouth, anorexia and decreased appetite. Most AEs were
 20 mild or moderate. **Level 1++ and level 1+**

21 In three studies, including the two studies with 52 weeks of follow-up,^{357,363} there were no
 22 treatment related AEs that were reported to occur significantly more in the duloxetine group
 23 than in routine care groups. Most AEs were moderate or mild. **Level 1++ and level 1+**

14.1.43 **Gabapentin**

25 **Outcomes**

26 Pain-related outcomes were measured throughout the papers using recognised and
 27 validated tools.

28 **Mean pain score**

29 Both placebo-based studies found significant decreases in pain score with gabapentin
 30 compared with placebo; -1.2 (-1.9 to -0.6), $p<0.001$ ³⁶⁶ and -2 vs -0.5 , $p<0.01$.³⁶⁷

31 For the titration to clinical effect doses (range from 900–3600 mg/day) gabapentin showed
 32 significantly greater reductions in final mean pain scores than the fixed dose of 900 mg/day,
 33 53.6% vs 43.3%, $p=0.009$.³⁶⁴

34 Although both gabapentin and amitriptyline showed significant reductions in pain intensity
 35 scores there was no significant difference between the drugs, this was also found for global
 36 pain score.³⁵¹ **Level 1+**

37 **Short-form McGill pain questionnaire**

38 There was a significant decrease in total SF-MPQ scores for gabapentin compared with
 39 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),
 40 $p<0.001$ and the present pain intensity score (PPI), -0.6 (-0.9 to -0.3), $p<0.001$.³⁶⁶ This
 41 significant difference between gabapentin and placebo for the total SF-MPQ was also noted
 42 in the other placebo-based study, though further detail was not reported.³⁶⁷

1 The titration to clinical effect group showed a significant decrease in the short-form McGill
2 Pain Questionnaire visual analogue scale (SF-MPQ VAS) compared with fixed dose
3 ($p < 0.001$) but was not significant in the total or PPI scores.³⁶⁴ **Level 1+**

4 **Sleep interference**

5 There was a significant decrease in sleep interference, at endpoint, compared with placebo
6 for gabapentin, -1.47 (-2.2 to -0.8), $p < 0.001$.³⁶⁶ Changes in sleep interference also showed
7 significant improvement in the gabapentin-treated group against placebo, further details were
8 not reported.³⁶⁷

9 The titration to clinical effect study showed significant improvements in sleep interference
10 compared with the fixed dose group (57% vs 37.2%, $p = 0.013$).³⁶⁴ **Level 1+**

11 **Short-form 36**

12 The gabapentin compared with placebo studies showed significant increases (denotes
13 improvement) in SF-36 results for; bodily pain 7.8 (1.8–13.8), $p = 0.01$; mental health 5.4 (0.5–
14 10.3), $p = 0.03$ and vitality 9.7 (3.9–5.5), $p = 0.001$.³⁶⁶ Again, Simpson DA³⁶⁷ stated there had
15 been significant differences without further details.

16 There was no significant differences found in the SF-36 results for the titration to clinical
17 effect compared with fixed-dose study.³⁶⁴ **Level 1+**

18 **PGIC and CGIC**

19 Gabapentin compared with placebo showed significant improvements in pain for both the
20 patient perception score and the clinician perception score ($p = 0.001$).³⁶⁶ Differences were
21 also identified for PGIC and CGIC in the other placebo-based study with 55.5% in the
22 much/moderately improved category for gabapentin compared with 25.9% for placebo.
23 Significance not reported.³⁶⁷

24 The titration to clinical effect group identified a significant improvement in the clinician
25 assessed score CGIC compared with the fixed dose, $p = 0.02$. However, there was no
26 significant difference found between the two groups in the PGIC.³⁶⁴ **Level 1+**

27 **Adverse events and dropout rates**

28 There were a significantly higher number of AEs of dizziness and somnolence experienced
29 by those in the gabapentin group than with placebo.³⁶⁶

30 The titration to clinical effect group showed higher occurrences of somnolence (20.1% vs
31 15.3%) and dizziness (16.6% vs 13.5%) than those in the fixed-dose group.³⁶⁴

32 For gabapentin compared with amitriptyline there was no significant difference in the
33 occurrence of the main AEs, such as sedation, dry mouth and dizziness.

14.1.44 **Pregablin**

35 **Outcomes**

36 Pain-related outcomes were measured throughout the papers using recognised and
37 validated tools.

38 **Mean pain score (recorded via pain diaries)**

39 Pregabalin was significantly effective in reducing the mean pain score at the 300 mg/day and
40 600 mg/day doses compared with placebo, this effect was seen from the end of the first

1 week of treatment and throughout the studies, this was identified in all three studies.³⁶⁸⁻³⁷⁰
 2 **Level 1++**

3 For those studies which included lower doses, 75 mg/day³⁶⁸ and 150 mg/day,³⁶⁹ there was no
 4 significant decrease in mean pain score found. **Level 1++**

5 Short form McGill pain questionnaire

6 Significant decreases were identified with pregabalin 300 and 600 mg/day, compared with
 7 placebo but not with the lower doses (see table 18.2). **Level 1++**

	Study ^a	Total ^a	VAS ^a	PP ^a
Pregabalin 75 mg/day ^a	Lesser (2004) ³⁶⁸	NS ^a	NS ^a	NS ^a
Pregabalin 150 mg/day ^a	Richter (2005) ³⁶⁹	NS ^a	NS ^a	NS ^a
Pregabalin 300 mg/day ^a	Lesser (2004) ³⁶⁸	-4.89 (-7.29 to -2.48) ^a p=0.0001 ^a	-18.09 (-23.11 to -9.08) ^a p=0.0001 ^a	-1.59 (-0.88 to -0.30) ^a p=0.0001 ^a
	Rosenslock (2004) ³⁷⁰	-4.41 (-7.32 to -1.49) ^a p=0.033 ^a	-18.19 (-24.52 to -7.86) ^a p=0.0002 ^a	-0.37 (-0.72 to -0.02) ^a p=0.0364 ^a
Pregabalin 600 mg/day ^a	Lesser (2004) ³⁶⁸	-5.18 (-7.58 to -2.79) ^a p=0.0001 ^a	-19.01 (-26.00 to -12.01) ^a p=0.0001 ^a	-0.61 (-0.90 to -0.32) ^a p=0.0001 ^a
	Richter (2005) ³⁶⁹	-5.83 (-8.43 to -3.23) ^a p=0.002 ^a	-14.67 (-21.92 to -7.41) ^a p=0.0002 ^a	-0.66 (-0.97 to -0.35) ^a p=0.0002 ^a

8

9 Sleep interference

10 There was a significant reduction in sleep interference at the 300 mg/day and 600 mg/day
 11 doses compared with placebo; p=0.001 for both,³⁶⁸ 600 mg/day -1.152 (-1.752 to -0.551),
 12 p=0.0004³⁶⁹ and p<0.0001, 300 mg/day.³⁷⁰ Again there was no significant reduction in sleep
 13 interference for the 75 and 150 mg/day groups.^{368,369} **Level 1++**

14 Short-form 36

15 This efficacy parameter was used in two of the papers and identified that there were
 16 significant improvements in the vitality domain for the 75 mg/day (p<0.02) and 300 mg/day
 17 (p<0.01) compared with placebo, while in the social functioning and bodily pain domains
 18 there were significant improvements in the 300 mg/day (p<0.05 and p=0.005) and 600
 19 mg/day (p<0.01 and p<0.0005) groups.³⁶⁸ For 300 mg/day compared with placebo,³⁷⁰
 20 improvements were identified in the bodily pain domain, 6.87 (0.70 to 13.04, p=0.0294). No
 21 significant changes were found in the other domains. **Level 1++**

22 Patient global impression of change

23 There were significant improvements in the patient perception for 300 mg/day and 600
 24 mg/day, compared with placebo:

- 25 • 300 mg/day (p=0.001, both studies)^{368,370}
- 26 • 600 mg/day (p=0.001, 368 p=0.002).³⁷⁰

27 **Level 1++**

28 Clinical global impression of change

29 Results showed that clinician perceptions echoed those of the patients:

- 30 • 300 mg/day (p=0.001 both studies)^{368,370}

1 • 600 mg/day (p=0.001,368 p=0.004).370

2 **Level 1++**

3 **Adverse events and dropout rates**

4 There were no major differences in the AE and dropout rates between the drug dosages than
5 placebo. AEs did occur more frequently in the treatment groups, with the most common
6 being dizziness and somnolence.

7 **Carbamazepine**

8 One RCT³⁷² reported a significant relief of pain in patients treated with carbamazepine
9 compared to those receiving placebo (p<0.05). No significant differences were found in terms
10 of ability to sleep and reduction of numbness when the two groups were compared. Another
11 RCT³⁷¹ showed that carbamazepine users experienced greater relief of pain compared to
12 placebo-treated patients. However, no statistical analysis was performed. **Level 1+**

13 The study comparing carbamazepine monotherapy with the combination of nortriptyline–
14 fluphenazine³⁷³ showed that both interventions produced significant reductions of pain and
15 paraesthesia. However, the study did not find a significant difference between the two
16 interventions. **Level 1+**

17 **Oxcarbazepine**

18 One RCT³⁷⁵ with a sample size of 146 reported that patients treated with oxcarbazepine
19 experienced a significantly larger decrease from baseline in average VAS-pain scores
20 compared with placebo (p=0.0108). The study also found a significantly greater number of
21 oxcarbazepine-treated patients reporting some improvement from baseline on the patient's
22 global assessment of therapeutic effect, compared to those receiving placebo (p=0.0003). No
23 significant differences were found in terms of quality of life. **Level 1+**

24 In contrast, the other RCT³⁷⁴ with a sample size of ³⁴⁷, did not find any significant difference
25 between oxcarbazepine (600 mg, 1,200 mg and 1,800 mg) and placebo in terms of pain
26 (VAS scale), assessment of therapeutic efficacy and quality of life. **Level 1+**

27 All five studies ^{371–375} demonstrated a higher incidence of AEs reported by patients receiving
28 the active intervention (carbamazepine or oxcarbazepine) compared to placebo. The most
29 common AEs reported were dizziness, headache and somnolence. No statistical analyses
30 were performed. **Level 1+**

14.3.5 From evidence to recommendations

32 The evidence reported suggested that tricyclic drugs, duloxetine, gabapentin, and
33 pregabalin, were all effective in at least some people with neuropathic pain of diabetes origin.
34 The evidence included very few comparative studies, and what there was suggested no
35 advantage for the newer drugs over the tricyclics. Clinical experience confirmed both the
36 limited efficacy of all of the drugs in some people, but also that failure with tricyclics did not
37 often predict failure with other drugs. In these circumstances, and given that side effects
38 were a common problem with all drugs, the GDG felt that first-line specific therapy should be
39 with a tricyclic drug on cost grounds, but that lack of necessary efficacy or problematic side
40 effects should then lead onto a trial of a new drug, with a trial of a third drug if side effects
41 again intervened. The GDG felt that carbamazepine should not be offered to patients due to
42 the drug interactions and intolerance. It was noted that these drug interactions make it
43 difficult for prescribers to monitor patients safely.

44 It was noted that for milder problems simple analgesia was sometimes all that is needed, and
45 that local measures including contact materials or relief from beddings were sometimes

1 helpful. Specific topical creams were not formally appraised, but it was noted these had not
2 entered widespread use.

3 A more holistic approach was often needed at discovery of the problem in helping people to
4 understand it, where secondary psychological problems occurred, and when onward referral
5 was needed to specialist pain teams for lack of response to conventional measures.

6 **21. Recommendations**

7 For the management of foot problems relating to Type 2 diabetes, follow recommendations in
8 'Type 2 diabetes: prevention and management of foot problems'.³⁸⁰

9 R113 Make a formal enquiry annually about the development of neuropathic symptoms
10 causing distress.

- 11 • Discuss the cause and prognosis (including possible medium-term remission) of
12 troublesome neuropathic symptoms, if present (bearing in mind alternative diagnoses).
- 13 • Agree appropriate therapeutic options and review understanding at each clinical contact.

14 R114 Be alert to the psychological consequences of chronic painful diabetic neuropathy
15 and offer psychological support according to the needs of the individual.

16 R115 Use a tricyclic drug to treat neuropathic discomfort (start with low doses, titrated as
17 tolerated) if standard analgesic measures have not worked, timing the medication to be taken
18 before the time of day when the symptoms are troublesome; advise that this is a trial of
19 therapy.

20 R116 Offer a trial of duloxetine, gabapentin or pregabalin if a trial of tricyclic drug does not
21 provide effective pain relief. The choice of drug should be determined by current drug prices.
22 Trials of these therapies should be stopped if the maximally tolerated drug dose is
23 ineffective. If side effects limit effective dose titration, try another one of the drugs.

24 R117 Consider a trial of opiate analgesia if severe chronic pain persists despite trials of
25 other measures. If there is inadequate relief of the pain associated with diabetic neuropathic
26 symptoms, seek the assistance of the local chronic pain management service following a
27 discussion with the person concerned.

28 R118 If drug management of diabetic neuropathic pain has been successful, consider
29 reducing the dose and stopping therapy following discussion and agreement with the
30 individual.

31 R119 If neuropathic symptoms cannot be controlled adequately, it may be helpful to further
32 discuss:

- 33 • the reasons for the problem
- 34 • the likelihood of remission in the medium term
- 35 • the role of improved blood glucose control.

36

15 Areas for future research

- 2 Metformin: confirmatory studies of the advantage in terms of cardiovascular outcome studies.
- 3 Studies of the role of sulfonylureas when starting a pre-mix.
- 4 Longer term studies of the role of self-monitoring as part of an integrated package with
5 patient education and therapies used to target.
- 6 The use of ACEI and A2RBS in combination in early diabetic nephropathy.
- 7 Comparison studies on tricyclics, duloxetine, gabapentin, and pregabalin

1 Appendix B: Clinical questions and

2 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 alpha-glucosidases 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*3
4

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

1

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 1986–2007 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 1986–2007 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

1
2

1 **Appendix C: Health economic analysis of** 2 **third-line therapy with insulins, glitazones** 3 **or exenatide in Type 2 diabetes**

4 **Introduction to the UKPDS outcomes model**

5 The purpose of economic modelling is to present the available evidence in a logical way to
6 inform decisions.⁴⁰⁰ An economic evaluation of a healthcare programme is only as good as
7 the effectiveness data it is built upon, so it is important to consider the quality and relevance
8 of the medical evidence. It also is important to consider how close the situation to be
9 modelled is to the situation where the published clinical studies were conducted.¹⁸¹

10 The clinical trials of insulins, glitazones or exenatide were run for approximately 3 months to
11 2 years and intermediate outcomes were measured, for example change in HbA1c from
12 baseline. In order to look at the cost effectiveness of these treatments it is necessary to
13 extrapolate these intermediate outcomes to quality adjusted life years (QALYs) saved.
14 Diabetes is a complicated disease and poor control can lead to the development of
15 macrovascular and microvascular complications, which affect both quality of life and survival.
16 In order to provide useful cost- effectiveness analysis, a model should take costs and health
17 consequences of these complications into account.

18 Using one model to analyse various treatments for diabetes will provide consistency and
19 allow the results to be compared. This will be beneficial for making decisions regarding
20 treatment algorithms.

21 The United Kingdom Prospective Diabetes Study (UKPDS) was conducted between 1977
22 and 1991.⁴⁰¹ 5,102 patients with newly diagnosed Type 2 diabetes were recruited aged
23 between 25 and 65 years. Patients had fasting plasma glucose (FPG) of above 6 mmol/l on
24 two occasions, had no recent history of myocardial infarction (MI), ischaemic heart disease
25 (IHD) or congestive heart failure (CHF), and had never had more than one major vascular
26 event or a severe concurrent illness that would limit life expectancy. Biochemical
27 measurements were taken, including HbA1c, systolic blood pressure, and lipid and
28 lipoprotein fractions.

29 Observational data on 3,642 patients, for whom annual data on potential risk factors was
30 available, were used to develop the UKPDS outcomes model. The model estimates the
31 relationship between exposure over time to glycaemia and other risk factors to the
32 development of macrovascular and microvascular complications (cardiovascular disease,
33 kidney failure etc.).

34 The model allows the following baseline population characteristics to be inputted:

- 35 • age at diagnosis
- 36 • ethnicity
- 37 • gender
- 38 • duration of diabetes
- 39 • body mass index (BMI)
- 40 • HbA1c (glycosylated haemoglobin)
- 41 • total: high density lipoprotein (HDL) cholesterol
- 42 • blood pressure (BP)
- 43 • smoking status
- 44 • atrial fibrillation at diagnosis

- 1 • peripheral vascular disease at diagnosis
- 2 • history of diabetes-related events.
- 3 The following risk factors can be inputted for each year the patient is in the model:
- 4 • HbA1c
- 5 • systolic blood pressure (SBP)
- 6 • total: HDL cholesterol
- 7 • smoking status.
- 8 All the inputs are used to estimate first occurrence of each of seven diabetes-related
- 9 complications:
 - 10 1. fatal or non-fatal MI
 - 11 2. other IHD
 - 12 3. stroke
 - 13 4. heart failure
 - 14 5. amputation
 - 15 6. renal failure
 - 16 7. eye disease.
- 17 The outcomes of the model are:
 - 18 • life expectancy
 - 19 • quality adjusted life expectancy
 - 20 • costs
 - 21 • cumulative event rate of all seven complications.
- 22 Quality adjusted life expectancy attaches a utility to each life year gained by effective
- 23 treatment. A utility score of 1 is given to perfect health, and 0 to death. So a treatment, which
- 24 extends the life of a person with diabetes by 4 years and gives perfect quality of life (4 yrs x
- 25 1) results in 4 quality adjusted life years (QALYs). A treatment that extends that person's life
- 26 by 5 years but does not improve their quality of life (if people with diabetes give their quality
- 27 of life a utility score of 0.8, due to pain etc) may result in the same number of QALYs (5 yrs x
- 28 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)

1

2 **Costs**

3 A cost analysis was conducted alongside the UKPDS.⁴⁰² All patients attended clinics every
4 3 or 4 months for the duration of the study. At each visit they were assessed to determine the
5 occurrence of any clinical events or hospital episodes since the previous visit. Where an
6 inpatient stay had occurred, details were obtained from the relevant hospital of dates of
7 admission and discharge, reasons for admission, and any major procedures undertaken.
8 Within the cost analysis, the cost of each episode of hospitalisation was estimated by
9 multiplying the length of stay by the average cost of the respective specialty, based on an
10 average of the Department of Health's (DH) National Health Service (NHS) Trust Financial
11 returns for 1997/8 and 1998/9. We have updated the costs to 2004 prices in the model using
12 the Hospital and Health Services Price Index.⁴⁰³

13 Information on non-inpatient healthcare resources was obtained using a cross-sectional
14 survey of 3,488 UKPDS patients conducted between January 1996 and September 1997. A
15 questionnaire was distributed at clinic visits or by post to patients who did not attend clinics
16 during the survey period. This survey recorded information on all home, clinic and telephone
17 contacts with general practitioners, nurses, podiatrists, opticians and dieticians, and with eye
18 and other hospital outpatient clinics over the 4 months prior to the survey.⁴⁰²

- 1 It was assumed that patient characteristics and complications had a multiplicative effect on
 2 costs.
- 3 The results of this cost analysis represented an estimate of the increase in all healthcare
 4 costs in the year in which the complication occurs. The hospital inpatient costs reported for a
 5 non-fatal stroke would capture any inpatient stays directly associated with the stroke, but
 6 also the potential indirect impact of the stroke, e.g. on lengths of inpatient stay for other
 7 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

8

9 **Utilities**

- 10 EuroQol EQ-5D (EQ-5D) data from 3,192 UKPDS patients in 1996 was used to measure the
 11 impact of diabetic complications on quality of life. It was assumed that multiple complications
 12 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	

13

1 **Limitations**

- 2 Limitations of the UKPDS outcomes model were identified by the authors. Only the first event
 3 is predicted in any single category of diabetes-related complications. Multiple events in the
 4 UKPDS were relatively infrequent and subsequent fatal events in specific categories of
 5 diabetes- related complications were included in the diabetes-related mortality equation.⁴⁰¹
- 6 Not all relevant complications are included in the model; peripheral neuropathy and
 7 ulceration were not included as major endpoints in the UKPDS and so could not be easily
 8 incorporated as outcomes in the model. Hypoglycaemia and hyperglycaemia were also
 9 excluded.⁴⁰¹
- 10 Some of the complications are represented in the model using a single state, e.g. the only
 11 state representing eye disease in the model is the endpoint of blindness in one eye. This is
 12 unlikely to fully describe the complex process of disease progression.⁴⁰¹
- 13 Limitations in the costing study identified were that the UKPDS patients were newly
 14 diagnosed and tended to be younger than people with Type 2 diabetes in the general
 15 population and the costs reported may not reflect the resource use associated with
 16 complications of some older patients in the general population.⁴⁰² The inpatient costs were
 17 based on clinical practice in the UK from 1977 to 1997, although treatment protocols may
 18 have changed, for example coronary stents are increasingly used in the treatment of patients
 19 with IHD.

20 **Aims of analysis**

- 21 The standard pathway of pharmacological treatment used in this model for a person with
 22 Type 2 diabetes is to start with metformin (unless intolerant or contraindicated) which has
 23 been shown to be cost-saving compared to conventional therapy primarily of dietary
 24 changes.^{33,34} After metformin the next step is to add a sulfonylurea, which was also shown to
 25 be cost effective as a monotherapy compared to conventional therapy.³³
- 26 Uncertainty arises in the third-line therapy. There are a number of insulins available in
 27 different forms, which work in different ways. Alternatively patients could be given a glitazone
 28 (rosiglitazone or pioglitazone) or the newly licensed exenatide. Sitagliptin and vildagliptin will
 29 not be covered in this guideline and so have not been included in this analysis.
- 30 The aim of this analysis is to determine what the third-line therapy should be, given the
 31 following options:
- 32 • human insulin – neutral protamine Hagedorn (NPH) or a premix of NPH/regular 30/70
 - 33 • biphasic analogues (either lispro or aspart) – twice daily
 - 34 • insulin glargine – once daily
 - 35 • glitazones (pioglitazone and rosiglitazone)
 - 36 • exenatide
- 37 The perspective of the analysis was that of the NHS. This includes direct costs to the NHS,
 38 not to the patients or their carers.
- 39 A cost-utility analysis was conducted with an outcome of cost per QALY gained.

40 **Population**

- 41 The following characteristics for the population were based on expert opinion agreed among
 42 the GDG as the UKPDS population characteristics were not thought to reflect the current
 43 characteristics of people with diabetes at the point at which third-line therapy was being
 44 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
HbA1c	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)		

1

2 The SBP, total cholesterol, HDL cholesterol and HbA1c were set to be the same at diagnosis
3 as for current values. It was assumed that at diagnosis of diabetes people had no history of
4 atrial fibrillation or peripheral vascular disease, and they were non-smokers.

5 A recent study by Calvert et al. 2007⁴⁰⁴ used data from 154 general practices in the UK
6 between 1995 and 2005, which included 14,824 people with Type 2 diabetes. Patients'
7 characteristics were as follows:

- 8 • mean age of 64.2 years (12.5 yrs)
- 9 • mean BMI of 30.1 kg/m² (SD 6.8 kg/m²)
- 10 • median time from initiation of the last oral agent to insulin for patients prescribed two or
11 more types of oral agents concurrently was 7.7 years (95% CI=7.4 to 8.5 yrs)
- 12 • mean HbA1c prior to insulin was 9.85% (SD 1.96%).

13 These population characteristics were used in a sensitivity analysis as the Calvert et al.
14 paper was identified after the main analysis had been conducted.

15 Discounting

16 Both costs and benefits were discounted by 3.5% for the first 30 years, and after 30 years by
17 3%. The discount rate reflects that people prefer to receive a benefit earlier and to incur a
18 cost later, even in a world with zero inflation and no bank interest.¹⁸¹

19 Time horizon

20 The model was run for 40 years to capture a lifespan time horizon. The costs were applied
21 for 40 years as people with diabetes are likely to need treatment for the rest of their lives. As
22 the clinical evidence available was for a maximum of 2 years, it seems likely that the benefits
23 of treatment would persist for some time beyond this. As a conservative estimate, we
24 assumed that treatment effects would persist for 3 years in the base case model (e.g. where
25 a treatment reduced HbA1c, HbA1c would be reduced in each of the first 3 years of
26 treatment when this reduction was assumed to stop). The median time from initiation of the
27 last oral agent to insulin was 7.7 years in the study by Calvert et al. 2007⁴⁰⁴ (see above for
28 description of this study). This suggests that the treatment effect from third-line therapy might
29 last for longer than 3 years. After the initial 3 years, the model was run with no additional

1 treatment effect, HbA1c would therefore gradually increase over time. The duration of effect
2 was tested in a sensitivity analysis.

3 **Treatments included**

4 Meta-analysis was conducted where more than one study was available for a comparison.
5 The following comparisons were found in published papers:

- 6 • biphasic analogue vs human insulin: 6 studies, total N=1,001^{182,183,186–189}
- 7 • glargine vs human insulin: 2 studies, total N=591^{196,199}
- 8 • biphasic analogue vs glargine: 3 studies, total N=435^{198,201,202}
- 9 • glargine vs rosiglitazone: 1 study, N=216¹³⁹
- 10 • rosiglitazone vs pioglitazone: 1 study, N=91¹³³
- 11 • exenatide vs glargine: 1 study, N=549⁴⁰⁵
- 12 • exenatide vs biphasic analogue: 1 study, N=501.⁴⁰⁵

13 After oral antidiabetics, the next option was human insulin premix or NPH (personal
14 communication, Philip Home 2 April 2007). It was not felt that the choice between NPH or
15 human insulin premix was a question that would need to be addressed by this analysis. As
16 human insulin premix could include NPH, the studies with NPH as a comparator were
17 combined with the human insulin premix studies to give the baseline treatment.

18 A random effect MA was used for glargine vs human premix comparisons.^{196,199}

19 Human premix was used as the baseline. Direct evidence from good-quality RCTs is
20 considered the gold standard. As there were no studies which had all comparators, a simple
21 indirect comparison was carried out using the results of a meta-analysis by adding weighted
22 mean differences in the treatment effects.

23 **Insulins (human, biphasic analogue, insulin glargine)**

24 See figure C1 for the meta-analysis results.

25 None of the papers included treatment effect on SBP or lipid profiles. It was assumed in the
26 base case that there was no difference in these outcomes between the insulins.⁴⁰⁶

27 A meta-analysis was identified by Rosenstock et al.¹⁹⁴ which found that there was no
28 difference in the level of HbA1c reduction between insulin glargine and NPH insulin. The
29 results of this meta-analysis were used in a sensitivity analysis, it was assumed that the
30 change in HbA1c for insulin glargine would be equal to that for human insulin in the
31 sensitivity analysis.

32 It was not possible to include all the treatment effects associated with the drugs evaluated
33 using the UKPDS model. Hypoglycaemic events are included in the UKPDS model based on
34 those observed but it was not possible to change the RR of events occurring for different
35 treatments. A simple sensitivity analysis was conducted with an increased quality of life for
36 patients receiving glargine, which is associated with decreased hypoglycaemic events. Only
37 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

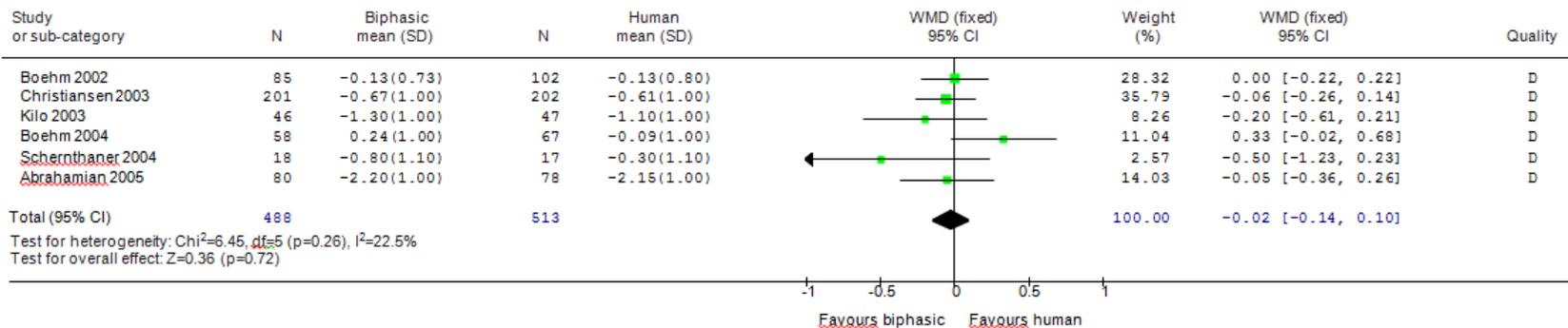
1

2 In the long-acting insulin technology appraisal (TA)¹⁹³ a utility decrement of 0.15 was applied
3 to each day in a severe hypoglycaemic event which was assumed to last for 4 days each
4 (0.0016 QALY loss per severe event). It was assumed that insulin glargine avoided three
5 episodes of symptomatic hypoglycaemia per person per year, and no reduction in HbA1c
6 levels compared to NPH insulin they also applied a utility decrement to represent fear of
7 hypoglycaemia, although this information was submitted as 'commercial in confidence'. The
8 TA analysis was updated by the TA group with new evidence on the utility associated with
9 hypoglycaemic events, and 0.0052 was applied to each hypoglycaemic event avoided.⁴⁰⁷
10 The cost of a severe hypoglycaemic event was £218.34. This gave a cost-effectiveness ratio
11 of £32,508 compared to NPH insulin, using the price of a vial of glargine. Using cartridges or
12 pens gave higher cost- effectiveness ratios, £41,236 and £43,411 respectively. The results
13 were most sensitive to the assumption on utility gained from reducing fear of hypoglycaemia.
14 If it was assumed that there was no utility gain from this, then the cost-effectiveness ratio
15 rose to approximately £10million per QALY.

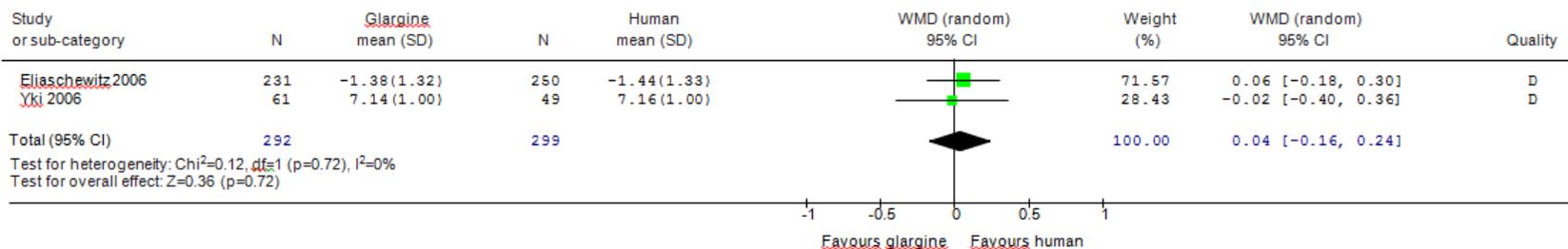
16

Areas for future research

Review: [Insulins in Type 2 diabetes](#)
 Comparison: [01 Biphasic vs human](#)
 Outcome: [01 HbA_{1c}](#)



Review: [Insulins in Type 2 diabetes](#)
 Comparison: [02 Glargine vs human](#)
 Outcome: [01 HbA_{1c}](#)



Review: [Insulins in Type 2 diabetes](#)
 Comparison: [03 Biphasic vs glargine](#)
 Outcome: [01 HbA_{1c}](#)

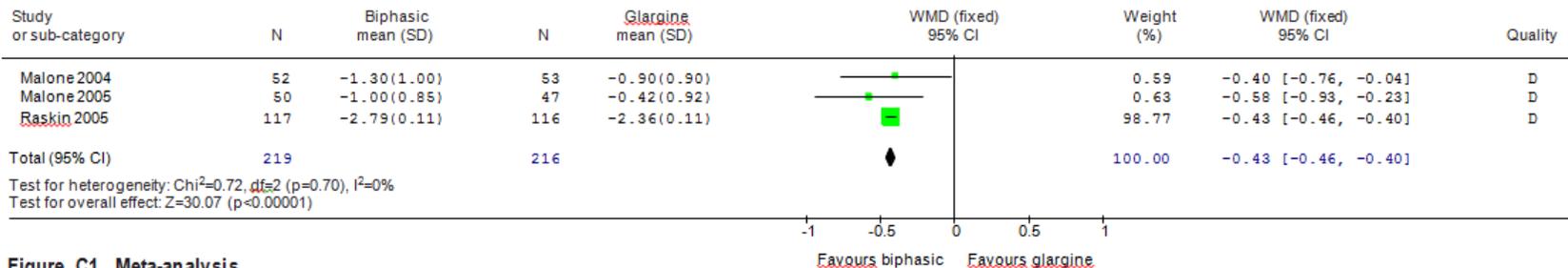


Figure C1. Meta-analysis

1 A recent study of utility related to fear of hypoglycaemia used pooled data from two postal
 2 surveys of subjects with confirmed diabetes (both Type 1 and Type 2), (N=1,305 responses),
 3 conducted in the UK.⁴⁰⁸ The Hypoglycaemia Fear Survey (HFS) (values from 0 to 52, 0=least
 4 worry) and the EQ-5D were used to characterise the fear of hypoglycaemia. They found that
 5 each severe hypoglycaemic event resulted in a change of 5.881 units of the HFS and one or
 6 more symptomatic events resulted in a change of 1.773 units on the HFS. They found that a
 7 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

8

9 Based on the Riddle et al. study²¹³ it was assumed that there would be 2.1 severe
 10 hypoglycaemic events per person per year and 3.7 non-severe symptomatic events. For
 11 each day in a severe hypoglycaemic event, we assumed a utility loss of 0.15 directly due to
 12 the symptoms for 4 days. In addition, we assumed a utility loss due to fear of hypoglycaemia
 13 of 0.047 and 0.014 respectively with severe and symptomatic events applied over the year.
 14 This gave an estimated QALY gain of 0.064 per year due to avoided hypoglycaemic events
 15 for each person treated with glargine rather than other insulins. Additionally using the
 16 updated TA evidence, a 0.52% reduction in utility per severe hypoglycaemic event was
 17 tested (0.0052 x 2.1 events=0.011 utility increased over a year treated with glargine).

18 Glitazones

19 Most studies examining the glitazones were placebo controlled. As the glitazones have only
 20 recently gained the license for triple therapy, there were very few studies available that had
 21 suitable comparators. One study was available that compared rosiglitazone (4 mg/day) to
 22 insulin glargine (10 IU).¹³⁹ Another study compared pioglitazone (15 mg/day) to rosiglitazone
 23 (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

24

Table C8 Rosiglitazone compared to pioglitazone in a 12-month study

	Rosiglitazone	Pioglitazone
Baseline <u>HbA_{1c}</u> %	8.1	8.20
12-month <u>HbA_{1c}</u> change	-1.3	-1.40
lower	-0.8	-1.10
upper	-1.8	-1.70
Baseline TC <u>mmol/l</u>	4.92	5.03
12-month TC	0.21	-0.50
lower	0.83	-0.01
upper	-0.41	-0.99
Baseline HDL <u>mmol/l</u>	1.09	1.14
12-month HDL <u>mmol/l</u>	-0.03	0.1
lower	-0.16	-0.06
upper	0.1	0.26

1

2 **Exenatide**

3 The GWAD¹⁶⁶ compared exenatide (10 µg BID) to biphasic insulin aspart 30/70 (BiAsp) twice
4 daily over 52 weeks. The inputs for change in the ratio of total cholesterol to HDL for the
5 model are reported in tables C53–55 at the end of the appendix. The population included in
6 this study had maximised their treatment on metformin and sulfonylurea treatment but were
7 unable to achieve optimal blood glucose levels, and would normally begin insulin
8 treatment.^{164,166,405} The whole intent-to-treat (ITT) population was used to estimate the
9 unadjusted treatment effects in the industry-submitted economic analysis. It was reported
10 that this would ensure consistency across the endpoints. This assumption led to a less
11 favourable change in HbA1c for exenatide.⁴⁰⁵ The inputs for change in the ratio of total
12 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

13

- 1 A total of 33.2% of exenatide patients and 0.4% of BiAsp patients reported nausea during the
 2 study period. The nausea was generally mild/moderate and transient in nature and only a
 3 small proportion of patients (4%) withdrew from the study due to nausea, 40–50% of patients
 4 reported at least one episode of nausea.⁴⁰⁵
- 5 The GWAA¹⁶⁴ study compared exenatide (10 µg BID) treatment to insulin treatment; insulin
 6 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

- 7
- 8 The EQ5D was given at baseline and at the 26-week endpoint in the trial with insulin glargine
 9 as a comparator. Although the data showed a significant improvement in quality of life for
 10 both treatment groups, there was no significant difference between the treatments (the mean
 11 differences were not reported in the SMC submission).⁴⁰⁵ As it was felt that more data were
 12 required as the clinical trial had demonstrated treatment differences which were felt to impact
 13 quality of life, more data were collected by a stakeholder. A study was carried out in 129
 14 people with diabetes using an initial set of health states developed based on clinical trial data
 15 and clinical expertise (table C11). They used the standard gamble method using one-month
 16 durations for the health states compared to perfect health.⁴⁰⁹
- 17 The utility changes used in the industry basecase model were:
- 18 • exenatide
- 19 ○ year 1=0.006
- 20 ○ year 2=0.032 (this appears to be assuming 5% weight loss, and no nausea or
- 21 hypoglycaemia)
- 22 • glargine:
- 23 ○ year 1=-0.045
- 24 ○ year 2=-0.065 (assuming 5% weight gain, and no nausea or hypoglycaemia)
- 25 The following description was provided as a comment during consultation by a stakeholder:
- 26 The health state utilities from the UK utility study were applied in the simulations according to
 27 the following assumptions, based on data from the GWAA clinical trial, with weight change
 28 referred to as a percentage change from baseline:
- 29 • exenatide
- 30 ○ year 1: utility for 3% weight loss (mean baseline body weight=87.5 kg, mean weight
 31 change=-2.3 kg, a 3% reduction); 57.1% patients experienced nausea with exenatide
 32 (assumed to last for 6 months)

- 1 • exenatide
- 2 ○ year 2: utilities for 5% weight loss (2 year clinical trial data show mean loss of -4.4 kg
- 3 from a baseline weight of 99 kg). No patients assumed to experience nausea
- 4 • insulin glargine
- 5 ○ year 1: utility for 3% weight gain (mean baseline body weight=88.3 kg, mean weight
- 6 change=+1.8 kg, a 2% increase); 8.6% of patients experienced nausea (assumed to
- 7 last for 6 months)
- 8 • insulin glargine
- 9 ○ year 2: utility for 5% weight gain based on a review of weight gain with insulin therapy
- 10 which found that weight continues to increase over time from insulin initiation with
- 11 insulin-treated patients found to gain an average of 5% of their body weight during the
- 12 first 2 years of treatment (UKPDS 24, 1998) in line with a recent review which shows
- 13 an average weight gain of 4.9 kg after insulin initiation (Heller, 2004). From a baseline
- 14 weight of 88.3 kg (GWAA) this equates to 5.5% weight gain. No patients were assumed
- 15 to experience nausea.
- 16 From year 3 onwards, patients in both treatment groups would be assumed to have a
- 17 disutility value of -0.0061 per unit difference in BMI over 25 (as per CODE-2 TTO) and no
- 18 disutility for nausea.
- 19 Using the assumptions from above and the values from table C11, the resulting
- 20 utility/disutility values for exenatide and insulin glargine in the GWAA model are therefore:
- 21 • exenatide
- 22 ○ year 1: utility=57.1%* 0.5 (years)* G+57.1%* 0.5 (years)* I+42.9%* I=0.006
- 23 ○ year 2: utility=100%* J=0.032
- 24 • insulin glargine
- 25 ○ year 1: utility=8.6%* 0.5 (years)* C+8.6%* 0.5 (years)* E+91.4%* E=-0.045
- 26 ○ year 2: utility=100%* F=-0.065
- 27 The utility/disutility values for exenatide and BiAsp in the GWAD model are based on similar
- 28 patterns of short-term weight change for exenatide (mean baseline body weight=85.5 kg,
- 29 mean change=-2.5 kg, 3% reduction and BiAsp (mean baseline body weight=83.4 kg, mean
- 30 change=+2.9 kg, 3% gain) as in the GWAA base case analysis. As for the base case, year 2
- 31 weight change was assumed to be 5% loss for exenatide patients, 5% gain for BiAsp
- 32 patients. The resulting treatment-related utility values are:
- 33 • exenatide
- 34 ○ year 1: utility=33.2%* 0.5 (years)* G+33.2%* 0.5 (years)* I+42.9%* I=0.012
- 35 ○ year 2: utility=100%* J=0.032
- 36 • biphasic insulin aspart
- 37 ○ year 1: utility=0.4%* 0.5 (years)* C+0.4%* 0.5 (years)* E+99.6%* E=-0.044
- 38 ○ year 2: utility=100%* F=-0.065
- 39

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)

1

2 Treatment inputs to model

3 Human insulin was the baseline treatment. The clinical evidence of human insulin compared
4 to placebo (oral antidiabetic agents alone) was not reviewed in the guideline and so it was
5 assumed that UKPDS observational data with no added treatment effect would approximate
6 to human insulin, treatments in the UKPDS included metformin, sulfonylurea and insulin. The
7 studies including insulins did not report changes in TC:HDL or SBP. The GDG agreed that
8 this was because there would be no difference in TC:HDL or SBP with insulin therapies and
9 that these did not need to be tested in a sensitivity analysis.

Table C12 Base case drug efficacy inputs

	Weighted mean difference % change in <u>HbA_{1c}</u>	Change in <u>TC:HDL</u> *	Change in <u>SBP</u>
Biphasic analogue vs human insulin	-0.02	0	0
<u>Glargine</u> vs human insulin	0.04	0	0
<u>Glargine</u> vs biphasic analogue	0.43	0	0
<u>Exenatide</u> vs <u>glargine</u>	0.08	-0.12	-3.58
<u>Exenatide</u> vs biphasic analogue	-0.09	0.1	-6.22
Rosiglitazone vs <u>glargine</u>	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 <u>HbA_{1c}</u>	Change in <u>TC:HDL</u>	Change in <u>SBP</u>
Biphasic analogue vs human insulin	0.1	0	0
<u>Glargine</u> vs human insulin	0.24	0	0
<u>Glargine</u> vs biphasic analogue	0.46	0	0
<u>Exenatide</u> vs <u>glargine</u>	0.32	0.2	0.43
<u>Exenatide</u> vs biphasic analogue	0.2	0.42	-2.39
Rosiglitazone vs <u>glargine</u>	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
<u>Glargine</u> vs human insulin	-0.16	0	0
<u>Glargine</u> vs biphasic analogue	0.4	0	0
<u>Exenatide</u> vs <u>glargine</u>	-0.15	-0.4	-7.6
<u>Exenatide</u> vs biphasic analogue	-0.38	-0.22	-10.05
Rosiglitazone vs <u>glargine</u>	0	-0.17	-3
Rosiglitazone vs pioglitazone	-0.9	-3.19	-3

1

2 **Base case treatment pathway**

3 The following diagram shows the comparisons available from the clinical evidence. All the
 4 treatments were compared to human insulin. For the analysis one pathway needs to be
 5 chosen from the available options for biphasic analogues, insulin glargine and exenatide.
 6 Rather than discard the other studies, different pathways were tested in the sensitivity
 7 analyses, these are listed below.

8 The weighted mean differences in treatments were added along the pathways, for example
 9 exenatide was not directly compared to human insulin in a RCT, it was compared to biphasic
 10 analogue insulin (weighted mean difference in HbA_{1c} reduction -0.09%), and there were
 11 studies in which biphasic analogue was directly compared to human insulin (weighted mean
 12 difference in HbA_{1c} reduction -0.02%), therefore making an indirect comparison gives a
 13 mean difference in HbA_{1c} reduction between human insulin and exenatide of -0.11%).

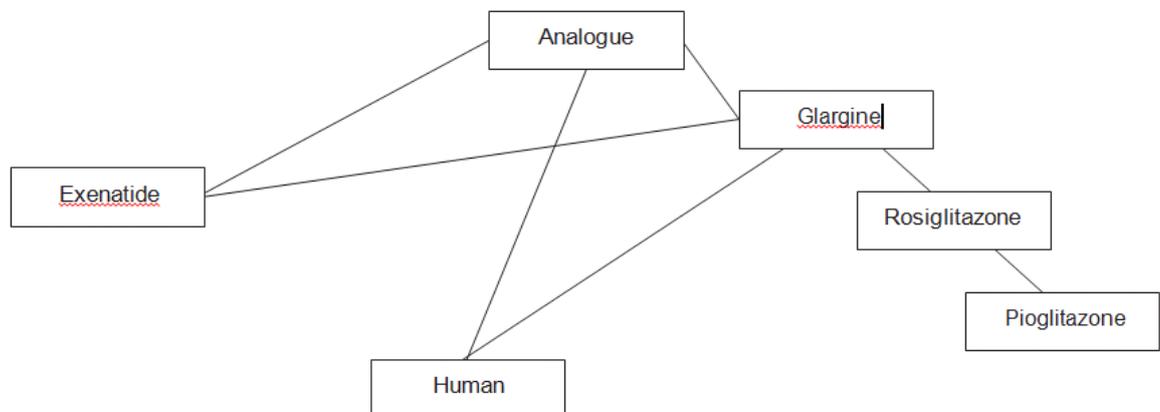


Figure C1 Human insulin vs biphasic analogue, biphasic analogue vs glargine, exenatide vs biphasic, rosiglitazone vs glargine, pioglitazone vs rosiglitazone

14

15

1 **Sensitivity analysis**

- 2 • Human insulin vs biphasic analogue, biphasic analogue vs glargine, exenatide vs
 3 glargine, rosiglitazone vs glargine, pioglitazone vs rosiglitazone
- 4 • Human insulin vs biphasic analogue, human insulin vs glargine, exenatide vs biphasic,
 5 rosiglitazone vs glargine, pioglitazone vs rosiglitazone
- 6 • Human insulin vs biphasic analogue, human insulin vs glargine, exenatide vs glargine,
 7 rosiglitazone vs glargine, pioglitazone vs rosiglitazone

8 The HTA on indirect comparisons by Glenny et al. (2005)⁴¹¹ highlighted issues that would be
 9 of concern, these included methodological quality of the trials, the degree of comparability of
 10 the treatments, participants and protocols of the trials. All the trials included in the HTA
 11 indirect analysis were given a positive score by the HTA clinical reviewers, which ensure
 12 good methodological quality.

13 The comparability of the insulins and glitazones seems to be acceptable as their main
 14 effectiveness is on HbA1c levels. Exenatide has other effects, on lipid levels, SBP, and
 15 weight, which may mean the indirect comparisons are not appropriate. A sensitivity analysis
 16 with only treatment effects on HbA1c was carried out.

17 Studies from the Type 2 diabetes guideline and the update were quickly scanned to identify
 18 those which reported a change in HbA1c, or the baseline and endpoint HbA1c values. All
 19 studies that were given a positive score and reported the change in HbA1c results were
 20 included in a series of meta-analyses. The studies varied in size (35 to 549 participants), and
 21 in duration (12 weeks to 24 months). There may be bias in the measurement of outcomes or
 22 the efficacy of treatment may differ in subpopulations of patients, for example if patients are
 23 more severely affected, older or younger, or more compliant with treatment. None of the trials
 24 were highlighted for particularly different inclusion and exclusion criteria, and so it is
 25 assumed that the efficacy data can be generalised to the Type 2 diabetes population as a
 26 whole.⁴¹¹

27 The model was run with 10,000 iterations to take into account variability in the population, i.e.
 28 that people with Type 2 diabetes who have the same characteristics can experience different
 29 outcomes. Also the model was run with 100 bootstraps in order to give approximate CIs
 30 around the UKPDS outcomes.

31 **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
<u>Glargine</u>	46 IU	32 IU	68 IU
Rosiglitazone	8 mg	4 mg	
Pioglitazone	30 mg	15 mg	45 mg
<u>Exenatide</u>	20 µg		

32

1 **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

2

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

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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

8

1 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.

2

3 Using the base case inputs human insulin was the most cost-effective treatment for third-line
 4 therapy, either dominating the other options, or with the other options having very high
 5 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

6

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

1

2 **Sensitivity analysis**

3 These analyses involve changing one characteristic of the base case population at a time.
 4 Human insulin remained the most cost effective option for third line therapy when the
 5 population characteristics were changed. For people with high systolic blood pressure or high
 6 cholesterol levels, pioglitazone was cost effective at £12,184 and £16,139 per QALY
 7 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

8

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

9

Table C25 Body mass index 33 kg/m²

	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/m²

	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. 2007⁴⁰⁴

	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

1

2 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-analysis¹³⁴

	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

3

4 Increasing the initial utility for patients on glargine as a simple estimation of the effects of
 5 glargine on hypoglycaemic events had no effect on the ranking of the results. Assuming an
 6 additional gain of 0.065 due to reduced hypoglycaemic events and reduced fear of
 7 hypoglycaemia over the three years of treatment effect, and a reduction in costs by £1,300
 8 for 2.1 severe events avoided per year for 3 years, the estimated cost per QALY for glargine
 9 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

1

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

2

3 It was not possible to include changes in weight in the model. As exenatide was associated
4 with weight reduction and this is considered an important benefit, a sensitivity analysis was
5 conducted in which the patients receiving exenatide were given a lower BMI than other
6 patients to allow for the health and quality of life benefits associated with a lower weight.
7 These results include additional benefits for exenatide from avoided microvascular and
8 macrovascular events estimated to result from an initial 3 kg/m² reduction in BMI. It can be
9 seen that this does not change the results, as the incremental cost-effectiveness ratio for
10 exenatide compared with the next best alternative (human insulin) remains over £100,000
11 per QALY.

Table C35 Exenatide patients with a body mass index of 27 kg/m² compared to a 30 kg/m² 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

1

2 Further sensitivity analyses were conducted assuming additional utility benefits for exenatide
3 based on the survey results in table C8 above. Although the cost effectiveness of exenatide
4 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/m² (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/m²

	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

5

Table C37 Exenatide patients with a BMI of 27 kg/m² (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/m²

	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

6

1 When the clinical evidence was presented for exenatide, the doses for the insulins were
 2 questioned as the GDG thought they were lower than would normally be given. Lower
 3 treatment efficacy was used to investigate if the reported results may overestimate the
 4 effectiveness of exenatide. As can be seen in table 39, a 0.29% reduction in the weighted
 5 mean difference for exenatide compared with biphasic analogue insulin (HbA_{1c} levels would
 6 increased by 0.2% compared to analogue insulin) led to a large increase in its estimated cost
 7 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

8
 9 It was highlighted by the GDG that exenatide would be an option for overweight or obese
 10 patients who would have to take large doses of insulins. No clinical evidence was available in
 11 this specific subgroup and so it was assumed the treatment efficacy was the same as
 12 reported in the studies available. The following sensitivity analysis compares the costs of the
 13 highest insulin dose reported in the studies available (70 IU per day) and higher monitoring
 14 costs with the mean doses of exenatide and glitazones. As no clinical evidence was available
 15 it is unknown whether patients who would require higher insulin doses would also require
 16 higher exenatide or glitazone doses to maintain their HbA_{1c} levels.

Table C39 Maximum daily dose of insulin to represent the doses given to overweight people with Type 2 diabetes (BMI 33 kg/m²)

	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

17
 18 Recent publications have highlighted increased risks with the glitazones for cardiac
 19 outcomes. Details of these studies can be found in the clinical evidence (chapter 10). A study
 20 comparing pioglitazone to placebo in 2,445 patients with Type 2 diabetes and previous MI
 21 reported that the incidence of CHF was significantly higher in patients receiving pioglitazone
 22 (13.5 vs 9.6%; p=0.003). The incidence of serious CHF (requiring hospitalisation) was also
 23 significantly higher in the pioglitazone group (7.5% vs 5.2%; p=0.022).¹⁵⁰

1 In a study comparing rosiglitazone in combination with metformin or sulfonylurea, compared
 2 to metformin in combination with sulfonylurea, patients in the rosiglitazone group had a
 3 significantly higher risk of CHF than patients did in the control group, with 38 versus 17
 4 adjudicated events (hazard ratio, 2.24; 95% CI 1.27 to 3.97).¹¹⁶ In a study comparing the
 5 rosiglitazone to a control group the odds ratio for MI was 1.43 in the rosiglitazone group (95%
 6 CI 1.03 to 1.98; p=0.03).¹¹⁵

7 It is not possible to change the RR for cardiac events in the UKPDS, but as an indirect
 8 indication of the potential sensitivity of the results to uncertainty over the cardiac risk
 9 associated with glitazones, we investigated in the impact of hypothetical differences in SBP
 10 between the insulins and glitazones (tables 41 and 42). Human insulin remained the most
 11 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

12

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

13

14 **Indirect comparisons – sensitivity analysis**

15 As there were studies available that had different comparators which could not be grouped
 16 together in a meta-analysis, it was important to test whether using different pathways for the
 17 comparisons would affect the results. Using the different indirect comparison results did not
 18 change the results and human insulin remained the most cost-effective option for third-line
 19 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.

1 Based on the median time from initiation of the last oral agent to insulin for patients
 2 prescribed two or more types of oral agents concurrently which was 7.7 years in the study by
 3 Calvert et al. 2007, a longer treatment effect for the third-line therapies was tested. Assuming
 4 a 10-year treatment effect had no impact of the results and human insulin remained the most
 5 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

6

7 **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

8

9 **Treatment efficacy – sensitivity analysis**

10 These analyses were carried out to test the generalisability of the results, if the treatments
 11 prove to be less effective in practice than in the trials. Using lower efficacy values for the
 12 insulins and the glitazones made no effect on the results. Increasing the efficacy of glargine
 13 and biphasic analogue did not improve their cost-effectiveness compared to human insulin.
 14 Increasing the efficacy of the glitazones did make pioglitazone cost effective, £1,447 per
 15 QALY. Although this seems to be driven mainly by reduction of the TC:HDL by -3.19 which
 16 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

1

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

2

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

3

4 Conclusions

5 Human insulin was consistently the most cost-effective option (table C20). It remained so in
6 different subgroups where one characteristic of the population was changed at a time (tables

- 1 C23 to C31). It also remained the most cost-effective option if it was assumed that the
2 treatment effect of all the therapies lasted for 10 years instead of only 3 years.
- 3 Clinical evidence has shown glargine to reduce hypoglycaemic events. If it was assumed that
4 people experienced a utility increment due to events avoided, and also a utility increment due
5 to reduction in fear of hypoglycaemic events, then glargine became cost effective: £4,352 per
6 QALY. Using the utility increments used in the TA update of 0.52% increment per
7 hypoglycaemic event avoided did not improve the results of glargine enough to make it cost
8 effective (table C33 to C34).
- 9 The UKPDS was chosen for the analysis before it was decided to include exenatide in the
10 guideline. The studies available that include exenatide have reported treatment effects on
11 weight reduction, lipid ratios and blood pressure. Treatment effect on weight loss could only
12 be tested in the model by changing the initial weight and the actual treatment effects may not
13 be represented accurately. From the results of the sensitivity analyses, giving people on
14 exenatide a lower initial BMI and a higher quality of life to represent the potential weight loss,
15 exenatide was unlikely to be cost-effective at current NICE thresholds¹ (lowest cost per
16 QALY was £29,865). Pioglitazone became the most cost-effective option when the daily dose
17 of insulin was increased to reflect that given to overweight or obese people with Type 2
18 diabetes (tables C35 to 41).
- 19 The glitazones were only recently licensed for third-line therapy and as such few clinical
20 studies were available for evidence. Pioglitazone became cost-effective in a number of the
21 sensitivity analyses (changing the initial total cholesterol and the initial SBP). Using the
22 combined pioglitazone/metformin tablet was cheaper than giving these separately (saving
23 approximately £60 per year) and it is likely if this combined tablet was given then pioglitazone
24 would be cost effective. Only one study¹³³ was available comparing pioglitazone to
25 rosiglitazone which showed pioglitazone to have a considerable effect on the TC:HDL ratio (-
26 1.08 compared to rosiglitazone). This treatment effect appears to have been driving the
27 results of pioglitazone. When only treatment effects on HbA1c were taken into account
28 pioglitazone was dominated by human insulin (table C52). The relative risks for heart failure
29 could not be incorporated into the UKPDS as inputs, and a sensitivity analysis was carried
30 out by raising the initial SBP levels of people on glitazones (150 mm/Hg compared to 140
31 mm/Hg for other treatments). Both pioglitazone and rosiglitazone were dominated by human
32 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	Glargine	Exenatide	Glargine	Exenatide	Glargine
Exenatide vs glargine	4.80	4.9	4.80	4.79		
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

1

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

2

Table C55 Calculations for change in TC:HDL – upper differences

Upper	Baseline		Endpoint		Difference	
	Exenatide	Glargine	Exenatide	Glargine	Exenatide	Glargine
Exenatide vs 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

1

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	

2

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)

1

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

2

3

4 **Appendix D: The cost-effectiveness of**

5 **treating to target compared to a fixed-dose**

6 **statin in patients with Type 2 diabetes**

7 **Introduction**

8 There were no published studies found considering the cost effectiveness of treatment using
 9 statins to pre-specified cholesterol level targets in patients with Type 2 diabetes. A denovo

1 model was built in to estimate the cost per QALY of titrating using pre-specified targets to a
2 maximum dose, compared with a fixed-dose treatment strategy using simvastatin 40 mg.
3 Two separate models were constructed for adults with Type 2 diabetes with prior or no prior
4 cardiovascular (CV) event/MI. The model takes a UK NHS costing and healthcare
5 perspective.

6 **Model assumptions**

7 **Treatment strategies**

8 The model compared five different strategies. The first one was a fixed-dose treatment
9 strategy. Patients are given simvastatin 40 mg and there is no further titration and no targets
10 are measured. We modelled four titration strategies using targets of 5 or 4 mmol/l total
11 cholesterol (TC), and using both one- and two-step titration strategies. In the one-step
12 treatment strategy, the model assumes that patients not reaching target on simvastatin 40
13 mg are then treated with the higher intensity simvastatin 80 mg with no further measurement
14 against target, and no further dose increase to follow. In the two-step model, patients not
15 reaching target on simvastatin 80 mg are assumed to be treated with atorvastatin 80 mg with
16 no further measurement against target, and no further dose increase to follow. Each increase
17 in dose is assumed to be preceded by a GP consultation and blood test.

18 **Patient population**

19 The population is defined with an initial distribution of TC levels corresponding to results from
20 The Health Improvement Network (THIN) database (see table D1). The average age of these
21 patients is 65 years and the average initial TC level is 6.0 mmol/l. This distribution was
22 assumed to be the average across people with prior or no prior cardiovascular disease
23 (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)

1

2 Treatment effects

3 We estimated the reduction in CV risk associated with each of the five treatment strategies
4 for the two population groups using a two-stage process.

5 Cholesterol reduction and statin use

6 First, we estimated the proportions of patients who would be expected to achieve the defined
7 TC targets of 4 and 5 mmol/l. The percentage reductions in TC associated with different
8 doses of simvastatin and atorvastatin were taken from the STELLAR trial (Jones PH,
9 Hunninghake DB, Ferdinand KC et al. 2004) (see table D1) in which 50% of the randomised
10 population had Type 1 and Type 2 diabetes.

- 1 This data was combined with the initial cholesterol distributions in table D1 to estimate the
- 2 proportion of patients achieving the target TC levels, table D3 for patients with diabetes and
- 3 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

4

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)

5

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)

6

- 7 These estimates then allow us to predict the proportion of patients who would be treated with
- 8 each drug and dose under the five strategies: Tables D6 and D7 show these results for
- 9 diabetic patients without and with prior CVD respectively. With the fixed-dose strategy, all

1 patients would be treated with simvastatin 40 mg. With one-step titration to a TC target of 5
 2 mmol/l, 24–26% of patients are expected to require the higher dose of simvastatin 80 mg.
 3 This rises to 60–65% if a lower target of 4 mmol/l is used. Introducing a second titration step,
 4 11–12% of patients would need atorvastatin 80 mg to reach the 5 mol/l target, and 50–56%
 5 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

6

7 **Reduction in cardiovascular risk**

8 We then estimated the reduction in CVD risk associated with the predicted use of each statin
 9 in tables D6 and D7 using equations derived from a meta-analysis by Law et al. 2003. The
 10 equations were applied in a two-stage procedure.

11 Firstly, the cholesterol lowering effects using both simvastatin and atorvastatin were
 12 measured using the following equations:

13 Reduction in TC by drug and dosage is given by:

14 = $-1.123 + 0.238TC + 0.384 \ln(\text{dose of simvastatin})$

15 = $-2.205 + 0.419TC + 0.475 \ln(\text{dose of atorvastatin})$

16 Then the relative risks of CVD/CVA events were estimated using the following equations
 17 respectively:

18 RR of CHD is given by:

19 RR of CHD per 1.2 mmol/l reduction in TC = $-0.745 \ln(\text{Age}) + 3.47$, so RR of CHD = $(-0.745 \ln(\text{Age}) + 3.47)^{\text{(Reduction in TC/1.2)}}$
 20

21 Where age = mean age of patient cohort in years RR of cerebrovascular disease/PAD is given
 22 by: RR of PAD/cerebrovascular disease per 1.2 mmol/l reduction in TC = 0.94, so
 23 RR = $0.94^{\text{(Reduction in TC/1.2)}}$

1 The resulting RR estimates from statin treatment effect for 65-year-old patient with a starting
 2 TC of 6 mmol/l (the mean for the diabetic populations in table D1) are presented in table D5
 3 by drug and dose. Only CHD and not cerebrovascular disease/PAD risk is age dependant as
 4 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

5

6 **Markov model assumptions**

7 A Markov model was built to estimate the impact of statin treatment on CVD events (defined
 8 as MI, stroke, PAD, TIA, heart failure, revascularisation, unstable angina, CV death, and
 9 death from other causes). The Markov model is a lifetime model which uses transitional
 10 probabilities (annual cycles) to estimate the number of CVD events from the initiation of
 11 statin treatment until death, or until the patient reaches an age of 100, whichever is the
 12 earlier of these two events. Using health state utility values assigned to each of the above
 13 health states, the model then calculates QALY for each of the modelled treatment strategies.
 14 The model also estimates the cost of each strategy, including healthcare costs of CVD as
 15 well as statin treatment.

16 **Transition probabilities**

17 **Primary prevention**

18 Baseline probabilities for the primary prevention model were taken from the statins
 19 technology appraisal (TA) 94. Data on PAD, heart failure and revascularisation were taken
 20 from Miejer et al. 1998, ONS 2000, and Johansen 1998 respectively. The baseline risk of
 21 CVD events was assumed to be 2% per year for a 65-year-old person without diabetes or
 22 prior CVD.

23 The GDG estimated that the risk of CVD events in people without existing CVD was between
 24 twofold to fourfold for diabetics compared with non-diabetics. For the purpose of this model
 25 we used an estimate of 2.5 fold and tested this assumption in a sensitivity analysis.

26 The model assumes the risk of CVD increases with age. The NICE statins TA 94 used data
 27 from the Health Survey for England 1998, and estimated a mathematical relationship
 28 between age and risk increase. For all males (all males, non-diabetic males and diabetic
 29 males) a linear relationship was the best-fitting mathematical model and the slope of the
 30 linear relationship was 0.0003. This represents an increase in the one year risk of 0.03% for
 31 a one year increase in age. For all females and non-diabetic females the best mathematical
 32 relationship was also found to be linear but the model fit was not as good as for males. No
 33 clear relationship between age and risk was found for diabetic females. The rate of increase
 34 was assumed to be the same for diabetic females as for all females, in the same way that the
 35 rate of increase was the same for all three male groups. The rate of increase used in the
 36 model is therefore 0.0002 which was the average between males and females. Table D2,
 37 appendix D1, shows the annual transition probabilities without treatment. Once patients had
 38 a first event, recurrent events were modelled as in the secondary prevention population.

1 **Secondary prevention**

2 Baseline annual transitional probabilities of CVD events following a previous MI are
3 estimated from data reported in the TNT, LaRosa et al. 2005 and IDEAL, Pedersen et al.
4 2005 clinical trials which were done in non-diabetic populations. These transitional
5 probabilities were then apportioned across patient age bands using data reported in the
6 literature. Kaplan 2002, Bots et al. 1997, ONS 2000, Miejer et al. 1998.

7 Data on patients with Type 2 diabetes was not readily available. We used evidence from
8 literature which suggests that diabetic patients have at least 1.5–2.6 fold increase in the risk
9 of CVD events compared with non-diabetics. The evidence was taken from the statin trials
10 CARE study Sacks et al. 1996, LIPID study 1998, and the 4S study Pyorala et al. 1997 and
11 one observational study from Finland by Haffner et al. 1998. These studies demonstrated
12 that there is increased risk of morbidity and mortality compared with the general population
13 or patients with prior CVD. For the purposes of this model, we have increased the observed
14 baseline risks in people after MI by factor of 1.9 which is the average of the risks reported
15 across the four studies mentioned above. These transitional probabilities are presented in
16 table D3, appendix D1.

17 Non-CVD mortality is modelled by using the age adjusted ‘all cause mortality’ rates from
18 Government Actuarial Department (GAD) 2006, and adjusting for CVD mortality. It is
19 assumed that diabetics have the same risk of dying from other causes as the general
20 population (table D5, appendix D1).

21 **Modelled costs**

22 Statin drug costs are taken from prices quoted on March 26 2008 by the Prescription Pricing
23 Authority (Drug Tariff 2008). Costs of treatment for CVD events are taken from published
24 literature (table D7, appendix D1).

25 Each uptitration in the target treatment arm of the model is assumed to be preceded by a
26 standard (approximately 10 minute) GP consultation and a blood test (assumed total cost per
27 uptitration of £26). Unit costs of GP visits and blood test are taken from literature Curtis et al.
28 2007 (table D8, appendix D1). In line with current NICE guidance (NICE technical manual
29 2006), an annual discount rate of 3.5% has been applied to future costs in the Markov model

30 **Quality of life (utility)**

31 In order for the model to estimate QALYs, each of the modelled CVD health states has been
32 assigned an assumed health-related quality of life utility score using previously published
33 values (table D9, appendix D1). Utility has been adjusted for age using data from the Health
34 Survey of England 1996 (table D10, appendix D1). Future QALY values are discounted at
35 3.5% per annum as recommended by NICE, (NICE technical manual 2006).

36 **Cost-effectiveness analysis**

37 The results of the cost-effectiveness analysis are summarised using an ICER – comparing
38 each strategy with the next most expensive, non-dominated strategy.

39 **Sensitivity analysis**

40 In addition to the deterministic base cases, which use the mean values of the included model
41 variables, the sensitivity of the base case ICER results to a range of univariate deterministic
42 sensitivity analyses have been tested.

1 **Base case results**

2 The base case results are presented for the hypothetical cohort with a mean age of 65 years
 3 and a mean TC level of 6 mmol/l and CVD risk of 5% pa before treatment. Results are
 4 presented separately for Type 2 diabetes patients with and without prior CVD. The fixed-
 5 dose treatment strategy is the strategy which is least costly, but also generates the smallest
 6 number of QALYs. As expected, the two-step titration strategies are more costly than the
 7 one-step titration strategies and having a target of 4 mmol/l is more expensive than a target
 8 of 5 mmol/l in both models, see figures D1 and D2. Results are interpreted using the
 9 £20,000/QALY threshold.

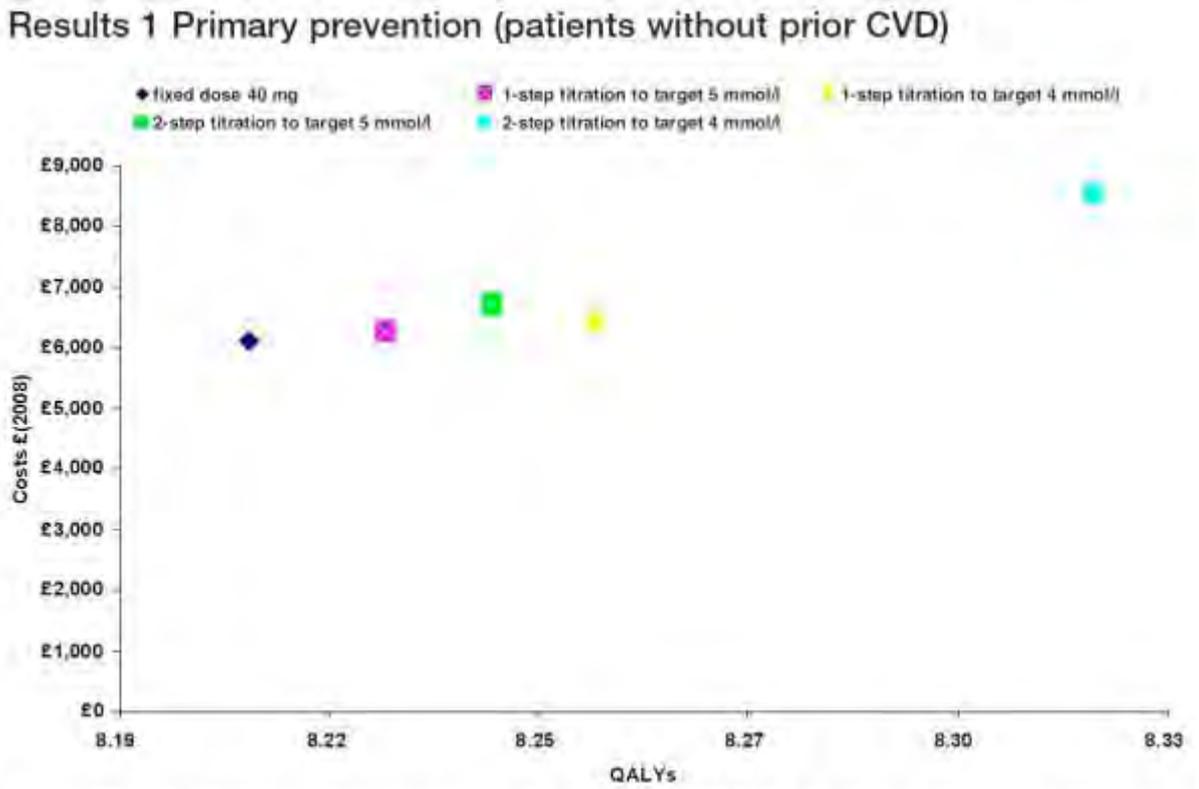


Figure D1 Cost-effectiveness plane, showing the costs and QALYs for the five strategies in patients with Type 2 diabetes without prior CVD

10

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/l	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

11

1 The model indicates that the one-step target four treatment strategy has extended
 2 dominance over the one-step target five strategy and has an ICER of about £7,878/QALY
 3 compared to the fixed-dose strategy. The two-step titration to 5 mmol strategy is dominated
 4 by the one-step 4 mmol strategy (that is, it costs more and produces less QALYs) and so
 5 both 5 mmol target strategies are excluded due to dominance. The ICER of the two-step
 6 target 4 mmol/l compared to the one-step target 4 mmol/l strategy is £30,321 and is therefore
 7 not cost-effective using the £20,000/QALY thresholds. Thus for primary prevention the most
 8 cost-effective strategy in patients with Type 2 diabetes is one-step titration to a target of 4
 9 mmol/l with an estimated ICER of £7,878/QALY compared to the fixed-dose strategy for 65-
 10 year-old patients with an initial CVD risk of 5% pa.

Results 2 Secondary prevention (patients with prior CVD)

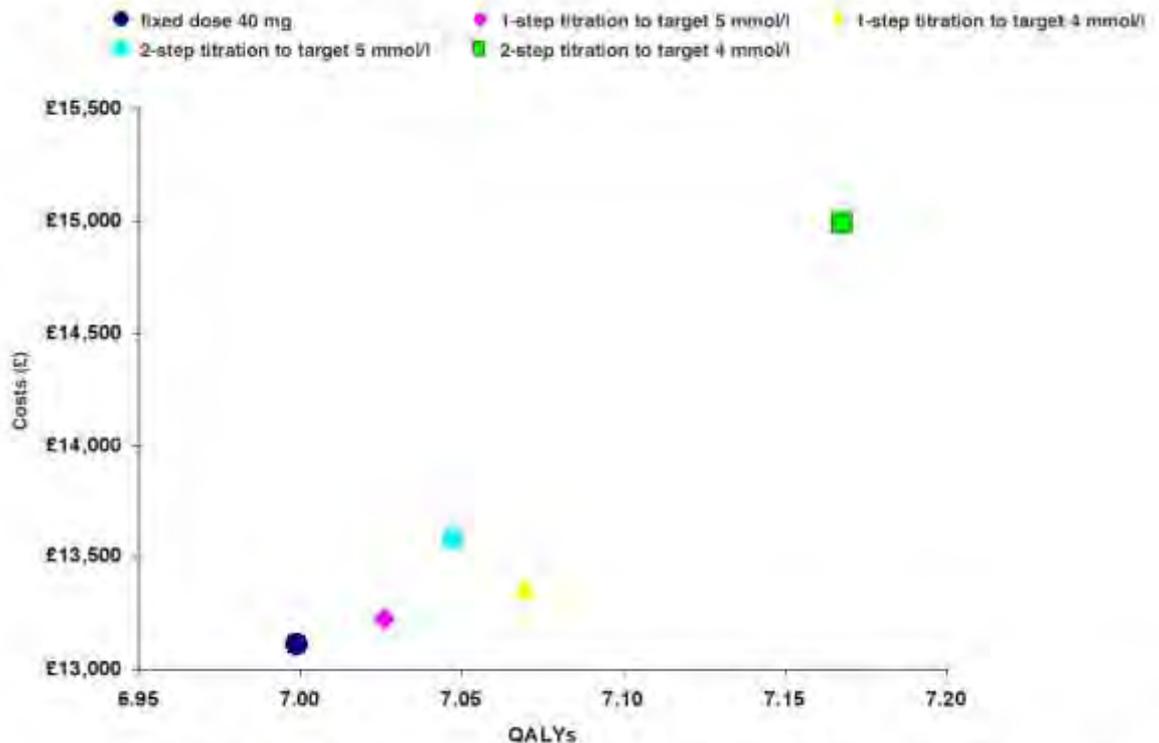


Figure D2 Cost-effectiveness plane, showing the costs and QALYs for the five strategies in patients with Type 2 diabetes and prior CVD

11

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

1
 2 The model indicates that the one-step target 4 treatment strategy has extended dominance
 3 over the one-step target 5 strategy and has an ICER of about £3,534 per QALY compared to
 4 the fixed-dose strategy. The two-step titration to 5 mmol strategy is dominated by the one-
 5 step 4 mmol strategy (that is, it costs more and produces less QALYs) and so both 5 mmol
 6 target strategies are excluded due to dominance. The ICER of the two-step target 4 mmol/l
 7 compared to the one-step target 4 mmol/l strategy is £16,482/QALY and is therefore cost-
 8 effective using the £20,000/QALY threshold. Thus for secondary prevention two-step target 4
 9 mmol/l is the most cost-effective treatment strategy using a threshold of £20,000 per QALY
 10 with an estimated ICER of about £16,482/QALY.

11 Univariate sensitivity analyses

12 Sensitivity analysis: RR of CVD events for diabetic population compared to non-diabetic
 13 population with/without prior CVD.

14 The base model assumed that people with Type 2 diabetes without prior CVD have a 2.5 fold
 15 increase in risk of CVD/CVA events compared to non-diabetics. This assumption was tested
 16 using the range provided by the GDG of between 2–4 fold. The ICER ranged between
 17 £9,188 to £6,110 when a risk of 2 and 4 were used respectively, when one-step titration to a
 18 target of 4 mmol/l is compared with fixed-dose strategy.

19 In patients with prior CVD in the base case, we assumed the risk of developing CVD events
 20 in patients with Type 2 diabetes compared with non-diabetics was 1.9 fold. Evidence from
 21 literature suggested the risk could be between 1.5 to 2.6 fold. We used these ranges in
 22 sensitivity analysis and the ICER for the two-step titration to a target of 4 mmol/l compared
 23 with one-step titration to a target of 4 mmol/l ranged from £21,500 to £11,670/QALY. These
 24 results suggest that risk of developing CVD events has to be at least 1.6 fold for two-step
 25 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

26

1 **Sensitivity analysis: RR of non-CVD mortality for diabetic** 2 **population compared with non-diabetic population** 3 **with/without prior CVD**

4 The base model assumed that people with Type 2 diabetes with or without prior CVD have
5 the same risk of dying from non-CVD causes compared with the general population. This
6 assumption was tested by assuming that the risk of non-CVD mortality is twofold compared
7 to the general population. For primary prevention the ICER slightly increased to
8 £9,480/QALY when one-step titration to a target of 4 mmol/l is compared with fixed-dose
9 strategy. In patients with prior CVD the ICER for the two-step titration to a target of 4 mmol/l
10 compared with one- step titration to a target of 4 mmol/l also increased to £19,335/QALY.
11 The base case conclusions are not changed by this sensitivity analysis.

12 **Sensitivity analysis: costs of CV events**

13 Increasing the costs of treatments for CV events will improve the cost-effectiveness of
14 interventions for CVD all else being equal. Using the upper range of the assumed base case
15 costs of CVD treatments (table D7, appendix D1) only marginally lowers the incremental cost
16 per QALY. For primary prevention the ICERs remained below £9,000/QALY when one-step
17 titration to a target of 4 mmol/l is compared with fixed-dose strategy. In patients with prior
18 CVD the ICERs for the two-step titration to a target of 4 mmol/l compared with one-step
19 titration to a target of 4 mmol/l remained below £18,000/QALY. Thus, the base case model
20 results are insensitive to the CVD event cost assumptions.

21 **Sensitivity analysis: health state utilities**

22 The health state utilities used in the model were obtained from literature. We used the ranges
23 provided for the upper and lower limit of utility scores. Where the ranges were not provided
24 we varied the mean values by 20% in sensitivity analyses. For primary prevention the ICERs
25 ranged between £7,600 to £8,400/QALY when one-step titration to a target of 4 mmol/l is
26 compared with fixed-dose strategy. In patients with prior CVD the ICERs for the two-step
27 titration to a target of 4 mmol/l compared with one-step titration to a target of 4 mmol/l ranged
28 between

29 £16–19,000/QALY. This is still under the £20,000 per QALY threshold. As such, although the
30 modelled ICERs are relatively sensitive to changes in health state utility values, our
31 sensitivity analyses indicates that the base case conclusion regarding cost-effectiveness are
32 not affected by changes in health state utility values.

33 **Sensitivity analyses: starting age**

34 The sensitivity of the ICERs was also tested against changes in the assumed starting age of
35 the patient cohort. We varied the starting age of the starting cohort from 45 years to 75
36 years, assuming fixed initial CVD risk. For primary prevention the ICER ranges from £6,632
37 to

38 £10,280/QALY when one-step titration to a target of 4 mmol/l is compared with fixed-dose
39 strategy. In patients with prior CVD the ICER for the two-step titration to a target of 4 mmol/l
40 compared with one-step titration to a target of 4 mmol/l varies from £16,400 to
41 £18,200/QALY. In all cases ICERs were increasing by age. The ICERs are thus relatively
42 stable to changes in patient age with a trend to slightly higher ICERs for older patient groups.
43 The conclusions of the base case analyses are however unchanged by this sensitivity
44 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

1

2 Sensitivity analyses: starting CVD risk

3 The above analysis does not take account of the relationship between CVD risk and age. In
 4 our base case primary prevention model, we assume an initial CVD risk of 2% per year in the
 5 absence of diabetes (hence 5% per year with diabetes). This is appropriate for an average
 6 cohort aged 65, but the levels of risk is generally higher in older patients and lower in
 7 younger patients, Hippisley-Cox et al. 2007. For diabetic patients with a baseline risk of CVD
 8 events below 1.5% per year, titration is no longer cost-effective at the £20,000 per QALY
 9 level for primary prevention. Conversely, two-stage titration to a target of 4 mmol/l becomes
 10 cost-effective for primary prevention in people with diabetes if their baseline CVD is greater
 11 than about 10.5% per year.

12 Sensitivity analysis, discounting cost and health benefits

13 NICE recommends that both future costs and future benefits are discounted at a rate of 3.5%
 14 per annum in order to allow for societal time preference. We tested the sensitivity of the base
 15 case ICERs to the discounting assumption using rates of 0% and 6%. Using these
 16 assumptions, for primary prevention the ICER ranges from £6,514 to £9,074/QALY when
 17 one-step titration to a target of 4 mmol/l is compared with fixed-dose strategy. In patients with
 18 prior CVD the ICER for the two-step titration to a target of 4 mmol/l compared with one-step
 19 titration to a target of 4 mmol/l varies from £13,870 to £18,690/QALY. The higher the
 20 discount rate, the higher the ICER, however the base case cost-effectiveness conclusions
 21 are not affected by this sensitivity analysis.

22 In summary, the sensitivity analyses have indicated that the base case ICERs are relatively
 23 stable to changes in input variable values. In primary prevention one-step titration is cost-
 24 effective when compared with a fixed-dose strategy at levels of risk usual for most diabetic
 25 patients. In secondary prevention, two-step titration appears cost-effective for most diabetic
 26 patients, although the ICER rises above £20,000 per QALY if the RR of developing CVD in
 27 patients with diabetes compared with those without diabetes is below 1.5.

28 Discussion and conclusion

29 Our model indicates that for primary prevention one-step titration to a target of 4 mmol/l is the
 30 most cost-effective strategy when compared with a fixed-dose strategy for most patients with
 31 Type 2 diabetes. The estimated ICER is about £7,878/QALY. Our model indicates that it is
 32 not cost-effective to try to get more patients to target by adding atorvastatin 80 mg because
 33 the ICER then increases to over £30,000 per QALY. These results were stable in sensitivity
 34 analysis, except for patients at unusually low or high levels of CVD risk. Titration was not
 35 cost-effective for primary prevention in diabetic patients with an initial CVD risk below 1.5%
 36 per year, whereas two-step titration (including atorvastatin 80 mg) to a target of 4 mmol/l
 37 became cost-effective above an initial CVD risk of 10.5% per year.

- 1 In the secondary prevention model, for patients with Type 2 diabetes who had a prior CVD
 2 event, a two-step titration to a target of 4 mmol/l is the most cost-effective strategy compared
 3 to one-step titration to a target of 4 mmol/l with an estimated ICER of about £16,482/QALY.
- 4 This result was stable in sensitivity analysis. The model was slightly sensitive to assumption
 5 about the RR of CVD disease between diabetics compared to non-diabetics.
- 6 In both models (for people with prior or no prior CVD) both treatment strategies using a target
 7 of 5 mmol/l are either extendedly dominated or dominated by the one-step titration strategy
 8 using a target of 4 mmol/l.
- 9 Our model results for primary prevention in people with diabetes are consistent with the
 10 model results for the Lipid guideline which demonstrated that one-step titration is cost-
 11 effective in secondary prevention patients without diabetes. Haffner et al. 1998 demonstrated
 12 that patients without diabetes but with prior CVD will benefit the same as patients with
 13 diabetes but without a prior CVD. In the Lipids model a two-step titration was not cost-
 14 effective with ICERs well above £60,000/QALY. Our secondary prevention model differs from
 15 the Lipids model in that people with diabetes are assumed to have an almost twofold
 16 increase in risk of CVD compared with non-diabetics as described in the methods section. If
 17 this risk is assumed to be less than 1.5 fold, then our model results will conclude the same as
 18 the Lipids guideline model, suggesting that two-step titration will not be cost-effective.
- 19 The Law and Wald equations used in the analysis estimated treatment benefit from
 20 cholesterol reduction in the non-diabetic population. We assumed the benefits to be the
 21 same in the diabetic population. This might not necessarily be the case, and people with
 22 diabetes may tend to have higher absolute benefit than the non-diabetic population. This will
 23 make our model conservative as it will underestimate treatment benefit.
- 24 Economic models are by definition a simplification of the real world. There is a lack of long-
 25 term clinical trials comparing titration strategies with fixed lower-intensity statin treatment
 26 strategies. As such, our model is predicated on the assumption that reductions in CVD
 27 events, resulting from reductions in TC levels from statin treatment are adequately
 28 represented by the Law and Wald equations. These equations are themselves predicated on
 29 the Framingham risk equations. The equations reflect the fact that higher intensity statins
 30 lead to greater reductions in cholesterol. RR reductions are greater for patients with a higher
 31 starting cholesterol level and for younger patients. Our base case model assumes a
 32 hypothetical cohort of patients with average starting TC of 6 mmol/l and average age of 65
 33 years.
- 34 The guideline group acknowledged that the results of the Law et al. 2003 meta-analysis
 35 overestimate reduction in cholesterol and CVD events in comparison to the longer-term trial
 36 results described by the Cholesterol Trialists Collaboration, and may yield over-optimistic
 37 estimates of treatment effects. However, it is reassuring that the cholesterol reduction
 38 estimates from the Law and Wald equations yielded similar answers to those observed in the
 39 STELLAR trial, Jones et al. 2004. The external validity of our model should be tested if and
 40 when long- term outcome data becomes available from trials comparing a fixed-dose
 41 treatment strategy with a target driven strategy.
- 42 There is also lack of good long-term safety and utility data for statin use. Although a number
 43 of safety studies and a meta-analysis on statin use were identified, the GDG felt the
 44 recruitment in these trials made it difficult to demonstrate any significant difference in side
 45 effects, since only those who could tolerate statins were included in the trials. As a result the
 46 trials reported that there was no significant difference between higher intensity and lower
 47 intensity statins with regards to major side effects, though there is a trend of greater 'minor'
 48 adverse events with increasing dose. There is also lack of health-related quality of life utility
 49 data, with which to estimate quality of life reductions resulting from adverse events
 50 associated with higher intensity statin treatment. Consequently, and in line with previously

1 published cost-effectiveness analyses in hyperlipidemia statins TA 94, our model assumes
2 no adverse events from treatment with higher intensity statins.

3 Another limitation of the model arises because of the nature of Markov models. These
4 assume that the probability of an individual moving to any given health state in one time
5 period depends only on their current health state (there is no 'memory' in the model). Thus
6 the probability of HF for a patient whose last CVD event was an MI is assumed to be the
7 same irrespective of how many CVD events they have previously had. Similarly, a patient's
8 health outcome and healthcare costs incurred are assumed to depend only on their current
9 health state. These assumptions are unlikely to be strictly true, and will tend to underestimate
10 overall costs and overestimate health outcomes for the cohort. Thus, interventions that
11 prevent more CVD events will tend to appear rather less cost-effective than they may be in
12 reality. So the model is conservative in this respect.

13 In conclusion, for primary prevention one-step titration to 4 mmol/l compared to fixed-dose
14 strategy is cost-effective and in secondary prevention a two-step titration strategy compared
15 to one-step titration is cost-effective in patients with Type 2 diabetes. These results were
16 relatively robust to sensitivity analyses.

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- 21

1 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	0.58	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.

2

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

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continued

Table D1.3 Baseline annual transition probabilities, in diabetic patients with stable coronary artery disease – continued						
<i>Estimated annual rates by age – assuming mean age of 65 in cohorts</i>						
<i>Post MI year 2 onwards to</i>						
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
<i>From stroke to</i>						
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
<i>Post SK to SK</i>						
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
<i>From TIA to</i>						
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

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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 1.8 multiplier to reflect the increased risk of CVD seen in diabetic patients compared to non-diabetics						

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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

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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				
	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	0.908
7	0.341	0.413	0.484	0.554	0.623	0.689	0.904

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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

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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	Kamon 2005
PAD (subsequent)	264	200	400	Assumption same as TIA
Heart failure	2,303	1,255	3,434	NHS ref cost 2007

continued.

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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

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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

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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	Lavander 1998
Post TIA	0.90	0.85	1.00	Assumption
PAD	0.90	0.86	0.98	Karnon 2005

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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

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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

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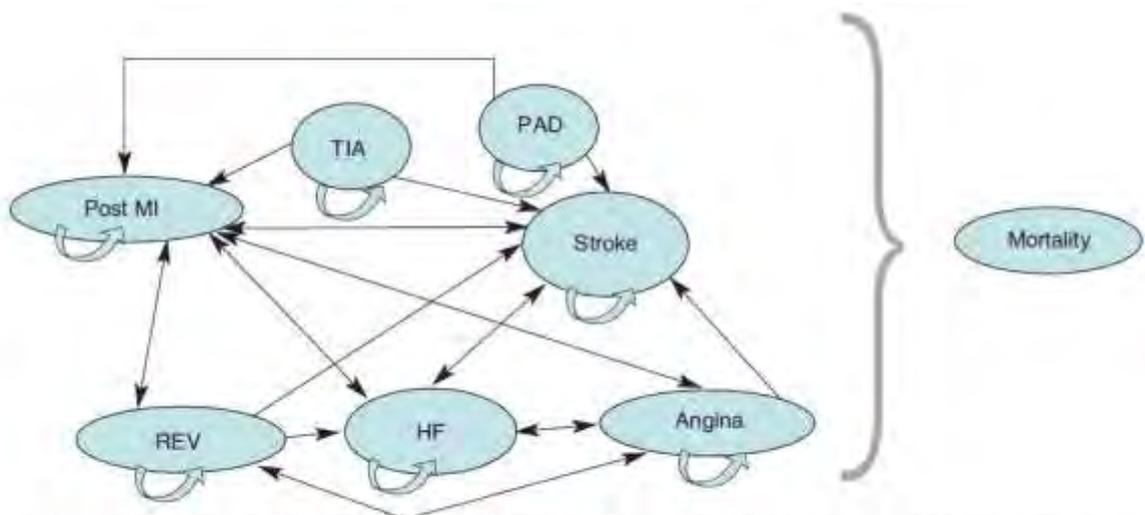


Figure D1.1 Model structure for cost-effectiveness of lower intensity statins versus higher intensity in the secondary prevention of CVD (used for the high low dose and treat to target models)

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