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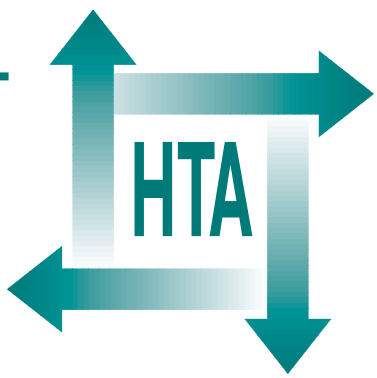
Rapid review

The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review

J Chilcott
J Wight
M Lloyd Jones
P Tappenden

Health Technology Assessment
NHS R&D HTA Programme



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The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review

J Chilcott*
J Wight
M Lloyd Jones
P Tappenden

University of Sheffield School of Health and Related Research, UK

* Corresponding author

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The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Rapid reviews are completed in a limited time to inform the appraisal and guideline development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidelines produced by NICE are informed by a wide range of sources.

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Contents

List of abbreviations

ACE	angiotensin-converting enzyme
1,5-AG	1,5-anhydro-glucitol*
AMI	acute myocardial infarction
BMI	body mass index*
CCTR	Cochrane Controlled Trials Register
CDSR	Cochrane Database of Systematic Review
CI	confidence interval
CPK	creatine phosphokinase
CPMP	Committee for Proprietary Medicinal Products
CPR	C-reactive protein (assumed abbreviation; see page 26)
CRIB	Current Research in Britain
CVD	cardiovascular disease
DARE	Database of Abstracts of Reviews of Effectiveness
DARTS	Diabetes Audit and Research in Tayside Scotland
DCCT	Diabetes Control and Complications Trial
DDD	defined daily dose
DR-FBG	decrease rating of fasting blood glucose
ECG	electrocardiograph
ESRD	end-stage renal disease
FBG	fasting blood glucose
FDA	Food and Drug Administration (USA)
FPG	fasting plasma glucose
GIR-BG	global improvement rating of blood glucose*
GP	general practitioner
GPRD	General Practice Research Database
HbA_{1C}	glycosylated (glycated) haemoglobin
HDL	high-density lipoprotein
HGP	hepatic glucose production*
IDDM	insulin-dependent diabetes mellitus
LDL	low-density lipoprotein
LEA	lower extremity amputation
LS	least squares
LYG	life-year gained
MRC	Medical Research Council
NA	not applicable*
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Clinical Excellence
NIDDM	non-insulin-dependent diabetes mellitus
NIH	National Institutes of Health (USA)
NRR	National Research Register
OGTT	oral glucose tolerance test*
OHE HEED	Office of Health Economics Health Economics Database
PD-FBG	percentage of decrease in fasting blood glucose
PPA	Prescription Pricing Authority
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REP	Rochester Epidemiology Project*
SCI	Science Citation Index
SD	standard deviation*
SE	standard error
SF-36	Short Form with 36 Items
TGD	total glucose disposal*
UKPDS	United Kingdom Prospective Diabetes Study
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy*

* Used only in appendices or tables

Executive summary

Background

Type 2 diabetes mellitus is a chronic metabolic disorder that results from defects in insulin secretion and action. The resulting build-up of glucose in the blood can cause a range of diabetic complications, including macrovascular disease (e.g. coronary, cerebral and peripheral vascular disease) and microvascular disease (e.g. retinopathy, nephropathy and neuropathies). People with diabetes are at particularly high risk of cardiovascular disease. This increased risk is related, in part, to hyperglycaemia, and also to hypertension and commonly associated conditions such as adverse lipid profiles.

Evidence from the United Kingdom Prospective Diabetes Study (UKPDS) has shown that maintaining good control of blood glucose reduces the incidence of diabetic complications. It is thought that approximately 1 million people in England and Wales suffer from diabetes, the majority of whom suffer from type 2 diabetes.

Clinical practice guidelines recommend a 'step-up' policy of treatment for type 2 diabetes, starting with diet and lifestyle advice, adding oral blood glucose-lowering agents (principally metformin and the sulphonylureas) and eventually using insulin, if targets are not achieved. Type 2 diabetes tends to be progressive, so therapies may be initially effective but subsequently control is lost. Pioglitazone is one of a new class of oral glucose-lowering drugs, the peroxisome proliferator-activated receptor-gamma agonists, which also include rosiglitazone. These new drugs have a mode of action that differs from that of existing medications.

Objectives

This review was performed to evaluate the use of pioglitazone in its licensed indication, in combination with metformin or sulphonylurea. For completeness, the review also considered its use in combination with insulin and as monotherapy (unlicensed indications).

Methods

A systematic review of the literature, involving a range of databases, was performed to identify all papers relating to pioglitazone, as well as economic or model-based assessments focusing on diabetes mellitus. Full details are described in the main report.

Results

The results of unpublished company-sponsored clinical trials were submitted in confidence to the National Institute for Clinical Excellence (NICE) by Takeda UK Ltd. Information from these studies was included in the version of the report that was sent to the Appraisals Committee, but is not reported here.

Number and quality of studies

Fifteen studies met the inclusion criteria, but full reports were available for only five. Of the 15 studies, nine dealt with pioglitazone alone or in combination with a strict antidiabetic diet. The remainder dealt with pioglitazone in combination with metformin, insulin or a sulphonylurea.

Clinical effectiveness

In both monotherapy and combination therapy, pioglitazone appeared to be effective in reducing blood glucose in patients with poorly controlled type 2 diabetes. However, the US Food and Drug Administration review observed that, when pioglitazone was used as monotherapy, those patients who were changed from another oral antidiabetic agent (metformin or sulphonylurea) to pioglitazone did not achieve the same level of glycaemic control as they had previously experienced. When used in combination with metformin, sulphonylurea or insulin, pioglitazone led to a significant fall in blood glucose and glycosylated haemoglobin (HbA_{1C}) at doses of 15 or 30 mg daily, with a greater effect seen at the higher dose. In addition, both monotherapy and combination therapy studies have demonstrated a fall in triglyceride levels and an increase in high-density lipoprotein cholesterol levels when doses of 30 mg or more of pioglitazone were used.

Pioglitazone treatment is associated with significant weight gain in the short term, which appears to be greater than that seen with other thiazolidinediones. This gain in weight also appears to be greater than that seen in the UKPDS with sulphonylurea or insulin treatment, which in turn was greater than that seen with metformin treatment. This weight gain continues, albeit at a lesser rate, for more than a year. Whether or not weight reaches a plateau after this point cannot be stated with certainty without longer-term follow-up.

There is no direct evidence available on the effect of pioglitazone on diabetic complications, including cardiovascular mortality. However, as the UKPDS study has shown that improved glycaemic control reduces the incidence of microvascular complications, it would be reasonable to expect that this beneficial effect would hold true if a similar improvement in metabolic control was achieved using pioglitazone. Changes in lipid levels could be expected to lead to a reduction in cardiovascular disease risk. However, many studies found that treatment was also associated with significant and progressive weight gain, which would have an adverse effect on the risk of coronary artery disease.

There is also no direct evidence that, for patients whose diabetes is poorly controlled by metformin or sulphonylurea, the addition of pioglitazone is any more effective in improving glycaemic control than moving to a metformin–sulphonylurea combination or starting insulin therapy.

Health economics

Takeda UK Ltd submitted data from a confidential economic model to NICE. Information about this study was included in the version of the report that was sent to the Appraisals Committee, but cannot be reported here.

Conclusions

The evidence suggests that, compared with placebo, pioglitazone is effective in reducing blood glucose in patients with inadequate glycaemic control, both when used as monotherapy and in combination with existing licensed therapies. However, there is no firm evidence to indicate that pioglitazone is more effective than any other antidiabetic agent, particularly when used in combination. Additionally, it is unclear how pioglitazone therapy affects the incidence of microvascular and cardiovascular complications.

Recommendations for research

Evidence is needed regarding:

1. the clinical effectiveness and cost-effectiveness of pioglitazone in combination therapy compared with other possible combination therapies (e.g. rosiglitazone in combination, or sulphonylurea plus metformin, or insulin with or without an oral antidiabetic agent)
2. whether or not the risk of microvascular complications is reduced by the improved glycaemic control achieved using pioglitazone
3. whether or not the risk of cardiovascular events is reduced by the changes in lipid levels achieved using pioglitazone.

Chapter 1

Aim of the review

The overall aim of this review is to evaluate the incremental clinical effectiveness and cost-effectiveness of pioglitazone in combination with either metformin or sulphonylurea in the treatment of patients with type 2 diabetes mellitus, as compared with established treatments. For completeness, the use of pioglitazone as monotherapy and in combination with insulin are also considered. Separate objectives are:

1. to evaluate the relative clinical effectiveness, in terms of glycaemic control
2. to estimate the relative clinical effectiveness, in terms of prevention of the longer-term complications of diabetes mellitus
3. to estimate the relative effect, if any, on overall mortality and quality-of-life-adjusted mortality
4. to evaluate the side-effect profile
5. to estimate the incremental cost-effectiveness of pioglitazone in comparison with conventional therapy
6. to estimate the possible overall cost in England and Wales.

Chapter 2
Background

Description of underlying health problem

With the permission of the National Institute for Clinical Excellence (NICE), this section has been based on Lord and co-workers' report[1] on rosiglitazone published by NICE, with only such minor changes as are necessitated by the context.

Definition of diabetes mellitus

Diabetes mellitus is a group of chronic disorders characterised by elevated glucose levels in the blood (hyperglycaemia). Glucose is the main source of energy for human cells. It is derived from carbohydrates in the diet and passes by the blood stream to the tissues for use as an energy source, or for storage in muscle and the liver. Stored glucose, together with glucose made from foods, can also be recycled through the liver and released into the blood for use by the tissues between meals and when fasting.

Diabetes is usually diagnosed by a single high random plasma or blood glucose level together with typical symptoms, or by repeated high random plasma or blood glucose measurements. Marginally elevated glucose levels require the diagnosis to be made based on fasting levels (plasma glucose ≥ 7.0 mmol/l) or after a 75-g oral glucose tolerance test (2-hour plasma glucose ≥ 11.1 mmol/l).

Hyperglycaemia is related to the production and use of a hormone called insulin, which is produced by islet β cells in the pancreas. Insulin helps cells to take up glucose. Diabetes occurs when the pancreas produces too little insulin for the body's needs. Two main **aetiological types** of diabetes have been identified.[2]

- **Type 1 diabetes mellitus** is a condition in which the pancreas makes little or no insulin because the islet β cells have been destroyed through an autoimmune mechanism. The body is then less able to use glucose for energy, and there is a build-up of glucose in the blood.
- **Type 2 diabetes mellitus** is a condition in which the pancreas is unable to produce enough insulin (for reasons unknown) to enable the insulin-dependent tissues to take up glucose. Often, usually in association with excess body weight, the tissues are very insensitive to insulin in people with type 2 diabetes, but the pancreas is unable to produce enough insulin to overcome this insensitivity.

In addition to type 1 and type 2 diabetes, the current WHO classification system includes a number of other aetiological types:

- other specific types
  - genetic defects of islet β cell function
  - genetic defects in insulin action
  - diseases of the exocrine pancreas
  - endocrinopathies
  - drug- or chemical-induced diabetes
  - infections
  - uncommon forms of immune-mediated diabetes
  - other genetic syndromes sometimes associated with diabetes
- gestational diabetes.

Individuals with diabetes mellitus may be further subdivided according to treatment, as follows:

- patients not requiring insulin
- patients who use insulin in order to control blood glucose levels
- patients who require insulin for survival.

The labels 'insulin-dependent diabetes mellitus' (IDDM) and 'non-insulin-dependent diabetes mellitus' (NIDDM) were previously used for type 1 and type 2 disease, respectively. However, because patients with type 2 disease may take injected insulin, these terms are no longer recommended.

Similarly, the terms 'juvenile-onset' and 'adult-onset' diabetes – corresponding to type 1 and type 2 disease, respectively – may be misleading. Although type 1 diabetes usually appears before the age of 40 years, it may occur at any age. The incidence of type 2 diabetes increases with age, but this type is increasingly found in people under the age of 35 years who are from non-European ethnic groups.

This review relates exclusively to the use of the drug pioglitazone in patients with type 2 diabetes.

Symptoms and complications

Individuals with type 2 diabetes sometimes present with the classical symptoms of hyperglycaemia (frequent urination, thirst, weight loss and recurrent infections). More usually it is diagnosed 5–10 years after onset as a result of the development of a complication (e.g. a heart attack or retinopathy), or by testing in high-risk individuals (e.g. obese persons). Occasionally, presentation may be as a result of severe hyperglycaemia, often in conjunction with an infection, leading to an emergency hospital admission with vomiting or lowered consciousness. Severe prolonged hyperglycaemia may lead to hyperosmolar coma, with these patients at risk of hyperviscosity and renal failure.

Hyperglycaemia can cause a range of chronic diabetic complications, including **microvascular** and **macrovascular** damage to various organs. Though partially preventable, these diabetic complications can cause severe morbidity, including visual handicap, kidney failure, angina, myocardial infarction, stroke, foot ulceration and erectile dysfunction. People with diabetes are at particularly high risk of cardiovascular disease (CVD), which is the main cause of their excess mortality. This increased risk appears to be related, in part, to hyperglycaemia, but also to hypertension, adverse lipid profiles and other co-existent risk factors.

The onset of diabetic complications may often precede the appearance of symptoms: by the time they present clinically, over 50% of people with type 2 diabetes already have significant complications.[3] Thus, early diagnosis is very important.

Evidence suggests that maintaining good control of blood glucose levels has beneficial long-term effects. The United Kingdom Prospective Diabetes Study (UKPDS) found that the risk of microvascular complications was reduced by 25% in patients with type 2 diabetes who were randomised to 'intensive' treatment with sulphonylureas or injected insulin, compared with 'conventional' treatment with diet alone ($p = 0.0099$).[4] Overweight patients randomised to 'intensive' treatment with metformin, rather than 'conventional' treatment, had a reduced risk of any diabetes-related end-point ($p = 0.0034$).[5] Statistically significant reductions in macrovascular risk at 10 years were observed only for obese patients treated with metformin. Recent debate has questioned the interpretation of the UKPDS results.[6] In particular, it has been pointed out that there was no clear correlation between blood glucose levels and treatment outcomes.

The UKPDS study has demonstrated that tighter control of blood pressure, by the use of beta blockers or angiotensin-converting enzyme (ACE) inhibitors, reduced diabetes-related mortality and the incidence of microvascular and macrovascular complications.[7,8] An economic evaluation based on the UKPDS data has shown that antihypertensive therapy for patients with type 2 diabetes mellitus is highly cost-effective.[9]

Symptoms of low blood glucose levels (hypoglycaemia), including shaking, sweating and disorientation, are not due to diabetes, but to the action of some glucose-lowering drugs or injected insulin when too little glucose is entering the blood due to a missed or late meal, or when too much glucose is being removed from the blood during or after exercise.

Epidemiology

Prevalence and incidence

Various estimates of the prevalence of diabetes exist. The prevalence of diagnosed diabetes is undoubtedly substantially less than the true prevalence of the disease overall. Because the prevalence increases with age, the increase in the number of elderly people in the population inevitably means that there will be a substantial increase in the overall number of people with diabetes. This increase is almost entirely due to an increase in the number of people with type 2 diabetes.

It is thought that about 2.4% of adults have been diagnosed with diabetes mellitus, which amounts to about 1 million people in England and Wales (*Table 1*).[10,11] The proportion of people with diabetes who have type 2 disease is estimated to be approximately 80%,[12] suggesting that the prevalence of type 2 diabetes is about 800,000 in England and Wales. Other estimates[13] suggest that the number of people with type 2 diabetes may currently be as high as 1.8 million and may rise further to 2.9 million in the year 2010.

Self-reported prevalence is rather higher than the above estimates. In the 1994 Health Survey for England, 3% of respondents reported that they suffered from diabetes mellitus.[14] Among those who did not report a history of diabetes, blood tests showed that 3% of men and 2% of women had elevated levels of glycosylated haemoglobin ($HbA_{1C} \geq 8\%$). This evidence is consistent with other data[15] suggesting that approximately half of the population with type 2 diabetes remain undiagnosed.

Extrapolating from the Poole Diabetes Study,[16] the incidence of type 2 diabetes mellitus in England and

TABLE 1 *Estimates of incidence and prevalence of diabetes mellitus in 1999*

	No. of people x 10^3		
	England	**Wales**	**England and Wales**
Total population[10]	49,300	2,900	52,200
Adult population[10]	39,200	2,300	41,500
Prevalence of all types of diabetes mellitus*	940	60	1,000
Prevalence of type 2 diabetes mellitus†	750	50	800
Incidence of type 2 diabetes mellitus‡	85	5	90
(95% CI)	(76 to 94)	(4 to 6)	(81 to 100)

CI, confidence interval

* *Diagnosed: 2.4% of adults*[11]

† *80% of diagnosed cases*[12]

‡ *1.73 (95% CI, 1.55 to 1.91) cases per 1,000 per annum age/sex-adjusted*[16]

Wales may be estimated at 90,000 (95% confidence interval [CI], 81,000 to 100,000) new cases per year (*Table 1*). However, this estimate is not adjusted to allow for the ethnic mix of the population.

Morbidity and mortality

Diabetic complications are a major cause of morbidity.[17,18]

- Diabetes is associated with a two- to three-fold increase in the risk of coronary heart disease and stroke.
- Diabetic retinopathy is the commonest cause of blindness in people of working age.
- About 30% of people with type 2 diabetes have kidney disease, and about 16% of patients undergoing renal replacement therapy for the first time have diabetes.
- About 15% of people with diabetes develop foot ulcers, and 5–15% of people with diabetic foot ulcers ultimately need amputations.

Estimates of diabetes-related mortality based on death certificate data are seriously misleading, because diabetes will have been a contributory factor in many deaths attributed to other underlying causes.[19]

It is clear that age- and sex-adjusted mortality rates are higher for people with type 2 diabetes than for non-diabetic individuals.[20–22] Precise estimates of the scale of this excess mortality are not available for the following reasons:

- difficulties in classifying type 1/type 2 disease
- the lack of reliability and validity of death certification
- selection bias (i.e. people with diabetes are also likely to have adverse risk profiles for other diseases).

Estimates of the all-cause excess mortality risk ratio associated with type 2 diabetes range from 1.07 to 3.01.[21] The greatest cause of excess mortality in people with type 2 diabetes is cardiovascular and cerebrovascular disease.[20–23]

Risk factors

The incidence and prevalence of diabetes mellitus are positively related to age, at least up to the age of 85 years (*Figure 1*).[24] A large majority of cases that occur in adulthood are due to type 2 disease. Type 2 disease is now more prevalent in men than in women (*Figure 1*).

The prevalence of type 2 diabetes varies by ethnic group. It is estimated to be 3–5 times more prevalent in South Asian people[25] and twice as prevalent in people of African–Caribbean origin,[26] compared with white Europeans.

Weight is a major risk factor for type 2 diabetes. It is estimated that 75% of people who develop type 2 diabetes are, or have been, obese.[11] This association may be causative, with excess weight being related to the onset of type 2 diabetes, possibly through increased insulin resistance. However, it is also possible that overeating and low physical activity are causative factors for both obesity and type 2 diabetes.

Current treatment options and service provision

Lifestyle modification

Type 2 diabetes can usually be managed through diet and exercise alone in the early stages. Data from five general practice or community studies show that 16–24% of people with known diabetes

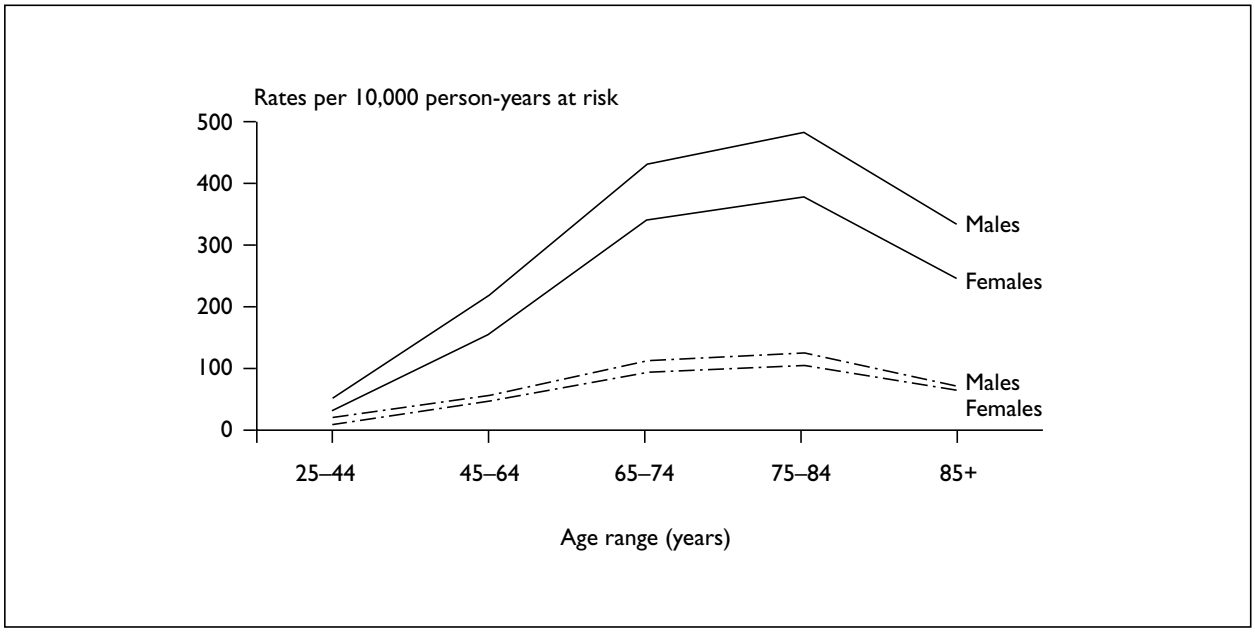

FIGURE 1 *Incidence (– · – · –) and prevalence (——) of diabetes mellitus by age and sex: rates per 10,000 person-years at risk*[24]

are not prescribed any oral glucose-lowering medication.[27] The purpose of a diet is to reduce energy input in order to promote weight loss and hence insulin sensitivity. However, type 2 diabetes is a progressive disease. Nearly all patients require oral glucose-lowering drugs after some time, and most patients eventually need insulin in order to maintain satisfactory blood glucose levels.

Current guidelines from the British Diabetic Asssociation recommend a diet that is similar to the healthy diet advised for the general population, with controlled intake of fat and a focus on wholegrains, fruit and vegetables.[28] Regular exercise is important to control weight, increase cell sensitivity to insulin and improve cardiovascular function.

Modification of other cardiovascular risk factors (e.g. smoking, alcohol and salt intake) is also important because diabetes is associated with a particularly high risk of CVD.

Medication

Patients with type 2 diabetes whose glucose levels are inadequately controlled by diet and exercise alone will need to take an oral glucose-lowering drug, while maintaining efforts to control diet and to exercise. There are four main groups of oral glucose-lowering drugs currently in the BNF.[29]

- **Sulphonylureas** (chlorpropamide, glibenclamide, glicazide, glimepiride, glipizide, gliquidone, tolazamide and tolbutamide). These drugs act by augmenting insulin secretion and are thus only suitable for type 2 diabetes, in which some pancreatic islet β cell activity is present. In the long term, sulphonylureas may have other modes of action, because the levels of insulin in the blood return to premedication levels while blood glucose remains reduced. Sulphonylureas are associated with weight gain and are therefore not the drug of first choice in obese patients; however, it may be necessary to use these drugs as an adjunct to metformin in such patients if satisfactory control cannot be achieved with metformin alone. Treatment with sulphonylureas may also lead to hypoglycaemia, which is rare and less common than with insulin, but may be a hazard for elderly patients. Chlorpropamide is no longer recommended because it has more side-effects than other sulphonylureas. Glibenclamide should be avoided in patients who are elderly or have renal impairment.
- **Biguanides** (metformin). Metformin reduces the release of glucose stored in the liver and increases peripheral utilisation of glucose. It works only if insulin is present. Unlike sulphonylureas, metformin does not lead to problems of hypoglycaemia or weight gain. However, it can cause the rare, but potentially very serious, problem of lactic acidosis. Because of this possible adverse effect, metformin is contraindicated if there is renal or hepatic impairment. Gastrointestinal symptoms, such as heartburn or diarrhoea, are a common problem with metformin and mean that some patients cannot tolerate this drug.

- **Alpha-glucosidase inhibitors** (acarbose). Acarbose slows the digestion and absorption of carbohydrates (by blocking the action of alpha-glucosidase enzymes), reducing the post-prandial spike in blood glucose. Thus, HbA_{1C} levels are kept closer to normal. Acarbose has a small but significant effect on blood glucose. It does not cause hypoglycaemia or weight gain, though it can lead to gastrointestinal side-effects (i.e. flatulence, diarrhoea and bloating). This drug is little used in the UK because it is less efficacious than the sulphonylureas or metformin, and the gastrointestinal side-effects are troublesome and common.
- **Meglitinides** (repaglinide). Oral repaglinide has an action similar to that of the sulphonylureas: it lowers blood glucose levels by stimulating the release of insulin from the pancreas. This drug is relatively short-acting and can cause hypoglycaemia.

If diet, exercise and oral medication do not provide adequate glycaemic control, then people with type 2 diabetes may need insulin.

The UKPDS study was not powered to show differences in effectiveness between the various agents.[4] However, it did show that intensive therapy with sulphonylurea or insulin was associated with weight gain. Among the overweight patients allocated to intensive treatment, there was a greater benefit for those treated with metformin than for those treated with a sulphonylurea or insulin, in terms of any diabetes-related end-point ($p = 0.0034$), all-cause mortality ($p = 0.021$) and stroke ($p = 0.032$).[5]

Sulphonylureas, metformin, adjunctive oral glucose-lowering drugs and insulin may be used in various combinations, as double or even triple combination therapy, if adequate glycaemic control cannot be achieved with a single agent alone.

Other medications, including antihypertensive therapy, may be required to reduce the risk of complications.[18]

Management guidelines

Several clinical practice guidelines for the treatment of type 2 diabetes have been developed recently.[12,23,30–34] These guidelines all recommend a 'step-up' policy of treatment, starting with diet and lifestyle advice alone, then adding various oral glucose-lowering agents and eventually insulin if targets are not achieved. Type 2 diabetes is progressive. Therefore, although initially patients may be managed adequately on diet alone, within 3 years of onset 50% of patients require combination therapy, and after 9 years this figure increases to 75%.[35]

The guidelines recommend that individual treatment targets should be set, based on the need to achieve good control of blood glucose and cardiovascular risk factors, while avoiding the risk of hypoglycaemia and maintaining an acceptable quality of life. The WHO blood glucose cut-offs (appendix 1) are designed for diagnosis and should not be used as therapeutic targets. Current European guidelines[34] suggest that targets should be based on an assessment of risk using the levels shown in *Table 2*.

The commencement of an oral glucose-lowering drug is advocated if blood glucose levels remain high after an adequate trial of lifestyle education. The European guidelines suggest initiation of an oral agent when HbA_{1C} exceeds 6.5% (fasting

TABLE 2 *Vascular risk assessment guidelines*[*]

	Low risk	At risk	High risk
Blood glucose			
HbA_{1C} (%)	≤ 6.5	6.5–7.5	> 7.5
Venous FPG (mmol/l)	≤ 6.0	6.0–7.0	> 7.0
Self-monitored FBG (mmol/l)	≤ 5.5	5.5–6.0	> 6.0
Blood lipids			
Total serum cholesterol (mmol/l)	< 4.8	4.8–6.0	> 6.0
Serum LDL cholesterol (mmol/l)	< 3.0	3.0–4.0	> 4.0
Serum HDL cholesterol (mmol/l)	> 1.2	1.2–1.0	< 1.0
Serum triglycerides (mmol/l)	< 1.7	1.7–2.2	> 2.2
Blood pressure (mmHg)	< 140/85		

FPG, fasting plasma glucose; FBG, fasting blood glucose

[*] *From European Diabetes Policy Group guidelines*[34]

plasma glucose [FPG] > 6.0 mmol/l) or occasionally (if other risk factors are low) when HbA_{1C} exceeds 7.5% (FPG > 7.0 mmol/l).[34] Attempts to modify lifestyle factors should continue alongside medical treatment.

The choice of the initial oral glucose-lowering drug depends upon the patient's weight (e.g. metformin is advocated for obese patients) and upon his or her expected susceptibility to the various side-effects. Dose titration is recommended, starting with a low dose and gradually increasing towards the ceiling dose if targets are not met. Doses should be reviewed and reduced if adverse effects are observed or if blood glucose is well within the target range.

In the case of failure with a single oral glucose-lowering agent, the guidelines differ with respect to the recommended sequence and timing of the next step. Some guidelines recommend a trial of another single oral agent before moving to combination therapy.[12] Other guidelines recommend adding another oral agent to current medication.[31,34] The European guidelines[34] suggest that triple therapy with three differently acting agents may be tried if targets cannot be achieved on the maximum tolerated doses of two drugs.

If blood glucose levels remain high after an adequate trial of oral glucose-lowering drugs, then insulin therapy is recommended, unless the patient has a poor life expectancy and is asymptomatic. The European guidelines suggest that, for most patients, insulin should be added to oral medication if HbA_{1C} is greater than 7.5% after "maximum attention" to diet and oral medication.[34]

The guidelines also make a range of other recommendations relating to:

1. antihypertensive therapy
2. the location and organisation of services (primary, secondary and shared care)
3. the professional skills that should be included in the diabetes team (general practitioner [GP] and practice nurse, consultant physician, diabetes specialist nurse, dietician, chiropodist and other specialists as necessary)
4. the need for structured patient education and self-care programmes
5. the need for self-monitoring and regular professional checks to ensure that blood glucose levels are maintained as close as possible to optimal levels
6. the need for a range of screening tests to monitor other risk factors, side-effects and complications (e.g. blood pressure monitoring, an annual test for urinary protein and microalbuminuria, as well as regular eye and foot checks).

The burden of disease

Estimates of the financial cost of diabetes vary enormously, depending on whether they include all costs or only healthcare costs, and on whether they include the costs of disease associated with or caused by diabetes.[36–40]

The estimated total cost to the NHS of treating diabetes mellitus (of all types), including inpatient, prescription and GP consultation costs, has been estimated at £243 million for the UK in 1995–96 (*Figure 2*).[41] This total cost represents a real-terms (i.e. inflation-adjusted) increase of about 25% since 1989. Prescriptions represent the largest component of this cost estimate, closely followed by inpatient care (*Figure 2*). However, this figure only includes the direct cost of treating disease specifically attributed to diabetes. It does not include the cost of treatments for disease to which diabetes was a contributory factor.

Another estimate, based on a survey of one district in South Wales,[42] found that the additional hospital costs for people with diabetes was £1800 per person. This figure represents 9% of UK hospital costs, that is, approximately £1.9 billion each year.[17]

Use of oral blood glucose-lowering medication

The Prescription Pricing Authority (PPA) estimated that about 135,000 people in England were taking oral glucose-lowering drugs (BNF section 6.1.2) in 1996–97.[43] This estimate is derived from the number of defined daily doses (DDDs)[44] prescribed over a given time period. There was a 42% increase in the use of oral glucose-lowering drugs between June 1992 and March 1996, mainly due to increasing use of glicazide and metformin.[43] Over this period, there was a 60% increase in the cost of the sulphonylureas, which account for 80% of the total expenditure on oral glucose-lowering drugs.

Data from the General Practice Research Database (GPRD),[45] which includes 288 practices in England and Wales, suggest that almost 1% of patients were prescribed an oral glucose-lowering drug at least once in 1996. This statistic implies that about 480,000 people in England and 30,000 in Wales would have been prescribed an oral glucose-lowering drug.

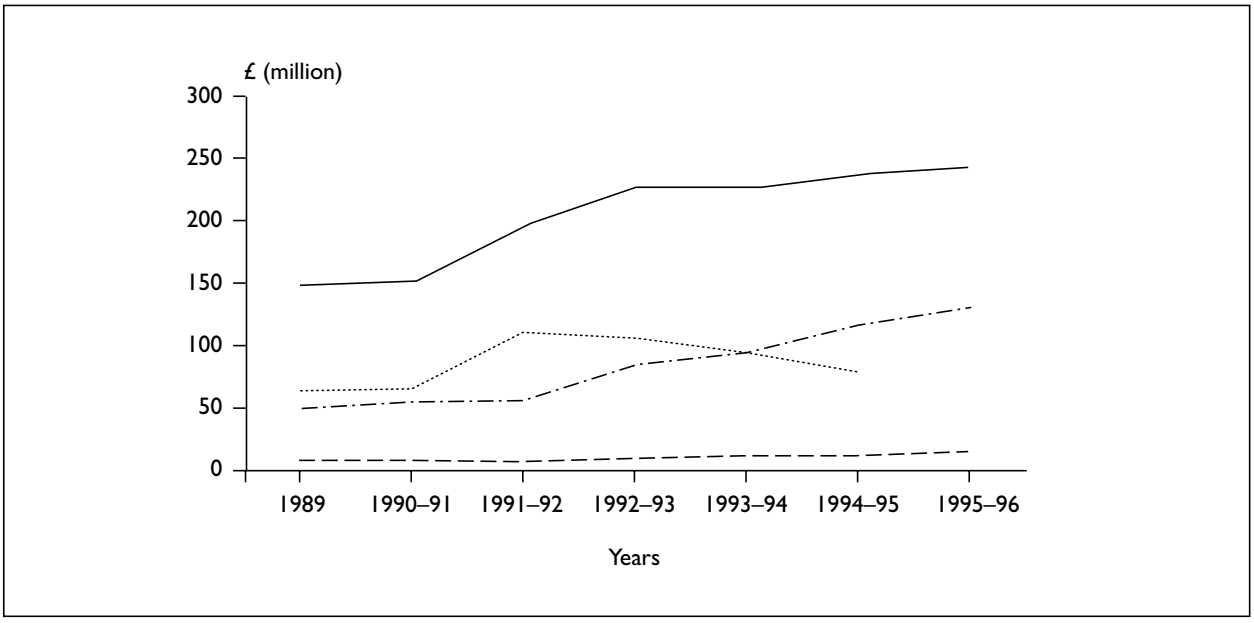

FIGURE 2 *Estimated NHS healthcare costs directly attributed to diabetes mellitus from 1989 to 1995/96 in England and Wales[41] (——, total cost; ....., inpatient care; – · – ·, prescriptions; – – –, GP care)*

The GPRD figure is more consistent with estimates of prevalence (*Table 1*) and of the proportion of patients with type 2 diabetes taking oral glucose-lowering drugs.[35] The large discrepancy between the PPA and GPRD data suggests that many patients may take oral glucose-lowering drugs intermittently or at doses lower than the DDDs.

Description of new intervention

The thiazolidinediones are a recently developed class of oral glucose-lowering drugs.[46,47] They are thought to work through the activation of peroxisome proliferator-activated receptor-gamma, thereby reducing insulin resistance.[48] Thiazolidinediones are not intended for type 1 diabetes.

There are currently two thiazolidinedione drugs licensed by the European Agency for the Evaluation of Medicinal Products:[49]

- rosiglitazone: Avandia® (SmithKline Beecham, Welwyn Garden City, UK)
- pioglitazone: Actos® (Takeda, High Wycombe, UK).

Troglitazone was the first of this class of drugs to become available in the USA and the UK. Following concerns over liver failure associated with troglitazone, the manufacturer advised that patients should undergo regular monitoring. The company recommended that liver function should be checked before starting treatment, monthly during the first year and quarterly from then on. Following a spate of adverse hepatic reactions, however, troglitazone was voluntarily withdrawn from both the UK and US markets, both for monotherapy and combination therapy.

There have also been isolated reports of hepatic problems associated with rosiglitazone in the USA,[50–52] although these reports have been contested by SmithKline Beecham.[53] The US Food and Drug Administration (FDA) is monitoring and evaluating such reports. The FDA has also recommended that patients should have liver enzyme tests before starting treatment with any of the thiazolidinediones, and periodically thereafter.

The European Committee for Proprietary Medicinal Products (CPMP)[49] recommended the granting of marketing authorisation for pioglitazone in July 2000.

Summary of product characteristics[49]

Pioglitazone is marketed as Actos, in 15- and 30-mg tablets. The wording of the licensed indication specifies:

> "Pioglitazone is indicated only in oral combination treatment of type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea:
>
> - in combination with metformin only in obese patients
> - in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated."

Pioglitazone is not licensed or marketed for use as monotherapy or in triple combination with other oral glucose-lowering drugs (metformin and a sulphonylurea) or in combination with insulin.

Takeda state that pioglitazone is contraindicated in patients with:

- known hypersensitivity to pioglitazone
- cardiac failure or history of cardiac failure
- hepatic impairment.

In addition, its use is not recommended in patients under 18 years of age or who are undergoing renal dialysis.[49]

The European CPMP recommended that treatment with pioglitazone be initiated by physicians experienced in the treatment of type 2 diabetes.

Outcome measures

The principal goals of treatment for type 2 diabetes are to prevent acute and chronic complications and thus to improve quality of life and to avoid excess mortality. These goals may be achieved through better control of blood glucose levels and through reductions in other cardiovascular risk factors. For some patients, there may be a trade-off between short- and long-term quality of life, due to treatment-related adverse effects.

There is a wide range of possible measures that could be used to evaluate the clinical effects of pioglitazone therapy.

Glycaemic control

Treatments may be compared based on blood glucose levels. The UKPDS demonstrated that good control of blood glucose, measured in terms of HbA_{1C} levels, reduces the risk of microvascular complications[4] and is thus a reasonable indicator of long-term morbidity. HbA_{1C} levels reflect the level of blood glucose retrospectively over a 2- to 3-month period.[54] Other measures, such as fasting blood glucose (FBG) or FPG, may also be used to evaluate treatments in the absence of HbA_{1C}.

Treatments also may be assessed by comparing the proportions of patients whose blood glucose is reduced by more than a given amount (responders) or who successfully achieve target blood glucose levels. Individual patient targets will vary, but indicative targets may be taken from the European guidelines (*Table 2*).

Cardiovascular risk factors

Individuals with type 2 diabetes are subject to a particularly high excess risk of CVD. Therefore, it is important that evaluations of oral glucose-lowering drugs should include an assessment of cardiovascular risk factors in addition to measures of blood glucose. Risk factors that may be affected by oral glucose-lowering drugs include:

- lipids
- blood pressure
- body weight and the distribution of fat.

Regarding lipids, low-density lipoprotein (LDL) is a recognised evidence-based indicator of cardiovascular risk. High-density lipoprotein (HDL) is also important and is independent from LDL cholesterol. A number of other cholesterol measures are often presented. Triglycerides are closely related to HDL cholesterol (although moving in opposite directions). Total cholesterol is really only a valid measure when triglycerides and HDL are in the normal range, thus not in type 2 diabetes.

Adverse events and tolerability

As with any medication, oral glucose-lowering drugs should be evaluated in terms of the incidence of adverse events and tolerability. Useful indicators are: (a) the proportion of patients who experience at least one adverse event, (b) the proportion of patients who withdraw from studies because of adverse events and (c) the overall proportion of patients who withdraw.

The major adverse events associated with glucose-lowering drugs are:

- hypoglycaemia (with sulphonylureas and insulin)
- gastrointestinal side-effects (with metformin and acarbose)
- fluid retention (with rosiglitazone).

Incidence of diabetic complications

A good measure of health outcome is provided by the incidence of various diabetic complications. Given the short time that pioglitazone has been available, there has not been follow-up of sufficient length to assess the incidence of long-term diabetic complications.

Quality of life, mortality and cost-effectiveness

It is essential to consider the patient's perspective in order to balance short-term clinical effects, the risk of acute and chronic diabetic complications, adverse clinical effects of treatment and the effect of treat-

ment on lifestyle.[55] A number of diabetes-specific instruments for measuring quality of life or health status have been developed, although no generally recommended battery of well-tested quality-of-life measures is currently available.[56] Alternatively, generic measures, such as the Short Form with 36 Items (SF-36) or EuroQoL, could be used.

Ultimately, this medication should be evaluated in terms of its overall effect on quality of life, mortality and the use of scarce resources. However, because of the newness of the drug, direct measurement of life-years gained or quality-adjusted life-years (QALYs) gained is not possible. Modelling may be used to estimate the overall impact of the introduction of pioglitazone, but care is needed to ensure that the data and modelling assumptions reflect the likely costs and effects for the population of people with type 2 diabetes in England and Wales.

Chapter 3

Effectiveness

Methods for reviewing effectiveness

Search strategy

The search strategy aimed to identify all papers relating to pioglitazone. Keyword strategies were developed using key references, which were retrieved through initial scoping searches. Search strategies did not include search terms or filters that would limit results to specific publication types or study designs. No date or language restrictions were used. Searches of the following databases were undertaken in June 2000:

- MEDLINE
- EMBASE
- Science Citation Index (SCI)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Controlled Trials Register (CCTR)
- NHS Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effectiveness [DARE], NHS Economic Evaluation Database [NHS EED] and HTA)
- Office of Health Economics Health Economics Database (OHE HEED).

In August 2000, a search of the last 6 months of PubMed was undertaken to identify recent studies not yet indexed on MEDLINE. A further search was undertaken on MEDLINE for papers relating to 'glitazones' and type 2 diabetes, with filters used to limit search results to clinical trials, reviews or economics studies. Keyword strategies for MEDLINE are listed in appendix 2. Keyword strategies for all other databases are available.

In addition to searches of electronic bibliographic databases, further sources were consulted to identify current research and grey literature. The National Research Register (NRR), Medical Research Council (MRC) Clinical Trials Register, US National Institutes of Health (NIH) Clinical Trials Register, and Current Research in Britain (CRIB) databases were searched. The publications lists and current research registers of HTA and guideline-producing agencies, and funding and regulatory bodies were consulted. Industry submissions and the reference lists of included studies were searched by hand, and citation searches using the SCI citation search facility were undertaken.

Inclusion and exclusion criteria

The search strategy above identified almost 800 references. On the basis of their titles and abstracts, these references were screened for relevance to the study question. The vast majority were either animal or preclinical studies, or general review articles. All relevant reviews were examined for further references to primary research.

Full copies were obtained of all papers that appeared relevant at this initial stage.

Studies were then assessed based on the following criteria, and all studies that met the criteria were included.

1. **Intervention** was pioglitazone alone or in combination with other antidiabetic drugs.
2. **Comparator** included other antidiabetic drugs or placebo.
3. **Subjects** were patients with type 2 diabetes mellitus.
4. **Outcome measures** included at least one of the following:
   – glycaemic control (blood glucose or HbA_{1C})
   – cardiovascular risk factors (lipids and weight)
   – pyruvate kinase
   – occurrence of adverse events.
5. **Study methodology** included at least one of the following:
   – systematic review
   – randomised controlled trial (RCT)
   – economic evaluations.
6. **Length of study** was at least 12 weeks on study medication.

Data extraction strategy

Data extraction was undertaken by two reviewers, using customised data extraction forms.

Quality assessment strategy

A standard checklist[57] was used to assess the methodological quality of the included RCTs. Because of the paucity of information relating to the included studies, formal quality assessment was possible in only four cases: two confidential studies[58] and two published studies.[59,60] Therefore, no studies were excluded on the basis of methodological quality.

Results*

Quantity and quality of research available[58–79]

Number of studies identified

No published structured reviews of primary research on pioglitazone were identified. In total, 25 references to primary clinical research were identified by the literature search. These references related to 11 trials that appeared to meet the inclusion criteria. Of the 25 references, 14 were conference abstracts (the majority from the 1999 American Diabetes Association meeting). Eight full papers were published in the *Japanese Journal of Clinical and Experimental Medicine* in Japanese, without an English abstract. English translations of these papers are available from Takeda UK Ltd, although six of these are not readily available in the public domain. One full study report[62] and two review articles[63,76] relating to trials PNFP-010 and PNFP-027 are available in English.

Substantially the greatest amount of clinical information available on pioglitazone in the public domain is found on the FDA website,[61] which contains the medical and statistical reviews of material submitted by the sponsors of the drug. It must be emphasised, however, that these are reviews rather than original material. It is clear that they relate to the same studies that have been reported in the conference abstracts identified in the literature search. Most of the other information in the public domain has largely been published in Japanese.

The submission from Takeda UK Ltd[58] included reports of two trials (PNFP-010 and PNFP-027) and synopses of a further seven (PNFP-001, CCT-012, OCT-003, OCT-016, PNFP-010 and two confidential studies). The reports relating to several of these trials (PNFP-001, PNFP-010, PNFP-014 and PNFP-027) appear to have formed the basis of the licensing submission to the FDA[61] and therefore of the medical and statistical reviews on the FDA website[61] referred to above. Further details of PNFP-027 have since been published as a report of the study,[62] and a review of PNFP-010 is also now available in the public domain.[63]

The submission from Takeda UK Ltd[58] also included some information about trials that apparently were not submitted to the FDA.[61] Three are studies of pioglitazone in combination with sulphonylureas (trials CCT-012, OCT-003 OCT-016), which have been published only in Japanese.[59,64,65] Of these, trial OCT-016 was a non-randomised, non-blinded study of 105 patients taking between 15 and 45 mg of pioglitazone daily. Of these patients, 80 were taking a sulphonylurea drug in addition to pioglitazone, and 25 were on no other drug. Patients were followed for 28 weeks, and efficacy was evaluated based on a decrease in HbA_{1C} and "final decrease rating of fasting blood glucose" (final DR-FBG). Safety was also evaluated. As this study was neither randomised nor controlled, it did not meet the inclusion criteria and therefore is not considered further.

The Takeda submission[58] also included additional data relating to some of the above studies, a pharmaceutical summary, and papers summarising the clinical effectiveness, safety and tolerability of pioglitazone on the basis of some of the above studies.

The synopses of trials PNFP-001 and PNFP-014 also contained more information than is available from the FDA on the inclusion and exclusion criteria, and statistical methods.[61]

Takeda UK also made available to the authors of this report translations of the full Japanese articles reporting studies OCT-003,[59] CCT-001[66] and CCT-011.[60] They also provided very brief details of all clinical trials of which they were aware. No other clinical studies met the entry criteria.

* Substantial data from trials defined as confidential by Takeda UK Ltd in their submission to NICE are not reported here (in text or tabular form) but were contained in the report considered by the NICE Appraisals Committee. The material provided by Takeda UK included both additional information on the organisation and management of the trials as well as further details of the results. Included were details about two European pioglitazone monotherapy studies, of which the synopses formed the only source of information available to the reviewers. The Takeda submission also included information regarding one Japanese combination therapy study and one Japanese monotherapy study. Furthermore, the full study reports of trials PNFP-010 and PNFP-027, which were submitted to NICE by Takeda, contained some evidence that is not available in published papers, in abstracts or on the FDA website.[61] Included within these reports were details of the ethical conduct of the trials and of the overall study design, including details of investigations undertaken at each visit, inclusion and exclusion criteria, criteria for removing patients, randomisation procedure, presentation of study medication, measurement of safety and efficacy variables, recording of adverse events, statistical methods used and sample size calculation.

Number and type of studies included

Eleven studies met the review's inclusion criteria, and four additional studies are not reported here because they were submitted to NICE in confidence by Takeda UK Ltd. All were prospective studies, with ten described as RCTs. The remaining study (PNFP-011) was an open-label extension of one of the RCTs (PNFP-001). Further details are given in *Table 3*.[59–63,66–74,78,79]

Included studies relate to four relevant comparisons:

- **licensed indications**
  1. pioglitazone in combination with metformin, compared with metformin and placebo (PNFP-027)
  2. pioglitazone in combination with a sulphonylurea, compared with a sulphonylurea and placebo (PNFP-010, OCT-003[59] and an unnamed study[71])
- **unlicensed indications**
  3. pioglitazone in combination with insulin, compared with insulin and placebo (PNFP-014)
  4. pioglitazone alone, compared with placebo (PNFP-001, PNFP-011, PNFP-012, PNFP-026, CCT-001[66] and CCT-011[60]).

Study design

Aspects of study design are summarised in *Table 4*. All trials were restricted to patients with type 2 diabetes. The cut-off HbA_{1C} level for inclusion differed between studies, with 7% being the lowest limit. There appears to have been a change in the protocol for study PNFP-001 during the course of the study.[61]

TABLE 3 *Studies included in the review*[*]

Study	Countries (no. of centres)	Treatment dates (month/year)	Source of report	Comparison	Study type
PNFP-001	USA	1/1996–3/1998[61]	Abstract,[67] FDA[61]	Pioglitazone vs placebo[61]	RCT
PNFP-011	USA		FDA[61]	Pioglitazone vs placebo	Open-label extension to PNFP-001
PNFP-012	USA		Abstract,[68] FDA[61]	Pioglitazone vs placebo, with dose titration	RCT
PNFP-026	USA		Abstract,[69,70] FDA[61]	Pioglitazone vs placebo	RCT
CCT-001[66]	Japan (54)[66]	8/1993–7/1994[66]	Journal article[66]	Pioglitazone vs placebo[66]	Double-blind, placebo-controlled RCT[66]
CCT-011[60]	Japan (45)[60]	4/1995–1/1996[60]	Journal article[60]	Pioglitazone vs placebo, with dose titration[60]	Double-blind, placebo-controlled RCT[60]
OCT-003[59]	Japan (59)[59]	9/1993–6/1994[59]	Journal article[59]	Pioglitazone + sulphonylurea vs placebo + sulphonylurea, with dose titration[59]	Single-blind, placebo-controlled RCT[59]
Unnamed study[71]			Abstract[71]	Pioglitazone + sulphonylurea vs placebo + sulphonylurea[71]	RCT[71]
PNFP-010	USA (54)		Abstracts,[72,78] FDA,[61] review article[63]	Pioglitazone + sulphonylurea vs placebo + sulphonylurea	Double-blind, placebo-controlled RCT
PNFP-014			Abstract,[73] FDA[61]	Pioglitazone + insulin vs placebo + insulin	Double-blind, placebo-controlled RCT
PNFP-027	USA		Journal article,[62] abstracts,[74,79] FDA[61]	Pioglitazone + metformin vs placebo + metformin	Double-blind, placebo-controlled RCT

[*] *Four studies are not reported here because they were submitted to NICE in confidence by Takeda UK Ltd*

TABLE 4 *Study design*

Study	Patients	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported	Comments
PNFP-001[61]	Type 2 diabetic patients, aged 30–75 years, both drug-naive and treated patients. BMI of 25–40 kg/m^2, FBG > 9 mmol/l, fasting C peptide > 1 ng/ml at screening, HbA_{1C} > 7% before randomisation	Placebo (79) Pioglitazone: 7.5 mg/day (80) 15 mg/day (79) 30 mg/day (85) 45 mg/day (76)	6-week washout for previously treated patients, 2-week baseline, 26 weeks of treatment	FBG, HbA_{1C}, body weight, triglycerides, cholesterol	Data on drug-naive and previously treated patients are presented separately on the FDA website[61]
PNFP-011[61]	Patients from the above study plus additional patients (entry criteria specified type 2 diabetic patients with HbA_{1C} > 7%)	Pioglitazone: 7.5 mg, titrated up to 60 mg/day	Open-label study, up to 72 weeks. **All** patients (including 'rollovers') started on 7.5 mg/day. Dose increased in stepwise fashion every 4 weeks if FBG > 9 mmol/l	FBG, HbA_{1C}, body weight	Note that the majority of 'rollover' patients previously treated with pioglitazone experienced a reduction in dose at the start of this open-label extension
PNFP-012[61]	"Same as for previous monotherapy studies" (i.e. PNFP-001 and PNFP-026)	Placebo (84) Pioglitazone: 7.5/15/30 mg/day (87) 15/30/45 mg/day (89)	6-week placebo washout. Dose in each of the treatment arms increased stepwise after 4 and 8 weeks. Total treatment period of 24 weeks	HbA_{1C}, FBG, insulin C peptide, HDL and LDL cholesterol	Data on drug-naive and previously treated patients are presented separately on the FDA website.[61] Patients were excluded from study for "insufficient therapeutic effect"
PNFP-026[61]	Type 2 diabetic patients, aged 30–75 years, both drug-naive and previously treated. BMI of 25–40 kg/m^2, HbA_{1C} > 7.55 at screening and > 8% after washout, fasting C peptide > 1 ng/ml at screening	Placebo (96) Pioglitazone: 30 mg/day (101)	5-week washout for previously treated patients. Treatment period of 16 weeks	HbA_{1C}, FBG, insulin C peptide, lipids	Data on drug-naive and previously treated patients are presented separately on the FDA website.[61] Patients were excluded from study for "insufficient therapeutic effect"
CCT-001[66]	Type 2 diabetic patients, aged 20–70 years, treated with diet alone, whose FBG levels at both the beginning and end of the run-in period were 8.3 mmol/l or higher, with a variation of < 1.7 mmol/l between the two FBG levels	Placebo (66) Pioglitazone: 15 mg/day (71) 30 mg/day (67) 45 mg/day (69)	4-week run-in, followed by 12 weeks of treatment	FBG, HbA_{1C}, blood insulin, blood CPR, lipids, body weight, PD-FBG, DR-FBG, GIR-BG (by HbA_{1C} change)	
CCT-011[60]	Type 2 diabetic patients, aged 20 or over, on diet therapy at entry, whose FBG levels at both the beginning and end of the run-in period were 8.3 mmol/l or higher, with a variation of < 1.7 mmol/l between the two FBG levels	Placebo (75) Pioglitazone: 30 mg/day (77)	4-week run-in, followed by 12 weeks of treatment	FBG, HbA_{1C}, 1,5-AG, blood insulin, lipids, body weight, PD-FBG, DR-FBG	

continued

TABLE 4 contd *Study design*

Study	Patients	Treatment groups (no. randomised)	Study procedure	Outcome measurements reported	Comments
OCT-003[59]	Type 2 diabetic patients, aged 20–70 years, treated with a sulphonylurea drug for at least 3 months at entry, whose FBG levels at both the beginning and end of the run-in period were 8.3 mmol/l or higher, with a variation of < 1.7 mmol/l between the two FBG levels	Placebo (66) Pioglitazone: 15 mg/day (72) 30 mg/day (68) 45 mg/day (70)	4-week washout/ run-in, followed by 12 weeks of treatment	FBG, HbA_{1C}, 1,5-AG, blood insulin, blood CPR, lipids, body weight, PD-FBG, DR-FBG, GIR-BG	
Unnamed study[71]	Type 2 diabetic patients, treated with a stable dose of sulphonylurea alone	Sulphonylurea + placebo (11) Sulphonylurea + pioglitazone: 45 mg/day (12)	4 months	FPG, mean plasma glucose during OGTT, HbA_{1C}, C peptide, HGP, TGD, free fatty acids, body weight, fat mass	
PNFP-010[61]	Type 2 diabetic patients, aged 30–75 years, treated with sulphonylureas alone or with acarbose or metformin. HbA_{1C} > 8% at screening and randomisation, fasting C peptide > 1 ng/ml	Sulphonylurea + placebo (187) Sulphonylurea + pioglitazone: 15 mg/day (184) Sulphonylurea + pioglitazone: 30 mg/day (189)	2-week screening period, then 4 weeks on sulphonylurea + placebo, then 16 weeks on allocated treatment. Patients were maintained on previous dose of sulphonylurea	HbA_{1C}, FBG, insulin C peptide, triglycerides, HDL and LDL cholesterol, body weight	
PNFP-014[61]	Type 2 diabetic patients, treated with insulin (> 30 units/day) for at least 30 days. HbA_{1C} > 8% at screening and randomisation, fasting C peptide > 0.7 ng/ml	Insulin + placebo (187) Insulin + pioglitazone: 15 mg/day (191) Insulin + pioglitazone: 30 mg/day (188)	2-week screening period, then 4 weeks on insulin + placebo, then 16 weeks on allocated treatment. "No attempt made to change insulin regimen"	HbA_{1C}, FBG, insulin C peptide, triglycerides, HDL and LDL cholesterol, body weight	
PNFP-027[61]	Type 2 diabetic patients, treated with metformin for > 30 days. HbA_{1C} > 8% at screening and randomisation, fasting C peptide > 1 ng/ml	Metformin + placebo (153) Metformin + pioglitazone: 30 mg/day (161)	2-week screening period, then 4 weeks on metformin + placebo, then 16 weeks on allocated treatment	HbA_{1C}, FBG, insulin C peptide, triglycerides, HDL and LDL cholesterol, body weight	

BMI, body mass index; CPR, C-reactive protein (assumed abbreviation; see page 26); PD-FBG, percentage decrease in fasting blood glucose; GIR-PD, global improvement rating of blood glucose; 1,5-AG, 1,5-anhydro-glucitol; OGTT, oral glucose tolerance test; HGP, hepatic glucose production; TGD, total glucose disposal

Initially, the inclusion criteria for randomisation included an FBG of less than 13.3 mmol/l. Patients were to be withdrawn for lack of efficacy if the FBG was greater than 15.5 mmol/l on two consecutive visits. The protocol was amended 6 months after the start of patient recruitment, eliminating any upper limit for patient recruitment and stating that patient withdrawal would occur only if the FBG was greater than 22.2 mmol/l on two consecutive visits. Patients could be withdrawn for hyperglycaemia that "presented a safety risk to the patient, in the investigator's opinion", but investigators were encouraged to make every effort to keep patients in the study.[61] The FDA reviewer made it clear that, in his view, it was unethical to allow patients who had previously been on active treatment to continue in the study on placebo (i.e. without active treatment) with this level of hyperglycaemia.[61]

The four US monotherapy studies (PNFP-001, PNFP-011, PNFP-012 and PNFP-026) recruited both drug-naive (i.e. not previously treated with hypoglycaemic drugs) and previously treated patients. In the case of patients who had been previously treated, there was a washout period of 4–6 weeks prior to starting on the experimental treatment. In two Japanese monotherapy studies (CCT-001 and CCT-011), patients were excluded who had used insulin or an oral hypoglycaemic drug within the 4-week period before the run-in period.[60,66]

In the studies of combination therapy, pioglitazone was added to previous hypoglycaemic treatment. If patients were taking combination therapy prior to the study, additional antidiabetic drugs were stopped in advance of the study (see below). Four of these trials specifically recruited patients whose blood glucose control was insufficient when treated with their current medication.[59,62,63,73] In the fifth study (unnamed), no indication was given of the level of blood glucose control.[71]

For the majority of the studies, the primary efficacy measure was the between-group difference in the mean change in HbA_{1C} between baseline and the study end-point. However, trials OCT-003 and CCT-001 took as their primary efficacy end-points both the percentage of decrease in fasting blood glucose (PD-FBG) and "decrease rating of fasting blood glucose" after 12 weeks of therapy, with the emphasis on the former at the study end-point.[59,66] Trial CCT-011 had PD-FBG and decrements of HbA_{1C} at the study end-point as primary efficacy end-points.[58,60] In the unnamed study, it was not clear which was the primary efficacy measure.[71] Various secondary outcomes were measured, including blood glucose, lipids, body weight and pyruvate kinase.

The inclusion of previously treated and drug-naive patients in the monotherapy studies gives rise to a number of problems. As well as the ethical issue discussed above as to whether it was right to expose them to the possibility of being randomised to treatment with placebo and then allow them to continue in the study with marked hyperglycaemia, problems also arise with regard to the analysis of the results. The primary outcome measure in the majority of monotherapy studies was the change in HbA_{1C} between baseline and the end of the study. However, in the majority of these studies, for patients who had been previously treated, the washout period of 5 or 6 weeks was inadequate to allow the HbA_{1C} level to rise to a steady 'untreated' level. HbA_{1C} was thus lower at baseline than it would have been had the washout period continued for a further few weeks and a steady level been reached. This effect can be clearly seen in *Figure 3*, which demonstrates that, in the previously treated patients, the HbA_{1C} continued to rise above the baseline level. The change in HbA_{1C} in previously treated patients randomised to pioglitazone thus underestimates the effect of the drug.

Because of these problems, the FDA asked the sponsoring company to analyse separately the results of drug-naive and previously treated patients. The FDA's review was then based primarily on the analysis of the drug-naive patients, and these data were in fact adequate to justify licensing.

A similar problem theoretically arises regarding the combination studies. In all these trials, with the exception of the unnamed study,[71] some of the patients who were recruited were taking antidiabetic medication other than the primary agent being combined with pioglitazone (e.g. metformin in addition to sulphonylurea, in study PNFP-010). In **four** studies, these additional drugs were discontinued at screening, which may have led to a deterioration in glycaemic control in these patients. The 4-week 'washout' period of treatment on primary agent plus placebo (in studies PNFP-010, PNFP-014, PNFP-027 and OCT-003) would not have been long enough for any deterioration in control to be reflected fully in the HbA_{1C} level. In these trials, a further deterioration in HbA_{1C} might therefore be expected in patients receiving placebo **after** randomisation (reflecting the proportion of patients who had had additional treatment discontinued), and the overall effect of pioglitazone on HbA_{1C} levels would be underestimated unless compared with the changes in placebo-treated patients.

Characteristics of study populations

Limited information is publicly available regarding the study populations. What information it has been possible to extract is presented in *Table 5*. The figures that are available suggest there were no significant differences in baseline characteristics between different treatment groups.

Little background information is available about co-morbidities or drop-outs in these studies. What information is available is presented here.

In the PNFP-010 trial, 30 of 187, 29 of 184 and 23 of 189 patients were withdrawn from the placebo, 15-mg pioglitazone and 30-mg pioglitazone arms, respectively. Of these patients, lack

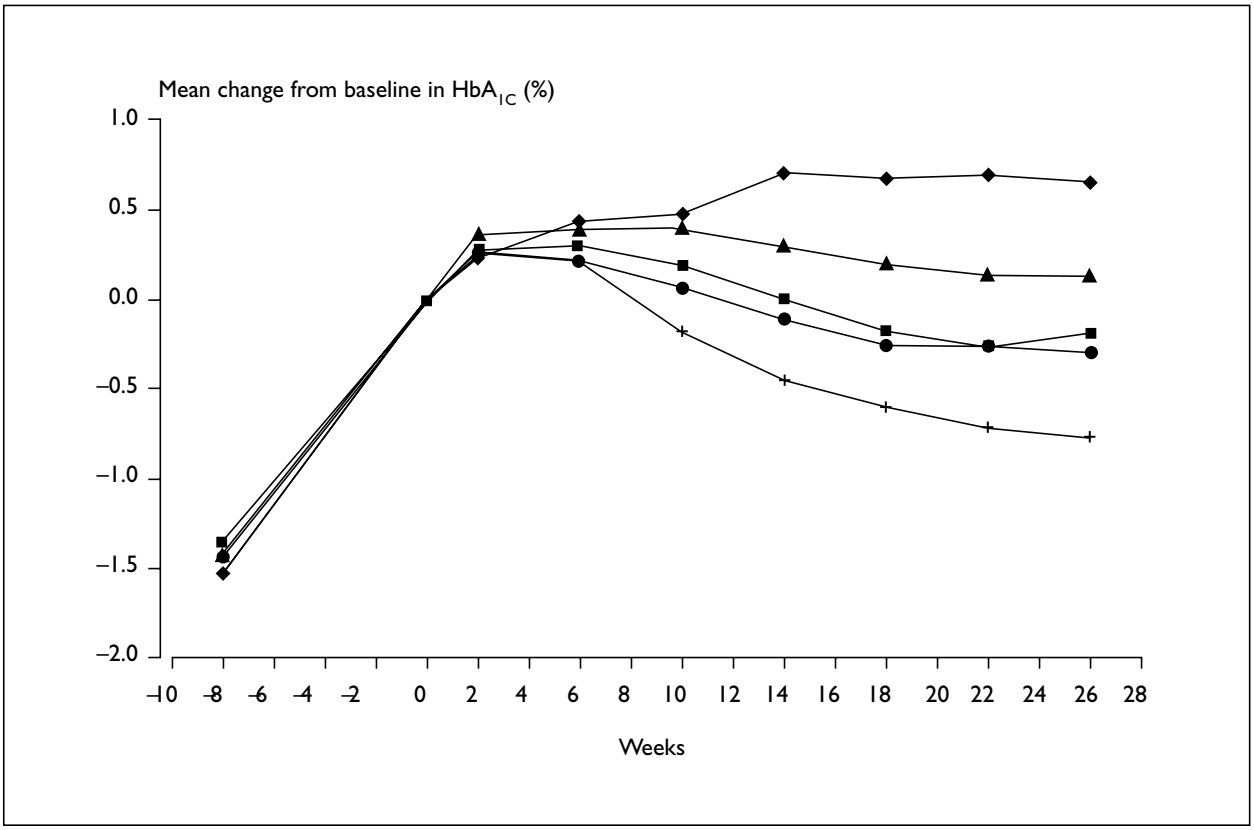

FIGURE 3 *Mean change from baseline for HbA_{1C} (last observation carried forward) in randomised patients who had received previous antidiabetic medication (–◆–, placebo; –▲–, pioglitazone [7.5 mg]; –●–, pioglitazone [15 mg]; –■–, pioglitazone [30 mg]; –+–, pioglitazone [45 mg])*

TABLE 5 *Characteristics of study populations*

Study	Mean age (years)	% male	% Caucasian	Mean duration of illness (years)	Mean BMI (kg/m^2)	Mean baseline HbA_{1c} (%)
PNFP-001[61]	54	58	78	NS	31.0	10.19
PNFP-011[61]	54	62	75	NS	NS	NS
PNFP-012[61]	56	56	82	NS	30.9	10.57
PNFP-026[61]	NS	NS	NS	NS	NS	10.53
CCT-001[66]	56	47	NS	7.8	24.9	9.3
CCT-011[60]	58	50	NS	NS	27.0	9.27
OCT-003[59]	57	50	NS	12.0	24.6	9.99
PNPF-010[61]	57	59	79	NS	32.0	9.93
PNPF-014[61]	57	47	73	NS	33.6	9.85
PNPF-027[61]	57	57	84	NS	32.1	9.81

NS, not specified

of efficacy was the reason in 13, 12 and four patients, respectively.[61]

In trial PNFP-027, patients with significant diabetic complications or co-morbidities were excluded.[62] Approximately 30% of patients had been previously taking another antidiabetic medication (predominantly sulphonylureas) in addition to metformin. These additional medications (but not metformin) were stopped at the start of the study. Overall, 50 of 160 and 29 of 168 patients were withdrawn from the placebo and 30-mg

pioglitazone groups, respectively, of whom 35 and 17, respectively, were due to lack of efficacy.[61] It should be noted that slightly different figures (37 and 21 patients, respectively) are given for the numbers of withdrawals due to lack of efficacy in the published paper reporting this study.[62] There were no statistically significant differences in baseline characteristics between the study groups in either the PNFP-010 or PNFP-027 study.

In trial CCT-001, 35% of patients had diabetic complications, the most common being diabetic nerve disorders (20%), nephropathy (17%) and retinopathy (15%). Many patients also had other medical conditions, most commonly hyperlipaemia (42%) and hypertension (32%).[66] In trial OCT-003, 62% of patients had diabetic complications, the most common being retinopathy (49%). Nerve disorders and nephropathy were noted in 32%, 25% and 5% of the patients, respectively (sic). The most common non-diabetic conditions were hyperlipaemia (38%) and hypertension (39%).[59] In CCT-011, 34% of patients had diabetic complications. Retinopathy, neuropathy and nephropathy were noted in 14–16% of patients. Obesity, hyperlipaemia and hypertension were also common.[60]

No data are publicly available on patient compliance for any of the studies.

Number and type of studies excluded

Study OCT-016 was neither randomised nor controlled, therefore it did not meet the inclusion criteria and is not considered further.

Quality of studies, characteristics of studies and evidence rating

It was possible to assess the methodological quality of only those trials for which full reports were available (OCT-003, CCT-001, CCT-011 and PNFP-027). Of these trials, three (CCT-001,[66] CCT-011[60] PNFP-027[62]) scored 5 on the Jadad scale.[57]

Results: monotherapy studies[*]

Formal meta-analysis of the results of the monotherapy studies (PNFP-001, PNFP-011, PNFP-012, PNFP-026, CCT-001 and CCT-011) was not possible because of lack of data as well as the different duration of the studies. The results of these studies are therefore presented separately. As can be seen, however, there is consistency between them.

When it has been possible to identify separately the effect of the drug on drug-naive patients, this information is presented in preference to the combined results of drug-naive and previously treated patients. If not possible, the overall results are given.

Effect on blood glucose

A significant fall in FBG level was seen with all doses of pioglitazone studied, and a clear dose–response effect was seen in studies PNFP-001 and PNFP-012. Similarly, falls in the HbA_{1C} level were seen in all treated groups, with the exception of patients treated with 7.5 mg of pioglitazone daily in study PNFP-001, in which HbA_{1C} did not significantly alter from baseline. In patients treated with placebo, HbA_{1C} continued to rise after baseline. The overall effect of pioglitazone on HbA_{1C} in drug-naive patients is shown in *Table 6*. It is worth noting that, in patients who had been previously treated, neither the FBG nor the HbA_{1C} returned to the levels recorded at screening (i.e. on treatment with other hypoglycaemic drugs) in any of the three studies. The smaller effect of pioglitazone on HbA_{1C} in study PNFP-026 was probably due to the shorter duration of the study, which would not have allowed the full effect of the reduced blood glucose level to be reflected in the HbA_{1C} level.

The effects of pioglitazone on HbA_{1C} after 12 weeks of treatment in the Japanese studies CCT-001 and CCT-011 are summarised in *Table 7*.

In study CCT-001, the 45-mg dose was associated with a statistically significant decrease in HbA_{1C} compared with both the 15-mg dose and placebo ($p < 0.05$), while in CCT-011, the 30-mg dose was associated with a statistically significant decrease in HbA_{1C} compared with placebo ($p < 0.05$).

FBG

The effect of pioglitazone on FBG in drug-naive patients is shown in *Table 8*.

The proportions of patients classified as responders to treatment in study PNFP-012 are shown in *Table 9*. Responders were defined as those whose HbA_{1C} decreased by 0.6% or whose FBG decreased by 30 mg/dl.

The effects of pioglitazone on FBG after 12 weeks of treatment in the Japanese studies CCT-001 and CCT-011 are summarised in *Table 10*.

[*] Data regarding European monotherapy studies were submitted to NICE in confidence and are not reported here. This information relates to changes in HbA_{1C} from baseline (analysed by intention to treat), the effects of pioglitazone on fasting blood glucose and the proportions of patients responding to treatment in these trials.

TABLE 6 *Effect of pioglitazone on HbA_{1c} (%) in drug-naive patients*

Study	Placebo	Pioglitazone dose			
PNFP-001[61]		**7.5 mg***	**15 mg***	**30 mg**	**45 mg**
Baseline %	9.04			9.31	9.96
Change at 26 weeks	+0.62			–0.64	–1.93
LS mean difference				–1.26	–2.55
PNFP-026[61]					
Baseline %	10.31			10.13	
Change at 16 weeks	+0.09			–0.89	
LS mean difference				–0.98	
PNFP-012[61]				**7.5/15/30 mg**	**15/30/45 mg**
Baseline %	10.21			10.25	10.36
Change at 24 weeks	+0.83			–1.45	–1.76
LS mean difference				–2.28	–2.59

* *Data submitted in confidence to NICE are not reported here*

TABLE 7 *Effect of pioglitazone on HbA_{1c} (change from baseline ± SD) in Japanese studies, analysed by intention to treat*

Study	HbA_{1c} (change from baseline ± SD)			
	Placebo	**Pioglitazone**		
		15 mg	**30 mg**	**45 mg**
CCT-001[66]	+0.43 ± 0.86	–0.48 ± 1.51	–0.95 ± 1.22	–0.96 ± 1.61
CCT-011[60]	–0.02 ± 0.99		–1.08 ± 1.47	

SD, standard deviation

TABLE 8 *Effect of pioglitazone on FBG (mmol/l) in drug-naive patients*

Study	Placebo	Pioglitazone			
PNFP-001[61]		**7.5 mg**	**15 mg**	**30 mg**	**45 mg**
Baseline (mmol/l)	12.7			12.5	13.1
Change at 26 weeks (mmol/l)	+0.8	–1.4*	–2.0*	–2.3	–3.6
LS mean difference				–3.1	–4.4
PNFP-026[61]					
Baseline (mmol/l)	14.8			14.0	
Change at 16 weeks (mmol/l)	+0.2			–3.2	
LS mean difference				–3.4	
PNFP-012[61]				**7.5/15/30 mg**	**15/30/45 mg**
Baseline (mmol/l)	13.8			13.5	13.1
Change at 24 weeks (mmol/l)	+1.7			–1.8	–3.6
LS mean difference				–3.5	–5.3

* *These figures are estimates taken from a graph on the FDA website*[61]

TABLE 9 *Percentage of patients, by drug dose, who responded to treatment in study PNFP-012*

Outcome measure	Patients responding (%)		
	Placebo	Pioglitazone	
		7.5/15/30 mg	15/30/45 mg
HbA_{1C}	9.6	52.9	49.4
FBG	17.9	62.2	63.5

TABLE 10 *Effect of pioglitazone on FBG (mean % change from baseline ± SD)*

Study	FBG (mean % change from baseline ± SD)			
	Placebo	Pioglitazone		
		15 mg	30 mg	45 mg
CCT-001[66]	+2.8 ± 14.2	–11.1 ± 17.0	–15.7 ± 15.6	–20.4 ± 17.3
CCT-011[60]	+3.2 ± 16.5		–14.0 ± 16.2	

TABLE 11 *Effect of pioglitazone on mean FBG (mmol/l), by visit, in study PNFP-011*[61]

Visit	Mean FBG (mmol/l)			
	Additional patients*	Rollover placebo patients	Rollover pioglitazone patients	All patients
Screening	12.2	12.9	12.6	12.4
Baseline	14.6	15.1	14.9	14.8
End-point of study PNFP-001	NA	15.5	12.9	13.5
Week 4	13.8	15.0	13.7	13.9
Week 8	13.0	14.7	13.5	13.3
Week 12	11.1	13.4	12.6	11.9
Week 24	10.0	12.2	11.7	10.9
Week 36	9.9	11.4	11.0	10.4
Week 48	9.7	10.6	10.5	10.0
Week 60	9.5	9.6	10.6	9.9
Week 72	10.5	8.9	10.0	10.1

NA, not applicable

* *Extra patients recruited after the end of study PNFP-001*

In study CCT-001, the 45-mg dose was associated with a statistically significant decrease in FBG compared with both the 15-mg dose and placebo,[66] while in CCT-011, the 30-mg dose was associated with a statistically significant decrease in FBG compared with placebo.[60]

The results of study PNFP-011 (the open-label extension study) show that the effect of pioglitazone on blood glucose was maintained for at least 72 weeks.[61] These data are summarised in *Table 11*.

Unfortunately, although the medical review on the FDA website[61] states that the falls in HbA_{1C} level and FBG were statistically significant, no confidence limits or *p*-values are quoted. The statistical review does present standard errors (SEs) and confidence limits for the change in HbA_{1C}, but only for all patients combined, not separately for drug-naive patients.

Effect on fasting C peptide and insulin

A statistically significant fall of approximately 10% was observed in the fasting C peptide and insulin levels in treated patients in study PNFP-026 ($p < 0.05$). This decrease was not observed in studies PNFP-001 and PNFP-012.[61] Trials CCT-001 and CCT-011 gave no information on fasting C

peptide levels. In CCT-001, a statistically significant decrease in blood insulin was observed in patients receiving 45 mg of pioglitazone, compared with those on either 15 mg or placebo;[66] however, in CCT-011, no statistically significant difference was seen between the treatment and control groups.[60]

Effect on blood lipids*

Again, the presentation of data on the FDA website[61] is complicated. The medical review contains a summary, drawn from studies PNFP-001, PNFP-026 and PNFP-012, of the effect of pioglitazone on lipids in drug-naive patients, but it does not provide any statistical analysis (*p*-values or confidence limits). The statistical review presents data from each study separately, with statistical analysis, but without separating out drug-naive from previously treated patients.

The medical review suggests that the 45-mg dose of pioglitazone did lead to a fall in triglyceride levels of the order of 1 mmol/l in drug-naive patients. Although a fall is reported at lower doses, it is not quoted as being statistically significant.

The statistical review, which analysed drug-naive and previously treated patients together, reports a consistent fall in triglycerides of the same order of magnitude in all three studies when pioglitazone was used at higher doses (45 mg in PNFP-001; 15, 30 and 45 mg in PNFP-012; 30 mg in PNFP-026). Falls were seen at lower doses, but they did not reach statistical significance.

There is no consistent statistically significant effect of pioglitazone on total cholesterol, HDL cholesterol or LDL cholesterol levels reported in either the medical or statistical review.

The report of the open-label follow-up study (PNFP-011)[61] does not contain any data on lipid levels.

In trial CCT-001, no statistically significant difference in blood lipids was observed between patients on pioglitazone and those on placebo,[66] but in CCT-011, treatment with pioglitazone was associated with a statistically significant increase in HDL cholesterol relative to the control group ($p < 0.05$).[60]

Effect on body weight*

There was a consistent increase in weight in patients treated with pioglitazone in studies PNFP-001 and PNFP-012 (changes in weight were not reported for PNFP-026), while patients receiving placebo experienced a weight loss. The

TABLE 12 *Effect of pioglitazone on weight (kg) in drug-naive and previously treated patients (combined data) in US and Japanese studies*

Study	Placebo	Pioglitazone			
PNFP-001		**7.5 mg**	**15 mg**	**30 mg**	**45 mg**
Baseline (kg)	90.35	93.54	91.19	90.29	90.77
Change at 26 weeks (kg)	–0.73	+0.04	+2.83	+2.92	+4.66
PNFP-012				**7.5/15/30 mg**	**15/30/45 mg**
Baseline (kg)	91.55			91.54	92.53
Change at 24 weeks (kg)	–1.70			+1.27	+2.58
LS mean difference				2.98	4.28
CCT-001					
Baseline (kg)	NS		NS	NS	NS
Change at 12 weeks (kg)	–0.08		–0.36	+0.55	+0.72
CCT-011					
Baseline (kg)	NS			NS	
Change at 12 weeks (kg)	+0.3			+0.8	

NS, not specified

* Data were submitted to NICE in confidence regarding the effects of pioglitazone on lipids and weight changes, as well as response by category of patient for company-sponsored trials. Some of this information is not publicly available and is thus not reported here.

extent of weight gain was related to pioglitazone dose.[61] The changes are summarised in *Table 12*.

In the report on study CCT-001, there is inconsistency between the text and a graph. According to the text, patients on 15 mg of pioglitazone lost 0.36 kg, but the graph shows a gain of approximately this amount. There was significant weight gain in patients on 30 and 45 mg of pioglitazone ($p < 0.05$).[66] In CCT-011, the difference in weight gain between the treatment and placebo groups was statistically significant.[60]

*Results: combination therapy studies**

Formal meta-analysis of the combination therapy studies (OCT-003, PNFP-010, PNFP-014, PNFP-027 plus the unnamed study) was neither possible nor appropriate because each evaluated pioglitazone in combination with a different drug.

Effect on blood glucose

There were statistically significantly greater reductions in HbA_{1C} and FPG, between baseline and end-point, for patients treated with the pioglitazone combination, compared with the placebo combination, in all three US studies. The overall effects of treatment on HbA_{1C} percentages are summarised in *Table 13*.

There was similarly a statistically significant effect on blood glucose levels in patients receiving the pioglitazone combination, compared with the placebo combination. Because the full fall in blood glucose took from 8 weeks (in studies PNFP-010 and PNFP-014) to 12 weeks (in study PNFP-027), the HbA_{1C} changes at 16 weeks may not reflect fully the fall in blood glucose and so underestimate the overall effect. The overall effects on FBG are summarised in *Table 14*.

TABLE 13 *Effect of pioglitazone on HbA_{1C} (%) in combination therapy*

Study	Placebo + monotherapy	Combination therapy		
PNFP-010	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg/day**	**Sulphonylurea + pioglitazone 30 mg/day**	
Baseline %	9.86	10.01	9.93	
Change at 16 weeks	+0.06	–0.82	–1.22	
LS mean difference		–0.88 (95% CI, –1.17 to –0.58)	–1.28 (95% CI, –1.57 to 0.99)	
PNFP-014	**Insulin + placebo**	**Insulin + pioglitazone 15 mg/day**	**Insulin + pioglitazone 30 mg/day**	
Baseline %	9.75	9.75	9.84	
Change at 16 weeks	–0.26	–0.99	–1.26	
LS mean difference		–0.73 (95% CI, –1.00 to 0.47)	–1.00 (95% CI, –1.27 to 0.74)	
PNFP-027	**Metformin + placebo**		**Metformin + pioglitazone 30 mg/day**	
Baseline %	9.77		9.92	
Change at 16 weeks	+0.19		–0.64	
LS mean difference			–0.83 (95% CI, –1.15 to 0.51)	
OCT-003	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg/day**	**Sulphonylurea + pioglitazone 30 mg/day**	**Sulphonylurea + pioglitazone 45 mg/day**
Baseline %	9.62	10.23	10.32	9.81
Change at 12 weeks	+0.47	–0.65	–1.15	–1.09

* Data regarding one Japanese combination therapy trial were submitted by Takeda in confidence to NICE, and therefore are not reported here nor included in the discussion.

Trial OCT-003 also showed a fall in HbA_{1C} of 1.09% in patients on 45 mg of pioglitazone, 1.15% in those on 30 mg and 0.65% in those on 15 mg, compared with an increase of 0.47% in those on placebo.[59] The unnamed study also saw a mean fall in HbA_{1C} of 1.7% in patients on pioglitazone; no information was provided in relation to the placebo group.[71]

In an open-label continuation of study PNFP-010, patients were treated with doses of 30–45 mg of pioglitazone in combination with sulphonylurea daily. The fall in HbA_{1C}, compared with baseline, was maintained over the extended period, with an overall mean fall at 40 weeks of 1.41% (SE, 0.11%).[63] Similarly, in an open-label extension of study PNFP-027, the fall was also maintained, with a mean decrease at 40 weeks of 1.06% (SE, 0.20)[63] and at 72 weeks of –1.36%.[62]

Proportion responding to treatment

Information on the proportion of patients responding to treatment in three combination studies (PNFP-010, PNFP-014 and PNFP-027) has been published in abstract form.[75,79,80] Response to treatment was defined in two ways, with reference to the HbA_{1C} and FBG. HbA_{1C} responders were defined as patients who achieved an HbA_{1C} of less than 6.1% and/or a fall of at least 0.6% from baseline. FBG responders were defined as patients who had a fall of at least 1.66 mmol/l. For patients who also received insulin, those whose insulin dose increased by more than 25% were not considered to be responders. The results are given in *Table 15*.

Thus, the addition of pioglitazone to other anti-diabetic medication appears to lead to a higher proportion of patients responding to treatment, compared with the addition of placebo, and there appears to be a dose–response effect.

FBG

In the open-label continuation of study PNFP-010,[63] the fall in FBG (actually reported as FPG, which is used interchangeably with FBG), compared with baseline, was maintained over the extended period, with an overall mean fall at 40 weeks of 3.4 mmol/l (SE, 0.3 mmol/l). Similarly, in the open-label extension of PNFP-027, the fall was also maintained, with a mean decrease at 40 weeks of 3.3 mmol/l (SE, 0.42 mmol/l).[63]

In trial OCT-003, the mean decrease in FBG was 21.7% in patients on 45 mg of pioglitazone, 20.0% in those on 30 mg and 11.8% in those on 15 mg, compared with a mean increase of 0.8% in those on placebo.[59] In the unnamed study, there was a mean decrease of 2.7 mmol/l in FPG in patients on pioglitazone, but no significant change was found in the placebo group.[71]

TABLE 14 *Effect of pioglitazone on FBG (mmol/l) in combination therapy*[61]

Study	**Placebo + monotherapy**	**Combination therapy**	
PNFP-010	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg/day**	**Sulphonylurea + pioglitazone 30 mg/day**
Baseline (mmol/l)	13.1	13.7	13.3
Change at 16 weeks (mmol/l)	+0.3	–1.9	–2.9
LS mean difference		–2.2 (95% CI, –2.9 to 1.5)	–3.2 (95% CI, –3.9 to 2.6)
PNFP-014	**Insulin + placebo**	**Insulin + pioglitazone 15 mg/day**	**Insulin + pioglitazone 30 mg/day**
Baseline (mmol/l)	12.3	12.3	12.7
Change at 16 weeks (mmol/l)	0.0	–1.9	–2.7
LS mean difference		–1.9 (95% CI, –2.8 to 1.1)	–2.7 (95% CI, –3.6 to 1.8)
PNFP-027	**Metformin + placebo**		**Metformin + pioglitazone 30 mg/day**
Baseline (mmol/l)	14.4		14.1
Change at 16 weeks (mmol/l)	–0.3		–2.4
LS mean difference			–2.1 (95% CI, –2.7 to 1.4)

TABLE 15 *Proportion of responders in combination therapy trials*

Pioglitazone dose	Combination drug	HbA_{1c} responders (%)	FBG responders (%)
Placebo only	Sulphonylurea	23.8	22.2
15 mg	Sulphonylurea	56.8	52.9
30 mg	Sulphonylurea	74.2	66.7
Placebo only	Metformin	21.6	23.6
30 mg	Metformin	54.0	59.4
Placebo only	Insulin	31.6	30.7
15 mg	Insulin	69.5	52.5
30 mg	Insulin	75.1	64.7

Effect on fasting C peptide and insulin*
There was a significant fall in both fasting C peptide and insulin levels in patients on pioglitazone combination treatment in studies PNFP-010 and PNFP-027. In study PNFP-014 (pioglitazone combined with insulin treatment), the fall in fasting C peptide levels was significant for the 15-mg pioglitazone group but not for the 30-mg group.[61]

The report of trial OCT-003 states that both "blood IRI" and "blood CPR" were improved in patients on 30-mg and 45-mg treatment, without explaining these measures or giving any figures.[59] IRI and CPR may refer to immunoreactive insulin and C-reactive protein level, respectively.

Effect on blood lipids
The level of triglyceride in the 30-mg pioglitazone combination group was significantly reduced, compared with the placebo combination group, in each of the three US trials, with a fall of the order of 0.7 mmol/l. HDL cholesterol levels increased in the pioglitazone combination treatment groups, compared with the placebo combination groups. There was no change in total cholesterol or LDL cholesterol levels. The details of the effect on lipids are given in *Tables 16–19*.

In study OCT-003, a statistically significant decrease in triglyceride was observed in patients on both 30- and 45-mg pioglitazone.[59] Treatment was not associated with any change in total cholesterol in this study.[59]

Also in OCT-003, HDL cholesterol levels increased in all groups. The increase was statistically significantly greater in the 45-mg pioglitazone group than in the other groups.[59]

LDL cholesterol levels were not measured in all patients. Furthermore, the table with details of the LDL cholesterol levels in study PNFP-014 appears to have been misprinted in the statistical review on the FDA website.[61] Therefore, the results are not reproduced here.

The published report of study PNFP-027[62] shows the changes in lipid levels in a different way, presenting the results as LS mean percentage change from baseline, rather than as absolute change. The results showed a significant percentage change from baseline in triglycerides, HDL, LDL and total cholesterol in patients on pioglitazone ($p < 0.05$), as well as a significant difference between the pioglitazone and placebo-treated groups in the change in triglyceride levels from baseline ($p < 0.05$).

The changes seen at 16 weeks (a fall in triglycerides and an increase in HDL cholesterol) were maintained at 40 weeks in both the metformin and sulphonylurea combination studies.[63] It is worth noting that there was no further change in lipid levels at 40 weeks compared with that reported at 16 weeks.

Effect on body weight
In the combination studies, body weight increased significantly in the pioglitazone groups compared with the placebo groups. The differences from placebo were related to the dose of pioglitazone administered and, with the exception of the Japanese study OCT-003, were greater when pioglitazone was combined with insulin or sulphonylurea than when it was combined with metformin. In study OCT-003, however, mean weight increases in patients taking pioglitazone and sulphonylurea were lower than those in patients in PNFP-027

* Data regarding one Japanese combination therapy trial were submitted by Takeda in confidence to NICE and therefore are not reported here. These data included information regarding the effects of pioglitazone on blood insulin when used in combination therapy.

TABLE 16 *Effect of pioglitazone on triglycerides (mmol/l) in combination therapy*[61]

Study	**Placebo + monotherapy**	**Combination therapy**	
PNFP-010	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg/day**	**Sulphonylurea + pioglitazone 30 mg/day**
Baseline (mmol/l)	2.92	3.07	2.93
Change at 16 weeks (mmol/l)	–0.03	–0.44	–0.80
LS mean difference		–0.41 (95% CI, –0.88 to 0.06)	–0.77 (95% CI, –1.24 to –0.30)
PNFP-014	**Insulin + placebo**	**Insulin + pioglitazone 15 mg/day**	**Insulin + pioglitazone 30 mg/day**
Baseline (mmol/l)	2.74	2.60	2.96
Change at 16 weeks (mmol/l)	+0.12	–0.13	–0.56
LS mean difference		–0.25 (95% CI, –0.79 to 0.28)	–0.68 (95% CI, –1.21 to –0.15)
PNFP-027	**Metformin + placebo**		**Metformin + pioglitazone 30 mg/day**
Baseline (mmol/l)	3.39		3.37
Change at 16 weeks (mmol/l)	–0.23		–0.72
LS mean difference			–0.49 (95% CI, –0.94 to –0.04)

TABLE 17 *Effect of pioglitazone on cholesterol (mmol/l) in combination therapy*[61]

Study	**Placebo + monotherapy**	**Combination therapy**	
PNFP-010	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg/day**	**Sulphonylurea + pioglitazone 30 mg/day**
Baseline (mmol/l)	5.48	5.49	5.55
Change at 16 weeks (mmol/l)	+0.19	+0.02	+0.06
LS mean difference		–0.17 (95% CI, –0.40 to 0.05)	–0.13 (95% CI, –0.35 to 0.09)
PNFP-014	**Insulin + placebo**	**Insulin + pioglitazone 15 mg/day**	**Insulin + pioglitazone 30 mg/day**
Baseline (mmol/l)	5.54	5.52	5.37
Change at 16 weeks (mmol/l)	–0.08	0.00	–0.05
LS mean difference		0.08 (95% CI, –0.11 to 0.27)	0.04 (95% CI, –0.15 to 0.23)
PNFP-027	**Metformin + placebo**		**Metformin + pioglitazone 30 mg/day**
Baseline (mmol/l)	5.49		5.51
Change at 16 weeks (mmol/l)	–0.03		+0.15
LS mean difference			0.18 (95% CI, –0.03 to 0.39)

TABLE 18 *Effect of pioglitazone on HDL cholesterol (mmol/l) in combination therapy*[61]

Study	Placebo + monotherapy	Combination therapy	
PNFP-010	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg/day**	**Sulphonylurea + pioglitazone 30 mg/day**
Baseline (mmol/l)	1.11	1.07	1.08
Change at 16 weeks (mmol/l)	–0.03	+0.04	+0.10
LS mean difference		0.06 (95% CI, 0.02 to 0.11)	0.13 (95% CI, 0.08 to 0.17)
PNFP-014	**Insulin + placebo**	**Insulin + pioglitazone 15 mg/day**	**Insulin + pioglitazone 30 mg/day**
Baseline (mmol/l)	1.10	1.12	1.11
Change at 16 weeks (mmol/l)	–0.02	+0.06	+0.07
LS mean difference		0.07 (95% CI, 0.02 to 0.13)	0.09 (95% CI, 0.03 to 0.14)
PNFP-027	**Metformin + placebo**		**Metformin + pioglitazone 30 mg/day**
Baseline (mmol/l)	1.09		1.11
Change at 16 weeks (mmol/l)	0.00		+0.08
LS mean difference			0.08 (95% CI, 0.03 to 0.13)

TABLE 19 *Effect of pioglitazone on LDL cholesterol (mmol/l) in combination therapy*[61 *]

Study	Placebo + monotherapy	Combination therapy	
PNFP-010	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg/day**	**Sulphonylurea + pioglitazone 30 mg/day**
Baseline (mmol/l)	3.22	3.22	3.28
Change at 16 weeks (mmol/l)	+0.15	+0.08	+0.13
LS mean difference		–0.08 (95% CI, –0.23 to 0.08)	0.02 (95% CI, –0.18 to 0.14)
PNFP-027	**Metformin + placebo**		**Metformin + pioglitazone 30 mg/day**
Baseline (mmol/l)	3.06		3.09
Change at 16 weeks (mmol/l)	+0.07		+0.18
LS mean difference			0.11 (95% CI, –0.03 to 0.24)

[*] *The table with details of the LDL cholesterol levels in study PNFP-014 appears to have been misprinted in the statistical review on the FDA website.*[61] *Therefore, the results are not reproduced here*

taking pioglitazone and metformin. Those details of the changes in body weight that it is possible to extract from the data available are shown in *Table 20.*

Data on changes in body weight reported in the published papers[62,63] differ slightly, but not to any significant extent, from those quoted on the FDA website[61] for the same studies.

The unnamed study also specifically reports a mean increase in body fat content of 3.5 kg for patients on pioglitazone and sulphonylurea.[71]

TABLE 20 *Effect of pioglitazone on body weight (kg) in combination therapy*

Study	Placebo + monotherapy	Combination therapy		
OCT-003[59]	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg/day**	**Sulphonylurea + pioglitazone 30 mg/day**	**Sulphonylurea + pioglitazone 45 mg/day**
Change at 12 weeks (kg)	–0.07	+0.62	+1.26	+0.98
Unnamed study[71]	**Sulphonylurea + placebo**			**Sulphonylurea + pioglitazone 45 mg/day**
4 months	Data not available			+3.6
PNFP-010[61]	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg/day**	**Sulphonylurea + pioglitazone 30 mg/day**	
Change at 16 weeks (kg)	–0.83	+2.18	+3.92	
PNFP-014[61]	**Insulin + placebo**	**Insulin + pioglitazone 15 mg/day**	**Insulin + pioglitazone 30 mg/day**	
Change at 16 weeks (kg)	–0.11	+2.53	+3.92	
PNFP-027[61]	**Metformin + placebo**		**Metformin + pioglitazone 30 mg/day**	
Baseline (kg)	93.96		93.24	
Change at 16 weeks (kg)	–1.06		+1.41	
LS mean difference			2.48 (95% CI, 1.72 to 3.23)	

A review of the safety and tolerability of pioglitazone[76] includes a figure combining data from the monotherapy and combination studies, which shows weight changes over a period of up to 60 weeks (European and Japanese studies) and 96 weeks (US studies). Although the text of the paper states that "weight increases tended to occur over the first months of treatment and then stabilised", this is not in fact born out by the figure itself. This figure shows weight in the European and Japanese studies continuing to increase for as long as the data were recorded (60 weeks), and in the US study continuing to increase up to 84 weeks. Whether or not the weight gain reaches a plateau cannot be stated with certainty without longer-term follow-up studies.

In the US studies, there appears to have been a mean increase of up to 4 kg, while the increase was less in the European and Japanese studies. The European studies placed greater emphasis than the American studies on dietary advice.

Effect on blood pressure

There are no data either in the abstracts or on the FDA website[61] on the effect of pioglitazone on blood pressure. One published study review[76] found no change in patients on pioglitazone or placebo, but reported that diastolic blood pressure tended to show small decreases in those receiving pioglitazone, compared with placebo.

Response by category of patients*

The FDA website[61] contains data showing the response to pioglitazone in men and women. In both the PNFP-010 and PNFP-027 studies, the fall in HbA_{1C} was greater in women than men *Table 21*. The website also shows data on the different effect in patients below and above the

* Data regarding one Japanese combination therapy trial were submitted by Takeda in confidence to NICE and are therefore not reported here. These data included information regarding mean changes from baseline in HbA_{1C} (%) according to patients' baseline HbA_{1C} value (< or > 9%).

TABLE 21 *Mean change from baseline in HbA_{1C} (%), by gender*

Study	Placebo + monotherapy	Combination therapy	
PNFP-027	**Metformin + placebo**		**Metformin + pioglitazone 30 mg**
Men: baseline mean (%)	9.74		9.83
Mean change (%)	+0.28		–0.44
SE	0.12		0.16
Women: baseline mean (%)	9.74		10.00
Mean change (%)	+0.39		–0.94
SE	0.19		0.15
PNFP-010	**Sulphonylurea + placebo**	**Sulphonylurea + pioglitazone 15 mg**	**Sulphonylurea + pioglitazone 30 mg**
Men: baseline mean (%)	9.87	9.81	9.85
Mean change (%)	+0.03	–0.62	–0.96
SE	0.119	0.118	0.133
Women: baseline mean (%)	9.83	10.29	10.02
Mean change (%)	+0.03	–1.07	–1.56
SE	0.115	0.135	0.129

age of 65 years. In neither study was there any statistically significant difference.

Assessment of effectiveness

Summary of evidence available and synthesis of information

Limited evidence relating to the clinical effectiveness of pioglitazone is available in the public domain. Currently, there is one full study report[62] published in English that has gone through the peer-review process. Indeed, the only published evidence that we were able to find consisted of a number of conference abstracts, clinical trial reports in a Japanese journal (written in Japanese, with no readily available English translation), as well as the medical and statistical reviews undertaken by the US FDA and available on their website.[61] These reviews relate to the same clinical trials reported in the abstracts. The submission received from Takeda UK[58] includes further details relating to these studies and also synopses of other studies carried out in Europe.

Nevertheless, what evidence is available does indicate that pioglitazone is effective at reducing blood glucose in patients with poorly controlled type 2 diabetes, both when it is used as monotherapy and when used in combination with metformin, sulphonylurea or insulin.

Clinical effect size

The trials indicate that, when used as monotherapy, pioglitazone at doses from 7.5 to 45 mg daily leads to a fall in blood glucose and HbA_{1C} that appears to be sustained for at least 72 weeks. The extent of the fall in HbA_{1C} in the studies was between 0.56% and 1.93%. There appears to be a dose–response effect. However, those patients who were transferred from another oral hypoglycaemic agent (metformin or sulphonylurea) to pioglitazone did not achieve the same level of glycaemic control as they had previously experienced, indicating lesser efficacy as a monotherapy than comparator agents. Only one study[58] has directly compared pioglitazone with another antidiabetic agent.

When used in combination with metformin, sulphonylurea or insulin, pioglitazone at doses of 15 or 30 mg daily led to a significant fall in blood glucose and HbA_{1C}. The effect was greater at the higher dose than at the lower dose. The extent of the fall in HbA_{1C} was between 0.64% and 1.26%. This effect was maintained for at least 40 weeks.[63]

There is no direct evidence available on the effect of pioglitazone on diabetic complications, including cardiovascular mortality. The UKPDS study[4,5,77] demonstrated that improved glycaemic control reduces the incidence of microvascular complications. It would not be unreasonable to expect that this effect would hold true if the improved glycaemic control is achieved through using pioglitazone, provided that there are not

any adverse effects on cardiovascular and microvascular risk factors.

There is evidence from the clinical trials that pioglitazone has an impact on recognised cardiovascular risk factors. When used as monotherapy, pioglitazone at a dose of 30–45 mg tended to lead to a significant fall in triglyceride levels, although this decrease was not seen in all studies. There was no consistent effect on other lipid fractions. However, when used in combination therapy, there was a consistent fall in triglycerides when pioglitazone doses of 30 mg or more were used, and also a statistically significant increase in HDL cholesterol levels. These changes were achieved within 8 weeks of treatment and were maintained for at least 40 weeks.[63] Other things being equal, the changes in lipids could be expected to lead to a reduction in cardiovascular risk.

Any consequent reduction in cardiovascular risk would be countered, however, by the increased risk associated with the significant and progressive weight gain observed in patients on treatment. This weight gain is a consistent feature of the studies and persists for at least a year.[76] How these two competing effects balance out will become apparent only if careful long-term, longitudinal follow-up studies are undertaken.

The approved indication for pioglitazone is "in oral combination treatment for type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated dose of oral monotherapy with either metformin or a sulphonylurea:

- in combination with metformin only in obese patients
- in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated."

Underlying this approved indication is an assumption that the combination of metformin and sulphonylurea is to be preferred, unless it is contraindicated.

There are no reports of pioglitazone in combination therapy compared directly with other possible combinations (e.g. sulphonylurea plus metformin, or rosiglitazone in combination, or insulin with or without an oral antidiabetic agent). This lack of evidence is unfortunate because, from the clinical point of view, the natural role for pioglitazone would be as an adjunct to one of the established oral hypoglycaemic agents, and what is needed is information about clinical effectiveness and cost-effectiveness in comparison with alternative drug regimens.

Adverse effects of the intervention

The size and length of the studies reviewed here are such that they could not be expected to detect rare adverse events or those that depend on prolonged exposure.

Hepatitis

A significant safety concern associated with pioglitazone was the possibility that it might be associated with hepatitis in the same way that troglitazone was (and which led to its withdrawal). In the studies reviewed by the FDA,[61] the reported incidence of elevation of alanine transaminase greater than three times the upper limit of normal was no different between pioglitazone-treated patients and those who received placebo. At 0.26%, the reported rate was lower than the rate in troglitazone-treated patients in controlled trials (1.90%) and therefore is in line with the reported rate for other antidiabetic agents. However, the relatively small number of patients with long-term exposure to pioglitazone means that a longer-term tendency to produce hepatitis cannot be ruled out. The therapeutic dose of pioglitazone is lower than that of troglitazone. Consequently, if hepatotoxicity is equivalent on a weight-for-weight basis, it will take longer for liver damage to become apparent than was the case with troglitazone, because of the lesser amount of the drug actually used.

Other possible adverse effects are oedema, a fall in haemoglobin, creatine phosphokinase (CPK) elevation and hypoglycaemia.

Oedema[*]

Oedema was reported more commonly as an adverse event in patients treated with pioglitazone than with placebo, in both the monotherapy and combination therapy trials (*Table 22*).[58,59,61,62,76] The overall figures quoted on the FDA website[61] for oedema are 6.6% for pioglitazone-treated patients and 2.3% for placebo-treated patients.

In the Japanese monotherapy study CCT-001, 3% of patients (two of 63) in the 45-mg pioglitazone

[*] Empirical evidence of oedema as a result of pioglitazone monotherapy was provided within the information provided in confidence to NICE by Takeda. This information is not reported here.

TABLE 22 *Prevalence of oedema in combination therapy trials:* n *(%)*[*]

Study	Placebo	Pioglitazone 15 mg	Pioglitazone 30 mg	Pioglitazone 45 mg
OCT-003[59] Oedema				
PNFP-010 Oedema/peripheral oedema				
PNFP-014[58] Oedema/peripheral oedema				
PNFP-027[62] Oedema/peripheral oedema	*n* = 160 *n* = 4 (2.5%)		*n* = 168 *n* = 10 (5.9%)	

[*] *Much of the data originally contained within this table were submitted to NICE in confidence and are therefore not reported here*

group and 1.5% (one of 66 patients) in the placebo group suffered oedema,[66] whereas in the CCT-011 study, 11.7% of patients (nine of 77) taking pioglitazone suffered oedema, compared with none in the placebo group.[60]

Haemoglobin
There is a consistent, but not clinically significant, fall in haemoglobin (of the order of 0.38 g/dl) in patients treated with pioglitazone.

Cardiac
One patient in study PNFP-026 was noted to have developed left ventricular hypertrophy and left bundle branch block on electrocardiograph (ECG), which resolved when the drug was withdrawn. Five other patients were noted to have cardiomegaly on X-ray. New ECG findings were equally distributed between pioglitazone- and placebo-treated patients.[61]

CPK
Seven male patients in the US studies were reported to have CPK values greater than ten times the normal upper limit. These values normalised in four patients still on the drug and in two patients off the drug, and one patient had falling, but not yet normal, levels on follow-up.[61] In one of the Japanese studies (OCT-003[59]), episodes of elevated CPK were more common in patients on pioglitazone than in those on placebo; in another study (CCT-011[60]), the number of episodes was the same in either group.

Weight gain
As noted earlier, weight gain is a worrying side-effect of pioglitazone treatment. Weight gains of up to 4 kg have been observed[76] over the course of 1 year of treatment. Whether or not the weight gain reaches a plateau cannot be stated with certainty without longer-term follow-up studies.

Summary and conclusions of the evidence for and against the intervention

The evidence reviewed in this report indicates that pioglitazone is clinically effective at reducing blood glucose in patients with type 2 diabetes mellitus when used alone or in combination with other oral antidiabetic agents (metformin or a sulphonylurea). It is to be expected that this treatment will lead to a reduced risk of diabetic complications.

However, no evidence is available as to the relative effectiveness of pioglitazone compared with other oral antidiabetic agents (metformin, sulphonylureas or rosiglitazone) or insulin, when used as an alternative additional agent for patients who have inadequate glycaemic control on oral monotherapy.

No evidence is available as to the longer-term effect of pioglitazone on glycaemic control, nor is any direct evidence available as to the effect on diabetic complications, including death from cardiovascular causes. The progressive weight increases associated with pioglitazone treatment must remain a concern.

Chapter 4

Economic analysis

Overview of economic assessment

A limited number of direct assessments have been undertaken that assess the economic outcomes of treatments for type 2 diabetes mellitus. One of the key RCTs in the field of diabetes was undertaken by the Diabetes Control and Complications Trial (DCCT) Research Group;[80] however, this study focused on type 1 diabetes. Within the UK, the most pertinent study is the UKPDS, a large randomised study observing the effects of various interventions on the incidence of diabetes-related complications in people with type 2 diabetes. Most economic assessments within the field of diabetes have been undertaken using largely homogeneous modelling methods, which utilise the data from the DCCT[80] together with a limited number of other cohort studies.

Our economic analysis includes a systematic review of the cost-effectiveness evidence relating to pioglitazone. In addition, modelling literature concerning the treatment of type 2 diabetes mellitus is reviewed.

Methods

A systematic literature search was undertaken for economic assessments of pioglitazone. Methodological details of this search strategy are presented in chapter 3 (see *Search strategy*).

A broader topic search was undertaken for economic or model-based assessments within diabetes. This search was used to identify assessments that attempt to estimate the long-term impact of glucose-lowering treatments in type 2 diabetes mellitus and that do not limit their scope to individual complications of diabetes. The purpose of this topic review was to generate classification criteria for the evaluation of submitted economic evidence. A generic pro forma for the critical appraisal of modelling studies in health economics is used in systematically reviewing studies identified. This appraisal is supplemented by a detailed review of the disease-specific factors within all modelling studies identified. Where possible, key outcomes are compared. The key outcomes reported within these studies are:

- mean lifetime risk for complication
- cost per life-year gained (LYG)
- years free from first significant complication
- estimated incidence of complication
- total lifetime costs for diabetes
- duration of stay in given health state.

Results of topic review for issues in health economic modelling of diabetes

The topic search for economic or model-based studies identified 81 studies that assessed the impact of treatments for type 2 diabetes mellitus on long-term complications. Details of the studies are available from the authors. Four studies focused on glucose-controlling interventions and addressed multiple complications of diabetes;[80–84] these studies are summarised in *Table 23* and appendix 3. Of the four published studies (five publications, four studies), two studies focused on type 2 diabetes mellitus; the remaining two studies focused on type 1 diabetes.

The key clinical events within the models of diabetes used in the four studies are identified below:

- **nephropathy**
  - no renal disease
  - microalbuminuria
  - macroalbuminuria
  - end-stage renal disease (ESRD)
  - kidney transplantation
  - haemodialysis
  - peritoneal dialysis
  - graft failure
  - ESRD-specific mortality

- **retinopathy**
  - no retinopathy
  - background retinopathy/non-proliferative retinopathy
  - proliferative retinopathy
  - macular oedema
  - blind/visual acuity less than 20/100 in better eye

- **acute myocardial infarction (AMI)**
  - no history of AMI
  - first AMI
  - thrombolysis
  - percutaneous transarterial coronary angioplasty
  - no reperfusion therapy
  - recurrent AMI
  - death following AMI

- **stroke**
  - no history of stroke
  - first stroke
  - recurrent stroke
  - death following stroke

- **amputation**
  - no history of amputation/no neuropathy
  - symptomatic neuropathy
  - first amputation
  - recurrent amputation
  - death following amputation

- **hypoglycaemia**
  - no hypoglycaemic event
  - severe hypoglycaemia requiring medical assistance
  - death from hypoglycaemic event

- **ketoacidosis**
  - no ketoacidosis event
  - ketoacidosis
  - death from ketoacidosis

- **other important events held within the models**
  - known epidemiology
  - effects of interventions
  - death from non-specific causes

- **observable events for use in calibrating and validating a model**
  - life expectancy
  - incidence of individual complications
  - incidence of non-complication-specific mortality.

Results of systematic search for economic studies of pioglitazone

There are no published studies investigating the health economics of pioglitazone or indeed of any other thiazolidinedione.

The only available economic evidence concerning pioglitazone is that obtained as part of the confidential submission by the sponsoring body, Takeda UK Ltd. The economic submission utilised a model of the use of pioglitazone in people with type 2 diabetes mellitus. The design of the model was based on work reported by Palmer and co-workers,[83] and information on the health service and other costs of type 2 diabetes was derived from the Diabetes Audit and Research in Tayside Scotland (DARTS)[85] database. Both the model and DARTS cost data were held to be confidential and are therefore not reported here.

A structured pro forma has been used in the critical appraisal of the economic submission for pioglitazone.[58] To determine how the unpublished submission compares with published models in diabetes, the same pro forma has been used in summarising the four studies identified above (see *Results of topic review for issues in health economic modelling of diabetes*).[80–84] A summary of the critical appraisal of these studies is included in appendix 4. A detailed discussion of some of the key factors, describing their handling in the published papers, is given below, together with a summary of conclusions of the critical appraisal of the confidential model.

Statement of the problem

The four published studies[80–84] focus on the impact of glucose-controlling interventions (for both type 1 and type 2 diabetes) on the associated long-term complications. These studies compare the effects of intensive glucose-controlling interventions against non-intensive management. The problem that has not yet been addressed, however, is an estimate of the impact of 'the effects on HbA_{1C}, total cholesterol and HDL cholesterol in type 2 patients' of treatment with pioglitazone combination therapy (added to either metformin or sulphonylurea), compared with other combination therapies or changing to insulin (i.e. comparison of different types of intensive glucose-controlling interventions in those people with type 2 diabetes whose blood glucose levels are poorly controlled by oral monotherapy with either metformin or sulphonylurea). Thus, while the underlying disease model may be appropriate and the direction of the results may be informative, the results of the published studies are not directly applicable to pioglitazone.

Cohort information

One of the key distinctions between the models is the focus on either type 1 or type 2 diabetes mellitus. Given that these are different diseases, the cohort data will vary significantly between models. It is known that type 1 disease has a significantly earlier onset than type 2 disease.

As the study by Palmer and co-workers[83] and the DCCT[80] considered the cost implications of type 1 diabetes, the age range of patients in the cohorts is markedly lower than that of patients used in the models proposed by Eastman and colleagues[81,82] and Vijan and co-workers.[84] The cohorts used in the models are described in *Table 24*.

The patient populations used within the model proposed by Eastman and colleagues[81,82] included 10,000 patients as a baseline cohort. In this cohort, 30.5%, 21.7%, 17.7% and 30.0% were within the age groups 25–44, 45–54, 55–64 and 65–74 years, respectively. The cohort used within the model by the DCCT Research Group[80] also included 10,000 patients. Equal proportions of males and females were included, and patients were also weighted by ethnicity. The mean age of model entry at clinical diagnosis of type 2 diabetes in the USA was 51 years. The patient population that was included in the two cohorts of patients in the model proposed by the DCCT Research Group[80] consisted of a sample of patients with type 1 diabetes in the USA who were considered eligible for enrolment in the DCCT (dependent on demographic and clinical characteristics). These two cohorts were classified as follows.

1. Patients in the conventional treatment arm (primary cohort) had neither retinopathy nor microalbuminuria, and a duration of disease of 1–5 years.
2. Patients in the intensive treatment arm had minimal-to-moderate non-proliferative retinopathy, excreted less than 200 mg of albumin in the urine per day and had a duration of diabetes of 1–15 years. It was assumed that approximately 17% of the US diabetic population would be eligible for enrolment.

It is important to note that the individual characteristics assigned to the patients in the DCCT[80] model will differ significantly from those of the model by Eastman and colleagues,[81,82] given the difference in disease type.

The patient population entering the model by Vijan and co-workers[84] is assumed to have an age range of 45–75 years; however, this age range is not explicitly stated within the literature. Patients within the cohort were assumed to have no clinically detectable microvascular complications at the time of diagnosis of diabetes. Patients who present with complications are already declared to be at high risk and therefore should be considered for intensive control. The study by Palmer and co-workers[83] focused on men with type 1 diabetes mellitus in Switzerland. The age of this representative cohort was 19 years

TABLE 23 *Summary of economic studies reviewed*

Study	Study design	Economic outcomes	Intervention type	Intervention	Scope
Eastman *et al.*, 1997[81,82]	Modelling	Cost-effectiveness	Glucose control	Conventional vs intensive therapy	Type 2 diabetes
Palmer *et al.*, 2000[83]	Modelling	Cost-effectiveness	Glucose control and screening	ACE inhibitors, conventional and intensive insulin therapy	Type 1 diabetes
Vijan *et al.*, 1997[84]	Modelling	None	Glucose control	Hypothetical	Type 2 diabetes
DCCT Research Group, 1996[80]	Modelling/ cost of illness	Cost-effectiveness	Glucose control	Conventional vs intensive therapy	Type 1 diabetes

TABLE 24 *Types of modelling used by the studies*

Study	Type of simulation	Type of model	Decision analysis	Monte Carlo technique
Eastman *et al.*, 1997[81,82]	Micro	Markov	Yes	Yes
Palmer *et al.*, 2000[83]	Micro (assumed)	Markov	Yes	Not stated
Vijan *et al.*, 1997[84]	Micro (assumed)	Markov	Yes	Not stated
DCCT Research Group, 1996[80]	Micro	Markov	Yes	Yes

because this is known to be the median age of onset of type 1 diabetes in Swiss men. This cohort age presents a limitation for the Palmer model because it does not recognise the variation in characteristics of individuals in the cohort.

Model structure and scope

The models by Eastman and colleagues[81,82] and the DCCT Research Group[80] use a Monte Carlo technique (*Table 24*). These two models take the form of a micro-simulation Markov model with a 1-year cycle, whereby patients enter the simulation as individuals rather than as a cohort. Upon beginning the simulation, patients are assigned individual characteristics, weighted to the incident cases of clinically diagnosed patients with type 2 diabetes in the US population, within the eligible age range criteria (type 1 diabetes in the DCCT[80]). The eligible age ranges used in these models are shown in the cohort information provided within *Table 25*.

These models by Eastman and colleagues[81,82] and the DCCT Research Group[80] reflect the typical model structure described in the paragraph above, incorporating the same three major complications associated with diabetes: neuropathy, nephropathy and retinopathy (*Table 26*). The model proposed by Palmer and co-workers[83] is similar to these models in terms of underlying structure, but it is presented in significantly more detail, proposing submodels for seven complications commonly associated with type 1 diabetes. These complications are neuropathy, nephropathy, retinopathy, stroke, AMI, ketoacidosis and hypoglycaemia. Clearly, the addition of these further complications into a diabetes model provides a more realistic representation of the complications typically experienced by patients with type 1 disease.

The model proposed by Vijan and co-workers[84] has by far the most limited scope. It calculates the risks for developing blindness and ESRD for patients at different ages of diabetes onset and different levels of glycaemic control. However, the model by Vijan and co-workers[84] excludes any complication-specific mortality and therefore considers only early-stage disease. Furthermore, while it is recognised that those patients at high risk of blindness and renal disease (as included in the model) have in turn a higher risk of developing neuropathy, Vijan and co-workers[84]

TABLE 25 *Cohort information used within the published models*

Study	Disease type	Cohort age range (years)	Source of cohort information	No. of patients in cohort
Eastman *et al.*, 1997[81,82]	Type 2 diabetes	25–74	WESDR	10,000
Palmer *et al.*, 2000[83]	Type 1 diabetes	19	Not stated	Not stated
Vijan *et al.*, 1997[84]	Type 2 diabetes	45–75 (assumed)	REP, WESDR	Not stated
DCCT Research Group, 1996[80]	Type 1 diabetes	13–39 (two cohorts)	WESDR	10,000

WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; REP, Rochester Epidemiology Project, Minnesota

TABLE 26 *Complications included within the published models*

Complication	Study			
	Eastman *et al.*, 1997[81,82]	Palmer *et al.*, 2000[83]	Vijan *et al.*, 1997[84]	DCCT Research Group, 1996[80]
Retinopathy	*	*	*	*
Neuropathy	*	*		*
Nephropathy	*	*	*	*
Heart disease	*	*		
Stroke		*		
Hypoglycaemia		*		
Ketoacidosis		*		

* *Complications included within the model*

do not include amputation and neuropathy in the model, as a result of an apparent lack of evidence. The model by Vijan and co-workers[84] calculates the risks of developing blindness and ESRD for patients at different ages of diabetes onset and different levels of glycaemic control.

Within the models proposed by Eastman and colleagues,[81,82] the DCCT Research Group[80] and Palmer and co-workers,[83] complications are presented as submodels and are linked to the consequences of CVD (for type 2 diabetes only) and a mortality submodel, which as a whole form the overall structure of the model. The data held within these two important factors in the models proposed by Eastman and colleagues[81,82] and the DCCT Research Group[80] are consistent with the known epidemiology of diabetes in the USA. Despite the DCCT[80] model's difference in focus from that of Eastman and colleagues[81,82] (i.e. type 1 versus type 2 diabetes, respectively), the underlying structure appears to be identical, because the complications represented as submodels are common to both type 1 and type 2 diabetes. The model proposed by Palmer and co-workers[83] has many distinct similarities to those proposed by Eastman and colleagues[81,82] and the DCCT Research Group[80] in terms of the underlying model structure, but the model by Palmer and co-workers[83] simulates the disease with markedly wider scope.

The models presented by Eastman and colleagues[81,82] and the DCCT Research Group[80] include three complications and a mortality submodel, which together are believed to reflect the natural history of vascular and neurological complications. The model by Eastman and colleagues[81,82] also includes a heart disease submodel. Within all the models reviewed,[80–84] there is no set sequence by which patients may experience the complications included within the model; rather, the submodels run in parallel. Another element of commonality is that all the submodels, for each study, are assumed to be mutually exclusive, and therefore no compound health states are included in the model.

Structure of submodels

Neuropathy submodel

The study by Eastman and colleagues[81,82] has a major strength in the explicit statements of hazard rates and transition probabilities, which are not provided by other authors. Besides slight disparities in terms of clinical definitions of health states, the DCCT[80] model is identical in structure to that of Eastman and colleagues.[81,82] In the models proposed by Eastman and colleagues[81,82] and the DCCT Research Group,[80] patients may be in one of three disease states, through which they follow a consecutive progression. The amputation submodel presented by Palmer and co-workers[83] includes five health states and is similar to the neuropathy structures proposed by Eastman and colleagues[81,82] and the DCCT Research Group,[80] whereby the patient begins the simulation with no history of amputation. However, the submodel proposed by Palmer and co-workers[83] also includes non-specific mortality.

Within the neuropathy submodel proposed by Eastman and colleagues,[81,82] adjustments are made for ethnicity. Patients enter the submodel with no neuropathy present. At the time of diagnosis, the prevalence of significant diabetic neuropathy was approximately 3.5% according to the National Health and Nutrition Examination Survey II in the Eastman and colleagues[81,82] model. The hazard rate allocated to this event predicted a cumulative incidence of 13% for symptomatic neuropathy 8 years after diagnosis, which is reflected in the results of the Rochester Epidemiology Project. The next health state in the submodel is that of first lower extremity amputation (LEA), and the hazard rates associated with LEA were also estimated by the Rochester Epidemiology Project. Hazard rates used in the progression to this state are conditional on the duration since diabetes onset. Similarly, hazard rates were calculated from the cumulative incidence of first LEA and later made conditional on the duration of diabetes represented in the model. Subsequent to experiencing a first LEA, patients are at a higher risk of a second LEA.

Palmer and co-workers[83] suggested that patients with type 1 diabetes are 14 times more at risk of non-traumatic LEA than a non-diabetic population. Within the submodel by Palmer and co-workers,[83] the probability of amputation was assumed to decrease by 41% with intensive therapy. The annual incidence of second LEA is four times higher than that of the first LEA. It is also known that patients have a higher risk of death once the first LEA has occurred.

The model proposed by Vijan and co-workers[84] does not include a neuropathy submodel.

Nephropathy

The epidemiology of type 2 diabetes indicates that 25–50% of patients develop microalbuminuria.[81,82] The nephropathy submodel contains four disease states within the submodels

proposed by the DCCT Research Group[80] and Eastman and colleagues.[81,82] According to these models, patients progress from one state to the next without missing a step. Upon entering the model, patients begin in the disease state of 'no nephropathy.' Using back-data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy, a baseline prevalence of microalbuminuria of 11.5% is assumed within the submodel by Eastman and colleagues.[81,82] Adjustments are made again for hazard rates in ethnic minorities.

Patients progress from the initial health state to microalbuminuria; the respective hazard rate is universal for all durations of disease. This hazard rate is again dependent on ethnicity. The subsequent health state sees the patient progress to proteinuria. The hazard rate for this progression is universal for all durations of diabetes. The progression from proteinuria to ESRD is dependent on the duration of diabetes; the hazard rates for this progression are 0.0042, 0.0385 and 0.074 for the durations of 1–11 years, 12–20 years and 21 years or longer, respectively. It should be noted that the clinical definitions of these two states differ among the various studies.

It is important to note that the intermediate disease states are referred to differently between the DCCT[80] model and the model presented by Eastman and colleagues[81,82]; hence, the differences between definitions may suggest differences in the internal structures of the submodels. The nephropathy submodel proposed by Vijan and co-workers[84] is largely similar to the model proposed by the DCCT[80] and Eastman and colleagues,[81,82] yet it also includes a non-complication-specific mortality state.

The nephropathy submodel proposed by Palmer and co-workers[83] differs slightly from those models used by other authors in that it includes ten health states. The four health states included in other submodels are included here, yet an additional six health states are also included. From ESRD, which is the final nephropathy health state in all submodels previously analysed, the Palmer model also includes the treatment of ESRD (e.g. haemodialysis) and a health state for ESRD-specific mortality. These additions represent a significant amount of extra detail, suggesting a closer reflection of the complication within this model proposed by Palmer and co-workers.[83]

Clearly, the transition probabilities for disease progression may differ between each of the models proposed by various authors.

Retinopathy

As with the other submodels proposed by the DCCT Research Group,[80] the retinopathy submodel is also largely identical to that of Eastman and colleagues[81,82] in terms of structure, despite slightly different clinical definitions of health states. The epidemiology of the disease shows that most people with type 1 diabetes develop non-proliferative retinopathy, and 62% develop proliferative retinopathy, so this information was used in the calculation of the transition probabilities within the model by the DCCT.[80] The retinopathy submodel presented by Eastman and colleagues[81,82] and the DCCT Research Group[80] includes five health states. The same applies for the submodels proposed by Vijan and colleagues[84] as well as Palmer and co-workers,[83] except that the macular oedema state is omitted and a non-complication-specific mortality state is included. There are, however, two different pathways through which patients may progress within the models by Eastman and colleagues[81,82] and the DCCT Research Group.[80] The hazard rates derived by Eastman and colleagues[81,82] for the progression of one state to the next was again obtained from the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Patients begin in the disease state of 'no retinopathy', with the exception of 20% of patients who, at the time of clinical diagnosis of diabetes, were assumed to have background retinopathy. The hazard rate of progression from 'no retinopathy' to 'background retinopathy' is dependent on the duration of the disease in the model by Eastman and colleagues.[81,82]

From the 'background retinopathy' disease state, patients may progress either to the subsequent disease state (proliferative retinopathy) or to significant macular oedema. The hazard rates of progression from proliferative retinopathy to severe vision loss, and from macular oedema to blindness are conditional on whether or not the patient receives treatment for the disease state. The hazard rates for the progression to either of these states is also conditional on the duration of diabetes. The health state of macular oedema is excluded from the model. Despite the author mentioning this disease state within the literature, no explanation is provided as to why this important factor is not included within the model. This is clearly a limitation of the model by Eastman and colleagues.[81,82]

Adjustments were made by Eastman and colleagues[81,82] for ethnic minorities who are more at risk of background retinopathy, macular oedema and proliferative retinopathy. As a result of insufficient data, the assumption was made

that Asian–Americans have the same risk as non-Hispanic white people. The final stage, given either pathway, is severe vision loss, whereby visual acuity is less than 20/100 in the patient's better eye.

Vijan and co-workers[84] used data derived from the DCCT[80] in order to establish early rates of progression, which were used as base-case analysis. The incidence and progression of retinopathy were defined as in the DCCT.

Other complications associated with diabetes mellitus

The complications discussed below (see *Heart disease, Stroke, Hypoglycaemia* and *Ketoacidosis*) are included only by Palmer and co-workers,[83] with the exception of the inclusion of CVD within the model proposed by Eastman and colleagues.[81,82] The addition of these complications is an advantage because it results in the Palmer model being significantly wider in scope, hence providing a truer representation of the complications encountered by patients with diabetes.

Heart disease

It should first be noted that Eastman and colleagues[81,82] include a CVD submodel. Within this submodel, the assumption is made that 50% patients have CVD, because the disease accounts for 50% of the deaths in patients with diabetes-related ESRD.

Palmer and co-workers[83] stated that, as with the probability of LEA, a patient's probability of developing AMI is dependent on previous heart conditions as well as demographic and clinical factors. According to Palmer and co-workers,[83] 6–10% of patients having a first AMI die immediately, dependent on age and sex. Patients with type 1 diabetes are at two to four times higher risk of developing AMI than the non-diabetic population.

Stroke

The stroke submodel proposed by Palmer and co-workers[83] suggests that, from having no history of stroke, patients progress to first stroke before moving either to death or to recurrent stroke and then death. At any point in the model, the patient may die of a non-specific cause. Palmer and co-workers[83] suggested that, based on the known epidemiology of diabetes, patients are at double the risk of stroke in comparison with the non-diabetic population. The incidence of experiencing a stroke is dependent on demographic and clinical factors. Approximately 16% of patients with diabetes who suffer a stroke die in hospital.

Hypoglycaemia

It is known that hypoglycaemia is common and ultimately an important recurrent complication for diabetic patients, yet it is not included in the models proposed by Eastman and colleagues,[81,82] the DCCT Research Group[80] or Vijan and co-workers.[84] Due to the brief duration of hypoglycaemia, non-complication-specific death is not included in the submodel proposed by Palmer and co-workers.[83] The progression of hypoglycaemia is simple. Patients enter the submodel without having experienced a hypoglycaemic event. Less serious events are not included in the model. The patient may then progress to experience an event in which he or she requires medical assistance. From this point, the patient either recovers and reverts back to the initial health state or progresses to the hypoglycaemic-specific death state. The patient cannot remain in the second health state described above because ongoing hypoglycaemia is regarded as fatal. The model by Palmer and co-workers[83] assumes a case fatality probability of 0.0001.

Ketoacidosis

Ketoacidosis is a complication that is generally specific to type 1 diabetes and is included within the model by Palmer and co-workers.[83] Similar to the hypoglycaemia submodel presented by Palmer and co-workers,[83] this complication is considered serious and often fatal; thus, non-specific mortality is not represented as a health state. The patient enters the submodel having experienced no ketoacidotic events. From that point, he or she experiences ketoacidosis and either recovers, reverting back to the initial health state, or dies.

Weight gain

None of the models included the potential impact of weight gain on mortality. As discussed in the review of the clinical effectiveness, pioglitazone has been shown to have a marked and progressive effect in increasing body weight (see *Effect on body weight* above). While the effect of obesity on mortality, independent of the effect of lipid concentrations, is controversial, there remains the possibility that the increase in body weight due to pioglitazone use may have an adverse impact on long-term mortality. It is a key shortcoming that these effects are not included in the models.

Mortality

The models by Eastman and colleagues[81,82] and the DCCT Research Group[80] include a separate submodel that simulates mortality of patients. Each year, the mortality model defines whether the individual survives or not. Within the model proposed by Palmer and co-workers,[83]

mortality is not contained in a separate model but is approached within the various submodels of complications. It is important to note that the model proposed by Vijan and co-workers[84] includes only early-stage disease and does not include a complication-specific mortality element. The model by Eastman and colleagues[81,82] uses life tables to obtain the typical life expectancy of a non-diabetic patient; this figure is then multiplied by a factor of 2.75 to reflect the life expectancy of a patient with type 2 diabetes. The model proposed by the DCCT Research Group[80] uses data from the US Department of Vital Statistics in order to obtain typical survival rates. It is not made clear how the model proposed by Palmer and co-workers[83] apportions mortality rates.

Cost aspects

The costs included in each of the models are approached in different ways. The inevitable result is a severe difficulty in making comparisons between the costs used in each of the models. The model by Vijan and co-workers[84] addresses the risks and benefits associated with improved glycaemic control yet does not directly evaluate costs; the motive behind this is that the costs of decreasing HbA_{1C} levels are not well defined for type 2 diabetes.

The models proposed by the DCCT Research Group,[80] Eastman and colleagues,[81,82] and Palmer and co-workers[83] include all direct medical costs (e.g. inpatient and outpatient care, laboratory tests and medical equipment) yet analyse these costs differently. Costs are in 1994 US dollars, except for Palmer and co-workers,[83] who described costs in 1996 Swiss francs.

Only Eastman and colleagues[81,82] provided actual unit costs used. They included the costs of screening, treatment and disability. The sources of these data were the DCCT,[80] published literature and US Medicare reimbursement information.

The model by Palmer and co-workers[83] includes direct costs and takes the perspective of a third-party payer. This study used cost data, classified into the cost of an event within the model (e.g. blindness), plus the first 12 months' costs following the event. Palmer and co-workers[83] found that the cost driver in the model was the cost of renal failure, which is substantially reduced with the addition of screening for microalbuminuria and the introduction of ACE inhibitor therapy.

The main costing areas included within the models are:

- screening costs
- treatment costs
- disability costs.

A major issue in the comparison of relevant costs of complications published in the literature is the issue of healthcare setting. Different settings have different implications for healthcare resource intensity and usage, making it difficult to define the costs of being in a particular health state. As largely the same sources have been used to derive data within the various models, one would expect the outcomes to be similar, yet this is not the case.

Clinical outcomes

The results from the various studies are as follows.

- Vijan and co-workers.[84] The primary outcome estimated was lifetime risk of adverse events. A reduction in HbA_{1C} levels from 9% to 7% for patients with diabetes onset before 50 years of age resulted in a 2.3% decrease in lifetime risk of blindness due to retinopathy. A decrease from 11% to 9% in a patient with onset before 50 years of age resulted in a 5.3% decrease in blindness risk. The same relationship holds true for the ESRD submodel. The conclusions drawn were that a substantially greater effect is achieved in moving from poor to moderate glycaemic control than from moderate to normal control.
- Palmer and co-workers.[83] The primary outcomes used in this study were mean total lifetime costs per patient, mean life expectancy and cost-effectiveness (measured in terms of costs per LYG). Intensive therapy increased LYGs but also increased total lifetime costs.
- DCCT Research Group.[80] The primary outcome used was LYGs, but the study also tracked sight-years, ESRD-free years, amputation-free years and QALYs. QALY values were 0.69 for blindness, 0.61 for ESRD, 0.80 for LEA, 0 for death and 1.00 for all other health states. The incremental cost per LYG was found to be US$28,661.
- Eastman and colleagues.[81,82] The primary outcome used was incremental cost per QALY. The incremental cost per QALY of intensive treatment over conventional therapy was US$16,002. This study used the same utility outcomes as those used in the DCCT[80] study, derived from largely the same sources. Maintaining an HbA_{1C} value of 7.2% was predicted to reduce the cumulative incidence of blindness, ESRD and LEA by 73%, 87% and 67%,

respectively. Total estimated life expectancy was increased by 1.39 years.

While each of the research groups presented their findings in different formats, they all tracked the average increase in life expectancy from conventional to intensive therapy, with the exception of the model proposed by the DCCT.[80] Despite this homogeneity, there are clearly differences between the findings due to the differences in the ages of diabetes onset and also the type of disease. It is likely that the increase in average life expectancy is higher for treatment of type 1 diabetes because the onset of the disease is earlier and hence the competing risks (of dying from other causes) are less. Another major impact is in the definition of comparator therapies. The earlier studies focused on the comparison of intensive glucose-control therapies with non-intensive therapies.

The average life expectancies are shown in *Table 27*.

Utility scores

There has been considerable debate about utility scores for patients with diabetes. Of the four studies evaluated, only the DCCT Research Group[80] and Eastman and colleagues[81,82] made an attempt to allocate quality-of-life scores to end-stage complications associated with type 2 diabetes. Both studies used identical scores for the end-stage diseases, which reflects the paucity of data in this area, rather than a high level of certainty in the values. The DCCT Research Group[80] made the assumption that, because compound health states are not incorporated in the model, when patients reach the end stage in two or more of the complications, the lower utility of the complications that they have experienced would apply. For example, when a patient reaches blindness and LEA, the quality-of-life score used is 0.69, which is the score for blindness. This scoring implies that the models are likely to underestimate the impact on quality of life for an individual, because patients who are blind and have had an amputation would clearly prefer not to have had an LEA; there should be a difference in quality of life between these two scenarios. A suggested (and more realistic) alternative would be to multiply the two utility scores. For example, in the compound health state described above, the resulting utility score would be $0.80 \times 0.69 = 0.552$.

It is important here to make the implicit assumption that any intervention that reduces the incidence of complications ultimately improves the quality of life.

Validation of the model used within the economic assessment

Takeda UK Ltd submitted data regarding the validity of the model used within the economic assessment of pioglitazone. This information was structured around a comparison of UKPDS results and predictions generated by the model for an equivalent population. However, these data are not reported here as they were submitted to NICE in confidence.

Conclusions on the health economics of treatment with pioglitazone in type 2 diabetes

The model of treatments for type 2 diabetes used for the confidential economic analysis of pioglita-

TABLE 27 *Average increases in life expectancy as described by the studies*

Study	Outcome measure	Increase as a result of intensive therapy	Target of intensive glycaemic therapy	Comments
Eastman *et al.*, 1997[81,82]	Average increase in life expectancy	3 years	Decrease of 2.8% in HbA_{1C} level (from 10.0% to 7.2%)	Assumes non-CVD mortality among diabetic population
Palmer *et al.*, 2000[83]	Average increase in life expectancy	7.4 years	Not stated	Assumes risk of AMI and stroke reduced by 41%. Conventional therapy vs screening + intensive therapy
Vijan *et al.*, 1997[84]	Average increase in life expectancy	1.3 years	Decrease of 2% in HbA_{1C} level (actual start level not specified)	Assumes age at onset: 45 years
DCCT Research Group, 1996[80]	NA	NA	NA	NA

zone* stands up to critical appraisal. The scope of the model used within the economic submission, in terms of the clinical aspects of diabetes and its complications, is good. While specific limitations of the scope of the model are not reported here for reasons of confidentiality, all aspects of the disease identified in previous published modelling studies have also been picked up in the economic model submitted to NICE in confidence. The depth or detail of the modelling for each disease complication sub-model is also at least as good as previous modelling attempts in this area.

Some of the key outputs from the model have been validated against the UKPDS trial. This validation is especially convincing given the fact that it represents a check of the predictive validity of the model, with the key disease transition probabilities being taken from different studies from the UKPDS.

The published models focusing on the economic aspects of intensive glucose-control interventions compared with non-intensive management in type 2 diabetes indicate that decreases of 2%[84] and 2.8%[81,82] have led to predicted increases in life expectancy of 1.3 and 3 years, respectively.

In an open-label continuation of study PNFP-010, patients were treated with doses of 30–45 mg of pioglitazone in combination with sulphonylurea daily. The fall in HbA_{1C} compared with baseline was maintained over the extended period, with an overall mean fall at 40 weeks of 1.41% (SE, 0.11%).[63] Similarly, in an open-label extension of PNFP-027, the fall was also maintained, with a mean decrease at 40 weeks of 1.06% (SE, 0.20)[63] and at 72 weeks of –1.36%.[62] The published models give an indication of the likely impact of these changes on long-term life expectancy with pioglitazone therapy in combination with either metformin or sulphonylureas, in patients whose blood glucose is poorly controlled on monotherapy.

* The full conclusions on the health economics of treatment with pioglitazone are not reported here because they were based upon information submitted to NICE in confidence by Takeda UK Ltd.

Chapter 5
Discussion

Very little evidence relating to the effectiveness and cost-effectiveness of pioglitazone is available in detail in the public domain. This paucity of evidence has to be borne in mind when considering the review of available information.

Clinical effectiveness

There is evidence from RCTs that, when used as monotherapy, pioglitazone at doses from 7.5 to 45 mg daily reduces blood glucose and HbA_{1C}, relative to placebo, over a period of 16–26 weeks. The extent of the fall in HbA_{1C} in the studies was between 0.56% and 1.93%. There appeared to be a dose–response effect. However, patients who were changed from another oral hypoglycaemic agent (metformin or sulphonylurea) to pioglitazone as monotherapy did not achieve the same level of glycaemic control as they had experienced previously.

When used in combination with metformin, sulphonylurea or insulin, pioglitazone at doses of 15 or 30 mg daily leads to a significant fall in blood glucose and HbA_{1C} (of an order of magnitude similar to that seen in the monotherapy studies), relative to placebo, over a period of 16 weeks. The effect is greater at the higher than at the lower dose and is maintained for at least 40 weeks.

The length of the studies was such that there is as yet no direct evidence that pioglitazone, either alone or in combination therapy, reduces the incidence of diabetic complications, including cardiovascular mortality. However, there is evidence from the UKPDS study[4,5,77] that improved glycaemic control reduces the incidence of microvascular complications. Thus, it is possible that this advantage would hold true for improved glycaemic control achieved through using pioglitazone, but it is impossible to be certain in the absence of studies of longer duration.

Relative to placebo, pioglitazone has been shown to affect a number of cardiovascular risk factors. It had a potentially beneficial effect in reducing triglycerides (by between 0.7 and 1.0 mmol/l) and, in combination studies, increasing HDL cholesterol (by between 0.07 and 0.10 mmol/l). However, it led to significant and progressive weight gain, which was sustained for considerable periods of up to 84 weeks.

It is not clear whether the weight gain was due primarily to fluid retention or to increased fat, and whether changes in fat distribution associated with pioglitazone may ameliorate changes in cardiovascular risk from weight increase.

Overall, therefore, the balance between the potentially beneficial and harmful effects is not clear, nor is the long-term effect of these changes on cardiovascular risk factors.

There is no direct evidence of the impact of pioglitazone on quality of life in the short or long term.

Comparison with other antidiabetic drugs

There is no evidence from RCTs relating to the relative efficacy of pioglitazone and rosiglitazone. Some evidence comes from a non-randomised study, which suggests that both drugs may be similar in their impact on blood glucose, but that pioglitazone was associated with both a greater beneficial effect on HDL cholesterol and triglycerides, and noticeably greater weight gain.[86] Evidence is also available from the NICE review of the effectiveness of rosiglitazone.[1] This review suggests that, when used in combination with sulphonylurea or metformin, rosiglitazone leads to a fall in HbA_{1C} of 0.5–0.9%. However, these comparisons should be made only with extreme caution, because there is no indication that the populations studied were equivalent.

Only one study, which was submitted to NICE in confidence, has directly compared pioglitazone with another antidiabetic agent. There is no evidence as to whether the addition of pioglitazone to existing therapy, with metformin or a sulphonylurea, is more effective in improving glycaemic control than using a metformin–sulphonylurea combination or starting insulin therapy.

Implications for equity

Secondary analysis of outcome data suggests that the effect of pioglitazone may be greater in women than men, and in those with higher than lower initial HbA_{1C}. However, in the absence of any clear evidence that the drug is significantly more effective than existing treatments, this difference is unlikely to lead to inequity of outcome of treatment for diabetes overall.

At least five, and possibly six, of the trials reviewed here (CPH-030A, CCT-001, CCT-011, CCT-012, OCT-003 and possibly the unnamed study) were conducted in Japan. Because of the differences between Japanese and European diabetic populations in terms of factors such as weight and the extent of insulin resistance, it is not clear to what extent the findings of these studies translate to a UK context.

Chapter 6
Conclusions

The evidence reviewed in this report suggests that pioglitazone is effective, relative to placebo, in reducing blood glucose in patients with inadequate glycaemic control, when used both as monotherapy as well as in combination with existing licensed therapies. However, there is no good evidence to indicate whether or not it is more effective than any other antidiabetic agent, particularly when used in combination. The evidence that specifically addresses comparison with other antidiabetic agents is of poor quality and does not suggest effectiveness.

Although improved glycaemic control, when achieved using pioglitazone, may be expected to lead to a fall in the risk of microvascular complications, there is no direct evidence that this is the case. In addition, the overall effect of pioglitazone therapy on cardiovascular risk is unclear.

Although pioglitazone may have a role in the treatment of type 2 diabetes, in the authors' opinion, more research is needed before it can be said with confidence to have any advantage over existing therapies.

Factors relevant to the NHS

There is a high level of uncertainty in the potential budgetary impact of pioglitazone on the NHS, and any estimates inevitably are based heavily on a series of assumptions, many of which cannot be justified easily.

It is thought that an estimated 800,000 people within England and Wales have type 2 diabetes.[12] This figure may be an underestimate because the King's Fund Report[87] of 1996 estimates that roughly 2 million people over the age of 16 in the UK suffer from type 2 diabetes mellitus. Crudely weighting this prevalence of type 2 diabetes in the UK to England and Wales alone[88] suggests that approximately 1.7 million people, diagnosed and undiagnosed, may suffer from the disease.*

The UK Drug Information Pharmacists Group makes the assumption that 50% of all diabetic patients currently on oral monotherapy are controlled inadequately.[89,90] These estimates have a major impact on the number of patients eligible for treatment with pioglitazone. The upper estimate of people potentially eligible for treatment with a thiazolidinedione in England and Wales is 212,000.[89,90]

A valid estimation of the costs to the NHS must include both the 30-mg pioglitazone dose and the lower 15-mg dose. In the absence of any information to support an estimate of the breakdown of prescribed doses, an assumption of a 50:50 split is just as valid as any other estimate. It should be noted in this regard that the economics of treatment with the 15-mg dose have not been addressed within the economic submission, except that the effect of the 15-mg dose of pioglitazone is fairly minimal.

The gross cost of pioglitazone should be considered, however, against potential savings in other available treatment options.

The key assumptions are:

- the proportion of eligible patients who receive treatment
- the average saving in the use of insulin by patients who receive pioglitazone
- the average saving in the use of sulphonylurea by patients who receive pioglitazone.

Recommendations for research

It is clear from this review that, not only is there a need for more research into the effects of pioglitazone, but also that research already undertaken should be published, preferably in peer-reviewed journals.

The most important unanswered questions are listed below, in order of priority.

* Information from the economic submission, relating to data sources and best estimates of the numbers of patients eligible for treatment, has been removed from the report because it was submitted to NICE in confidence.

- How does pioglitazone, when used in combination therapy, compare with other combination therapies in terms of glycaemic control?
- Does improved glycaemic control, when achieved using pioglitazone, convert into a reduction in the risk of microvascular complications?
- Are the changes in lipid levels seen upon treatment with pioglitazone converted into an actual reduction in the risk of cardiovascular events?

The first of these questions requires that straightforward studies are undertaken to assess the effect of pioglitazone in combination with sulphonylurea or metformin, compared with other established combination therapies (e.g. sulphonylurea and metformin), and compared with rosiglitazone. Appropriate outcome measures would be the change in HbA_{1C} and FBG, over a relatively short timescale (4–6 months). These studies should be sufficiently powered to detect equivalence between the regimens being compared (rather than to simply show no difference). Unless it can be confidently concluded that pioglitazone in combination is as effective as other combinations, not only must one remain cautious about advocating its use within the NHS, but also further studies of the longer-term effects of the drug may not be justified.

Studying the effect of pioglitazone on the risk of complications (microvascular or cardiovascular) necessitates longer-term follow-up of larger numbers of patients (over years). Although undoubtedly more difficult (and costly) to organise, it is important that this should be done now, while there is still clinical equipoise regarding the benefits or otherwise of the drug.

The extent of possible adverse effects of the drug also requires further evaluation. Because pioglitazone is a new drug, there is a lack of information regarding any adverse reactions that may take some time to become manifest (as may be the case with hepatitis) or are idiosyncratic. The two particular issues about which there must still be a degree of uncertainty and possible concern are the development of hepatitis and cardiac dysfunction.

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All responsibility for the contents of the report remains with the authors. The views expressed in this report are those of the authors, who are also responsible for any errors.

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Appendix 1

WHO diagnostic criteria*

Diagnosis	Glucose concentration, mmol/l (mg/dl)			
	Whole blood		Plasma	
	Venous	Capillary	Venous	Capillary
Diabetes mellitus				
Fasting	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)	≥ 7.0 (≥ 126)
and/or				
2-hour post-glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)	≥ 12.2 (≥ 220)
Impaired glucose tolerance				
Fasting (if measured)	< 6.1 (< 110)	< 6.1 (< 110)	< 7.0 (< 126)	< 7.0 (< 126)
and				
2-hour post-glucose load	≥ 6.7 (≥ 120) and < 10.0 (< 180)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 7.8 (≥ 140) and < 11.1 (< 200)	≥ 8.9 (≥ 160) and < 12.2 (< 220)
Impaired fasting glycaemia				
Fasting	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 5.6 (≥ 100) and < 6.1 (< 110)	≥ 6.1 (≥ 110) and < 7.0 (< 126)	≥ 6.1 (≥ 110) and < 7.0 (< 126)
and (if measured)				
2-hour post-glucose load	< 6.7 (< 120)	< 7.8 (< 140)	< 7.8 (< 140)	< 8.9 (< 160)

* *Adapted from* Table 1 *of the WHO report*[2]

Notes:

For epidemiological or population-screening purposes, the fasting or 2-hour value after 75 g of oral glucose may be used alone

For clinical purposes, the diagnosis of diabetes should always be confirmed by repeating the test on another day, unless there is unequivocal hyperglycaemia with acute metabolic decompensation or obvious symptoms

Glucose concentrations should not be determined on serum unless red blood cells are immediately removed, otherwise glycolysis will result in an unpredictable underestimation of the true concentrations. It should be stressed that glucose preservatives do not totally prevent glycolysis

If whole blood is used, the sample should be kept at 0–4°C or centrifuged immediately, or assayed immediately

Appendix 2

Search strategies

MEDLINE search strategies (OVID BioMed 1966 to June 2000)

Pioglitazone strategy

1 pioglitazone.af.
2 actos.af.
3 111025 46 8.rn.
4 ad 4833.af.
5 ad4833.af.
6 u 72107.af.
7 u 72107a.af.
8 or/1-7

Thiazolidinediones strategy

1 Thiazoles/
2 (thiazole$ or thiazolidinedione$).tw.
3 glitazone$.tw.
4 1 or 2 or 3
5 randomized controlled trial.pt.
6 controlled clinical trial.pt.
7 Randomized controlled trials/
8 Random allocation/
9 Double-blind method/
10 Single-blind method/
11 or/5-10
12 clinical trial.pt.
13 exp Clinical trials/
14 (clin$ adj25 trial$).tw.
15 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
16 Placebos/
17 placebo$.tw.
18 random$.tw.
19 Research design/
20 or/12-19
21 "comparative study"/
22 exp evaluation studies/
23 Follow-up studies/
24 Prospective studies/
25 (control$ or prospectiv$ or volunteer$).tw.
26 or/21-25
27 11 or 20 or 26
28 "animal"/
29 "human"/
30 28 not 29
31 27 not 30
32 Meta-analysis/
33 exp review literature/
34 (meta analy$ or metaanaly$).tw.
35 meta analysis.pt.
36 review academic.pt.
37 review literature.pt.
38 letter.pt.
39 review of reported cases.pt.
40 historical article.pt.
41 review multicase.pt.
42 or/32-37
43 or/38-41
44 42 not 43
45 "human"/
46 "animal"/
47 46 not 45
48 44 not 47
49 Economics/
50 exp "Costs and cost analysis"/
51 Economic value of life/
52 exp Economics, hospital/
53 exp Economics, medical/
54 Economics, nursing/
55 exp models, economic/
56 Economics, pharmaceutical/
57 exp "Fees and charges"/
58 exp Budgets/
59 ec.fs.
60 (cost or costs or costed or costly or costing$).tw.
61 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
62 Quality-adjusted life years/
63 or/49-62
64 4 and 31
65 4 and 48
66 4 and 62
67 64 or 65 or 66
68 exp Diabetes mellitus/
69 67 and 68

Appendix 3

Health economic studies relating to the treatment of complications associated with type 2 diabetes

	Specific studies			
	Eastman *et al.*, 1997[81,82]	**Palmer *et al.*, 2000[83]**	**Vijan *et al.*, 1997[84]**	**DCCT Research Group, 1996[80]**
Study design				
Modelling study	I	I	I	I
RCT				
Burden/cost of illness				
Economic outcomes				
Cost-effectiveness				
Cost-utility	I	I		I
Cost-minimisation				
Cost consequences				
Intervention type				
Intensive glycaemic control	I	I	I	I
Intensive blood pressure control				
Screening				
Educational interventions				
Scope				
General diabetes				
Specific type 1 diabetes		I		I
Specific type 2 diabetes	I		I	
Co-morbidities:				
• diabetic retinopathy	I	I	I	I
• diabetic neuropathy	I	I		I
• diabetic nephropathy	I	I	I	I
• cardiovascular disease	I			
Country	USA	Switzerland	Not stated	Not stated

Appendix 4

Critical appraisal of health economic studies of the treatments for complications of type 2 diabetes

Study		**Eastman *et al.*, 1997[81,82]**	**Palmer *et al.*, 2000[83]**	**Vijan *et al.*, 1997[84]**	**DCCT Research Group, 1996[80]**
Title		Model of complications of NIDDM	The cost-effectiveness of different management strategies for type I diabetes: a Swiss perspective	Estimated benefits of glycaemic control in microvascular complications in type II diabetes	Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial
Modelling assessments should include:					
1	A statement of the problem	To analyse prevention strategies for type 2 diabetes using modelling	The overall objective of this study was to determine the health outcomes and economic consequences of different combinations of diabetes interventions in newly diagnosed patients with type I diabetes in Switzerland	To evaluate the efficacy of glycaemic control in patients with type 2 diabetes	To examine the cost-effectiveness of alternative approaches to the management of type I diabetes
2	A discussion of the need for modelling versus alternative methodologies	Implied by the lack of empirical economic evidence though not stated directly	Implied by the lack of empirical economic evidence though not stated directly	Implied by the lack of empirical economic evidence though not stated directly	Implied by the lack of empirical economic evidence though not stated directly
3	A description of the relevant factors and outcomes	Factors included: disease incidence and progression, hazard rates (dependent on age and clinical factors), ethnicity adjustments, mortality submodel and CVD submodel. Costs of screening, treatment and disability are also included. This model covers end-stage disease progression. QALYs are suggested	Factors included: cumulative incidence, mortality incorporated into complication submodels and end-stage disease progression (dependent on demographic and clinical factors). Costs of event plus 12-month follow-up are included. Life expectancy and cost per LYG are also included as outcome	Factors included: model covers early-stage complication only. Lifetime risk and absolute reduction in risk for blindness are covered, but no costs are included	Factors included: mortality is incorporated within disease states. Costs of therapy (all direct medical included) are stated but not included. Also includes average years free from complications and cumulative incidence, with QALYs suggested. Model covers end-stage disease progression

continued

continued

Study		Eastman *et al.*, 1997[81,82]	Palmer *et al.*, 2000[83]	Vijan *et al.*, 1997[84]	DCCT Research Group, 1996[80]
4	A description of the model, including reasons for this type of model, and a specification of the scope, including time frame, perspective, comparators and setting*	Three complications plus CVD: • retinopathy (*n* = 5) • neuropathy (*n* = 3) • nephropathy (*n* = 4) • CVD (*n* = 2) State transition model used to simulate the progression of type 2 diabetes in patients aged 25–74 years Comparators used: conventional versus intensive glycaemic control Perspective: based on published data and Medicare reimbursement rates (1994 US$). Costed from the viewpoint of a single payer responsible for all direct medical costs. Costs and QALYs discounted at 5% and 7% per year	Seven complications modelled: • neuropathy (*n* = 5) • nephropathy (*n* = 10) • retinopathy (*n* = 5) • AMI (*n* = 8) • stroke (*n* = 5) • hypoglycaemia (*n* = 3) • ketoacidosis (*n* = 3) State transition model used to simulate the progression of type 1 diabetes in male patients aged 19 years (Swiss median age at onset) Comparators used: conventional insulin therapy, screening, intensive insulin therapy and ACE inhibitors used in combination Perspective: Swiss health insurance payer. Based on 1996 Swiss francs. Costs discounted at 3%, 5% and 6% per year	Two complications showing early-stage disease only: • nephropathy (*n* = 5) • retinopathy (*n* = 5) State transition model used to simulate the progression of type 2 diabetes in patients aged 45–75 years (assumed) Hypothetical drug used No costs	Three complications modelled: • retinopathy (*n* = 5) • neuropathy (*n* = 3) • nephropathy (*n* = 4) State transition model used to simulate the progression of type 1 diabetes in patients aged 13–39 years Perspective: healthcare perspective used for cost-effectiveness (all direct medical costs). Based on 1994 US$. Both costs and effects discounted at 3% per year
5	A description of data sources (including subjective estimates), with a description of the strengths and weaknesses of each source, with reference to a specific classification or hierarchy of evidence	Progression rates and cohort: DCCT, WESDR and REP All hazard rates are provided Costs: published data and/or prevailing Medicare reimbursement rates Other: Veterans Affairs cooperative study and Metformin Cooperative Trial	Progression rates and cohort: DCCT and published sources Other: mortality retrieved from US Department of Vital Statistics	Progression rates and cohort: DCCT, WESDR and REP Costs: NA Other: mortality retrieved from US Department of Vital Statistics	Progression rates and cohort: DCCT and WESDR Costs: resources based on DCCT trial and Medicare reimbursement Other: mortality retrieved from US Department of Vital Statistics
6	A list of assumptions pertaining to: the structure of the model (e.g. factors included, relationships and distributions) and the data	All major assumptions systematically reviewed	All major assumptions addressed but not in a systematic manner	All major assumptions addressed but not in a systematic manner	All major assumptions addressed but not in a systematic manner
7	A list of parameter values that will be used for a base-case analysis, and a list of the ranges for those values that represent appropriate confidence limits and that will be used in a sensitivity analysis	Disease progression rates derived from DCCT and published sources. Certain prevalence rates consistent with WESDR	Base-case rates of progression retrieved from DCCT and published sources. Non-exhaustive list provided within the text	Rates of early disease based on DCCT findings. Cohort data used for rates of subsequent progression to later disease Incidence: DCCT, Microalbuminuria Collaborative Study and REP	Base-case rates of progression retrieved from DCCT and published sources. Formulae shown within literature

WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy; REP, Rochester Epidemiology Project, Minnesota

* n = *number of health states within submodel*

continued

continued

Study		Eastman *et al.*, 1997[81,82]	Palmer *et al.*, 2000[83]	Vijan *et al.*, 1997[84]	DCCT Research Group, 1996[80]
8	The results derived from applying the model for the base case	Results derived from applying the model to the base case are systematically reported	Results derived from applying the model to the base case are systematically reported	Results derived from applying the model to the base case are systematically reported	Results derived from applying the model to the base case are systematically reported
9	The results of the sensitivity analyses, unidimensional, best/worst case, multi-dimensional (Monte Carlo/parametric) and threshold	Not described within the literature	One-way sensitivity analysis on all cost and probability parameters was performed, varying one parameter at a time by ± 10%. One-way sensitivity analysis showed the annual cost of intensive therapy had the greatest impact on the total lifetime costs. Reduced risk of AMI and the incidence and progression of micro-albuminuria with intensive therapy had the greatest impact on life expectancy	Three-way sensitivity analysis considering the impact of improved glycaemic control on lifetime risk for blindness. Main conclusions hold true	Sensitivity analysis conducted to examine the sensitivity of results to changes in incidence and progression of complications. Decreasing the incidence of micro-albuminuria by 50% in the conventional group increased the incremental cost per LYG to US$79,883
10	A discussion of how the modelling assumptions might affect the results, indicating both the direction of the bias and the approximate magnitude of the effect	Where applicable, all assumptions are systematically reported and analysed	Where applicable, all assumptions are systematically reported and analysed	Where applicable, all assumptions are systematically reported and analysed	Where applicable, all assumptions are systematically reported and analysed
11	A description of the validation undertaken, including concurrence of experts, internal consistency, external consistency and predictive validity	Validity could be strengthened by data on progression rates and costs from clinical trials, but these data were not available – results are an approximation only. Therefore, reported results are conservative	Not described within the literature	Sensitivity analysis resulted in a range of outcomes that do not substantially affect the main conclusions	Results of the analysis extend the findings of the DCCT trial
12	A description of the settings to which the results of the analysis can be applied and a list of factors that could limit the applicability of the results	Settings described within the systematic review	Settings described within the systematic review	Settings described within the systematic review	Settings described within the systematic review
13	A description of research in progress that could yield new data that could alter the results of the analysis	Data on progression rates and costs and the resource usage from actual clinical trials could strengthen any study	Data on progression rates and costs and the resource usage from actual clinical trials could strengthen any study	Data on progression rates and costs and the resource usage from actual clinical trials could strengthen any study	Data on progression rates and costs and the resource usage from actual clinical trials could strengthen any study

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair
Professor Kent Woods
Director,
NHS HTA Programme, &
Professor of Therapeutics
University of Leicester

Professor Bruce Campbell
Consultant General Surgeon
Royal Devon & Exeter Hospital

Professor Shah Ebrahim
Professor of Epidemiology
of Ageing
University of Bristol

Dr John Reynolds
Clinical Director
Acute General Medicine SDU
Oxford Radcliffe Hospital

Dr Ron Zimmern
Director, Public Health
Genetics Unit
Strangeways Research
Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director
Professor Kent Woods
Director, NHS HTA
Programme, &
Professor of Therapeutics
University of Leicester

Chair
Professor Shah Ebrahim
Professor of Epidemiology
of Ageing
University of Bristol

Deputy Chair
Professor Jon Nicholl
Director, Medical Care
Research Unit
University of Sheffield

Professor Douglas Altman
Director, ICRF Medical
Statistics Group
University of Oxford

Professor John Bond
Director, Centre for Health
Services Research
University of Newcastle-
upon-Tyne

Ms Christine Clark
Freelance Medical Writer
Bury, Lancs

Professor Martin Eccles
Professor of
Clinical Effectiveness
University of Newcastle-
upon-Tyne

Dr Andrew Farmer
General Practitioner &
NHS R&D
Clinical Scientist
Institute of Health Sciences
University of Oxford

Professor Adrian Grant
Director, Health Services
Research Unit
University of Aberdeen

Dr Alastair Gray
Director, Health Economics
Research Centre
Institute of Health Sciences
University of Oxford

Professor Mark Haggard
Director, MRC Institute
of Hearing Research
University of Nottingham

Professor Jenny Hewison
Senior Lecturer
School of Psychology
University of Leeds

Professor Alison Kitson
Director, Royal College of
Nursing Institute, London

Dr Donna Lamping
Head, Health Services
Research Unit
London School of Hygiene
& Tropical Medicine

Professor David Neal
Professor of Surgery
University of Newcastle-
upon-Tyne

Professor Gillian Parker
Nuffield Professor of
Community Care
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Dr Tim Peters
Reader in Medical Statistics
University of Bristol

Professor Martin Severs
Professor in Elderly
Health Care
University of Portsmouth

Dr Sarah Stewart-Brown
Director, Health Services
Research Unit
University of Oxford

Professor Ala Szczepura
Director, Centre for Health
Services Studies
University of Warwick

Dr Gillian Vivian
Consultant in Nuclear
Medicine & Radiology
Royal Cornwall Hospitals Trust
Truro

Professor Graham Watt
Department of
General Practice
University of Glasgow

Dr Jeremy Wyatt
Senior Fellow
Health Knowledge
Management Centre
University College London

continued

continued

Diagnostic Technologies & Screening Panel

Members

Chair
Dr Ron Zimmern
Director, Public Health Genetics Unit
Strangeways Research Laboratories
Cambridge

Dr Philip J Ayres
Consultant in Epidemiology & Public Health
The Leeds Teaching Hospitals NHS Trust

Mrs Stella Burnside
Chief Executive, Altnagelvin Hospitals Health & Social Services Trust
Londonderry
Northern Ireland

Dr Paul O Collinson
Consultant Chemical Pathologist & Senior Lecturer
St George's Hospital, London

Dr Barry Cookson
Director, Laboratory of Hospital Infection
Public Health Laboratory Service, London

Professor Howard Cuckle
Professor of Reproductive Epidemiology
University of Leeds

Dr Carol Dezateux
Senior Lecturer in Paediatric Epidemiology
Institute of Child Health
London

Professor Adrian K Dixon
Professor of Radiology
Addenbrooke's Hospital
Cambridge

Mr Steve Ebdon-Jackson
Head, Diagnostic Imaging & Radiation Protection Team
Department of Health, London

Dr Tom Fahey
Senior Lecturer in General Practice
University of Bristol

Dr Andrew Farmer
General Practitioner & NHS Clinical Scientist
Institute of Health Sciences
University of Oxford

Mrs Gillian Fletcher
Antenatal Teacher & Tutor
National Childbirth Trust
Reigate

Professor Jane Franklyn
Professor of Medicine
University of Birmingham

Dr JA Muir Gray
Joint Director, National Screening Committee
NHS Executive, Oxford

Dr Peter Howlett
Executive Director – Development
Portsmouth Hospitals NHS Trust

Professor Alistair McGuire
Professor of Health Economics
City University, London

Mrs Kathlyn Slack
Professional Support
Diagnostic Imaging & Radiation Protection Team
Department of Health
London

Mr Tony Tester
Chief Officer, South Bedfordshire Community Health Council
Luton

Pharmaceuticals Panel

Members

Chair
Dr John Reynolds
Clinical Director – Acute General Medicine SDU
Oxford Radcliffe Hospital

Dr Felicity J Gabbay
Managing Director, Transcrip Ltd
Milford-on-Sea, Hants

Mr Peter Golightly
Director, Trent Drug Information Services
Leicester Royal Infirmary

Dr Alastair Gray
Director, Health Economics Research Centre
Institute of Health Sciences
University of Oxford

Mrs Jeannette Howe
Senior Principal Pharmacist
Department of Health, London

Dr Andrew Mortimore
Consultant in Public Health Medicine
Southampton & South West Hants Health Authority

Mr Nigel Offen
Head of Clinical Quality
NHS Executive – Eastern
Milton Keynes

Professor Robert Peveler
Professor of Liaison Psychiatry
Royal South Hants Hospital
Southampton

Mrs Marianne Rigge
Director, College of Health
London

Dr Frances Rotblat
Manager, Biotechnology Group
Medicines Control Agency
London

Mr Bill Sang
Chief Executive
Salford Royal Hospitals NHS Trust

Dr Eamonn Sheridan
Consultant in Clinical Genetics
St James's University Hospital
Leeds

Mrs Katrina Simister
New Products Manager
National Prescribing Centre
Liverpool

Dr Ross Taylor
Senior Lecturer
Department of General Practice & Primary Care
University of Aberdeen

Dr Richard Tiner
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Association of the British Pharmaceutical Industry
London

Professor Jenifer Wilson-Barnett
Head, Florence Nightingale Division of Nursing & Midwifery
King's College, London

Mr David J Wright
Chief Executive
International Glaucoma Association, London

Therapeutic Procedures Panel

Members

Chair
Professor Bruce Campbell
Consultant General Surgeon
Royal Devon & Exeter Hospital

Professor John Bond
Professor of
Health Services Research
University of Newcastle-upon-Tyne

Ms Judith Brodie
Head of Cancer
Support Service
Cancer BACUP, London

Ms Tracy Bury
Head of Research
& Development
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Physiotherapy, London

Mr Michael Clancy
Consultant in A&E Medicine
Southampton General Hospital

Professor Collette Clifford
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University of Birmingham

Dr Katherine Darton
Information Unit
MIND – The Mental Health
Charity, London

Mr John Dunning
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Professor David Field
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The Leicester Royal Infirmary
NHS Trust

Professor FD Richard Hobbs
Professor of Primary Care
& General Practice
University of Birmingham

Mr Richard Johanson
Consultant & Senior Lecturer
North Staffordshire Infirmary
NHS Trust, Stoke-on-Trent

Dr Duncan Keeley
General Practitioner
Thame, Oxon

Dr Phillip Leech
Principal Medical Officer
Department of Health, London

Professor James Lindesay
Professor of Psychiatry for
the Elderly
University of Leicester

Professor Rajan Madhok
Director of Health Policy
& Public Health
East Riding & Hull
Health Authority

Dr Mike McGovern
Branch Head
Department of Health
London

Dr John C Pounsford
Consultant Physician
Frenchay Healthcare Trust
Bristol

Dr Mark Sculpher
Senior Research Fellow in
Health Economics
University of York

Dr Ken Stein
Consultant in Public
Health Medicine
North & East Devon
Health Authority, Exeter

Expert Advisory Network

Members

Professor John Brazier
Director of Health Economics
University of Sheffield

Mr Shaun Brogan
Chief Executive, Ridgeway
Primary Care Group
Aylesbury, Bucks

Mr John A Cairns
Director, Health Economics
Research Unit
University of Aberdeen

Dr Nicky Cullum
Reader in Health Studies
University of York

Professor Pam Enderby
Chair of Community
Rehabilitation
University of Sheffield

Mr Leonard R Fenwick
Chief Executive
Freeman Hospital
Newcastle-upon-Tyne

Ms Grace Gibbs
Deputy Chief Executive
West Middlesex
University Hospital

Dr Neville Goodman
Consultant Anaesthetist
Southmead Hospital, Bristol

Professor Robert E Hawkins
CRC Professor & Director of
Medical Oncology
Christie Hospital NHS Trust
Manchester

Professor Allen Hutchinson
Director of Public Health &
Deputy Dean, ScHARR
University of Sheffield

Professor David Mant
Professor of General Practice
Institute of Health Sciences
University of Oxford

Professor Alexander Markham
Director
Molecular Medicine Unit
St James's University Hospital
Leeds

Dr Chris McCall
General Practitioner
Corfe Mullen, Dorset

Dr Peter Moore
Freelance Science Writer
Ashtead, Surrey

Dr Sue Moss
Associate Director, Cancer
Screening Evaluation Unit
Institute of Cancer Research
Sutton, Surrey

Mrs Julietta Patnick
National Coordinator
NHS Cancer Screening
Programmes, Sheffield

Professor Jennie Popay
Professor of Sociology &
Community Health
University of Salford

Professor Chris Price
Professor of
Clinical Biochemistry
St Bartholomew's & The
Royal London School of
Medicine & Dentistry

Mr Simon Robbins
Chief Executive
Camden & Islington
Health Authority, London

Dr William Rosenberg
Senior Lecturer &
Consultant in Medicine
University of Southampton

Dr Sarah Stewart-Brown
Director, Health Services
Research Unit
University of Oxford

Dr Gillian Vivian
Consultant in Nuclear
Medicine & Radiology
Royal Cornwall Hospitals Trust
Truro

Mrs Joan Webster
Former Chair
Southern Derbyshire
Community Health Council
Nottingham

Feedback

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We look forward to hearing from you.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

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