

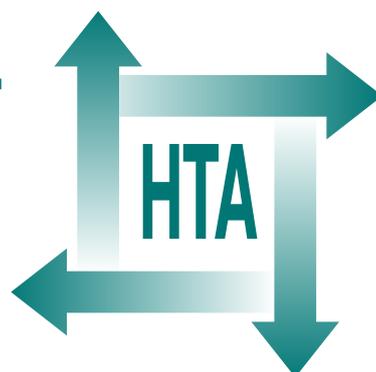
Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation

N Waugh, E Cummins, P Royle, C Clar,
M Marien, B Richter and S Philip



July 2010
10.3310/hta14360

Health Technology Assessment
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Declared competing interests of authors: Dr Cummins provided a report commissioned by Greater Glasgow Health Board (GGHB) on the cost of the current targeted hepatitis B immunisation programme. GGHB received financial support from GlaxoSmithKline for this study. The study was undertaken between November 2005 and July 2006. Dr Philip has received funds for reimbursements for travel expenses and lecture fees from GlaxoSmithKline, Merck Sharpe & Dohme, Eli Lilly, Novo Nordisk and Sanofi-aventis.

Published July 2010

DOI: 10.3310/hta14360

This report should be referenced as follows:

Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, *et al.* Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010; **14**(36).

Health Technology Assessment is indexed and abstracted in *Index Medicus/MEDLINE*, *Excerpta Medica/EMBASE*, *Science Citation Index Expanded (SciSearch®)* and *Current Contents®/Clinical Medicine*.

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The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 08/05/01. The protocol was agreed in May 2008. The assessment report began editorial review in September 2008 and was accepted for publication in January 2010. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

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Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.



Abstract

Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation

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Background: In May 2008, the National Institute for Health and Clinical Excellence (NICE) issued an updated guideline [clinical guideline (CG) 66] for the management of all aspects of type 2 diabetes. This report aims to provide information on new drug developments to support a 'new drugs update' to the 2008 guideline.

Objective: To review the newer agents available for blood glucose control in type 2 diabetes from four classes: the glucagon-like peptide-1 (GLP-1) analogue exenatide; dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin and vildagliptin; the long-acting insulin analogues, glargine and detemir; and to review concerns about the safety of the thiazolidinediones.

Data sources: The following databases were searched: MEDLINE (1990–April 2008), EMBASE (1990–April 2008), the Cochrane Library (all sections) Issue 2, 2008, and the Science Citation Index and ISI Proceedings (2000–April 2008). The websites of the American Diabetes Association, the European Association for the Study of Diabetes, the US Food and Drug Administration, the European Medicines Evaluation Agency and the Medicines and Healthcare Products Regulatory Agency were searched, as were manufacturers' websites.

Review methods: Data extraction was carried out by one person, and checked by a second. Studies were assessed for quality using standard methods for reviews of trials. Meta-analyses were carried out using the Cochrane Review Manager (REVMAN) software. Inclusion and exclusion criteria were based on current standard clinical practice in the UK, as outlined in NICE CG 66. The outcomes for the GLP-1 analogues, DPP-4 inhibitors and the long-acting insulin analogues were: glycaemic control, reflected by glycated haemoglobin (HbA_{1c}) level, hypoglycaemic episodes, changes in weight, adverse events, quality of life and costs. Modelling of the cost-effectiveness of the various regimes used the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model.

Results: Exenatide improved glycaemic control by around 1%, and had the added benefit of weight loss. The gliptins were effective in improving glycaemic control, reducing HbA_{1c} level by about 0.8%. Glargine and detemir were equivalent to Neutral Protamine Hagedorn (NPH) (and to each other) in terms of glycaemic control but had modest advantages in terms of hypoglycaemia, especially nocturnal. Detemir, used only once daily, appeared to cause slightly less weight gain than glargine. The glitazones appeared to have similar effectiveness in controlling hyperglycaemia. Both can cause heart failure and fractures, but rosiglitazone appears to slightly increase the risk of cardiovascular events whereas pioglitazone reduces it. Eight trials examined the benefits of adding pioglitazone to an insulin regimen; in our meta-analysis, the mean reduction in HbA_{1c} level was 0.54% [95% confidence interval (CI) -0.70 to -0.38] and hypoglycaemia was marginally more frequent in the pioglitazone arms [relative risk (RR) 1.27, 95% CI 0.99 to 1.63]. In most studies, those on pioglitazone gained more weight than those who were not. In terms of annual drug acquisition costs among the non-insulin regimes for a representative patient with a body mass index of around 30 kg/m², the gliptins were the cheapest of the new drugs, with costs of between £386 and £460. The glitazone costs were similar, with total annual costs for pioglitazone and for rosiglitazone of around £437 and £482, respectively. Exenatide was more expensive, with an annual cost of around £830. Regimens containing insulin fell between the gliptins and exenatide in terms of their direct costs, with a NPH-based regimen having an annual cost of around £468 for the representative patient, whereas the glargine and detemir regimens were more expensive, at around £634 and £716, respectively. Comparisons of sitagliptin and rosiglitazone, and of vildagliptin and pioglitazone showed clinical equivalence in terms of quality-adjusted life-years (QALYs), but the gliptins were marginally less costly. Exenatide, when compared with glargine, appeared to be cost-effective. Comparing glargine with NPH showed an

additional anticipated cost of around £1800. Within the comparison of detemir and NPH, the overall treatment costs for detemir were slightly higher, at between £2700 and £2600.

Limitations: The UKPDS Outcomes Model does not directly address aspects of the treatments under consideration, for example the direct utility effects from weight loss or weight gain, severe hypoglycaemic events and the fear of severe hypoglycaemic events. Also, small differences in QALYs among the drugs lead to fluctuations in incremental cost-effectiveness ratios.

Conclusions: Exenatide, the gliptins and detemir were all clinically effective. The long-acting insulin analogues glargine and detemir appeared to have only slight clinical advantages over NPH, but had much higher costs and did not appear to be cost-effective as first-line insulins

for type 2 diabetes. Neither did exenatide appear to be cost-effective compared with NPH but, when used as third drug after failure of dual oral combination therapy, exenatide appeared cost-effective relative to glargine in this analysis. The gliptins are similar to the glitazones in glycaemic control and costs, and appeared to have fewer long-term side effects. Therefore, it appears, as supported by recent NICE guidelines, that NPH should be the preferred first-line insulin for the treatment of type 2 diabetes. More economic analysis is required to establish when it becomes cost-effective to switch from NPH to a long-acting analogue. Also, long-term follow-up studies of exenatide and the gliptins, and data on combined insulin and exenatide treatment, would be useful.



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List of abbreviations

ADA	American Diabetes Association	HbA _{1c}	glycated haemoglobin
ADOPT	A Diabetes Outcome Progression Trial	HDL	high-density lipoprotein
BIAsp 30	biphasic insulin aspart 30	HFS	Hypoglycaemia Fear Survey
BMI	body mass index	HOMA-beta	homeostasis model assessment beta
BNF	<i>British National Formulary</i>	HR	hazard ratio
CADTH	Canadian Agency for Drugs and Technologies in Health	ICER	incremental cost-effectiveness ratio
CG	clinical guideline	IDF	International Diabetes Federation
CHF	chronic heart failure	IFG	impaired fasting glucose
CI	confidence interval	IGT	impaired glucose tolerance
CORE	Center for Outcomes Research	ISPOR	International Society For Pharmacoeconomics and Outcomes Research
CSII	continuous subcutaneous insulin infusion	ITT	intention to treat
DAFNE	Dose Adjustment For Normal Eating	IU	International Unit
DAWN	Diabetes Attitude Wishes and Need	LAR	long-acting release
DCCT	Diabetes Control and Complications Trial	LDL	low-density lipoprotein
DPP-4	dipeptidyl peptidase-4	LEAD	Liraglutide Effect and Action in Diabetes
DSC-R	Diabetes Symptom Checklist-Revised	MDI	multiple daily injection
EASD	European Association for the Study of Diabetes	MHRA	Medicines and Healthcare Products Regulatory Agency
EMA	European Medicines Evaluation Agency	MI	myocardial infarction
EQ-5D	European Quality of Life-5 Dimensions	MTRAC	The Midlands Therapeutics Reviews and Advisory Committee
FBG	fasting blood glucose	NICE	National Institute for Health and Clinical Excellence
FDA	Food and Drug Administration	NPH	Neutral Protamine Hagedorn
FPG	fasting plasma glucose	OAD	oral antidiabetic
GDG	Guideline Development Group	OGLA	oral glucose-lowering agent
GLP-1	glucagon-like peptide-1	OHA	oral antihyperglycaemic agent
		OR	odds ratio
		PG	plasma glucose

continued

PGWB	Psychological General Well-Being Index	SMC	Scottish Medicines Consortium
PPAR-g	peroxisome proliferator-activated receptor-g	TA	technology appraisal
PSSRU	Personal Social Services Research Unit	TAR	technology assessment report
PSU	Prescribing Support Unit	TFS	Treatment Flexibility Scale
QALY	quality-adjusted life-year	THIN	The Health Improvement Network
QoL	quality of life	TZD	thiazolidinedione
RCPE	Royal College of Physicians of Edinburgh	UKPDS	United Kingdom Prospective Diabetes Study
RCT	randomised controlled trial	UTI	urinary tract infection
RR	relative risk	VAS	visual analogue scale
SBP	systolic blood pressure	VLDL	very-low-density lipoprotein
SD	standard deviation	WMD	weighted mean difference
SE	standard error	YHPHO	York and Humber Public Health Observatory
SF-36	Short Form questionnaire-36 items		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



Executive summary

Background

The National Institute for Health and Clinical Excellence (NICE) issued an updated guideline [clinical guideline 66 (CG 66)] for the management of all aspects of type 2 diabetes in May 2008. However, new drug developments mean that this guideline itself already requires an update. This technology assessment report (TAR) aims to provide information to support the Short Guideline Development Group (GDG) which will produce a 'new drugs update' to the 2008 guideline.

The four classes of drugs that the GDG has been asked to consider are:

- The glucagon-like peptide-1 (GLP-1) analogue, exenatide, in its currently available form, given by injection twice daily. The second drug in that class, liraglutide, was not licensed in time to be included in the guideline update, and nor was the long-acting form of exenatide.
- The dipeptidyl peptidase-4 (DPP-4) inhibitors, sitagliptin and vildagliptin.
- The long-acting insulin analogues, glargine and detemir. Glargine had been the subject of a previous technology appraisal (TA 43) but it was felt that this needed updating. Detemir had not previously been appraised by NICE.
- The thiazolidinediones (TZDs) (hereafter referred to as the glitazones), more from the safety aspects than for glycaemic control.

Methods

Systematic review of clinical effectiveness studies (systematic reviews and new trials) and economic evaluations.

The bibliographic databases searched were MEDLINE (1990–April 2008), EMBASE (1990–April 2008), the Cochrane Library (all sections) Issue 2, 2008, and the Science Citation Index (SCI) and ISI Proceedings (2000–April 2008). The websites of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), the US Food and Drug

Administration (FDA), the European Medicines Evaluation Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA) were searched, as were manufacturers' websites. References cited by retrieved studies were checked for other trials. AutoAlerts were set up so that new studies were identified as they appeared. For the review of the DPP-4 inhibitors, we searched only for studies published since the time of the searches for the 2008 Cochrane review of these drugs, and used data from that review.

Abstracts of retrieved studies were checked for relevant studies by two reviewers, and in cases where there was doubt, copies of full papers were obtained. Only English language studies were obtained.

Data extraction was carried out by one person, and checked by a second, using predefined tables. Studies were assessed for quality using standard methods for reviews of trials as appropriate.

Meta-analyses were carried out using the Cochrane Review Manager (REVMAN) software.

Inclusion and exclusion criteria were based on current standard clinical practice in the UK, as outlined in NICE CG 66. This meant that only studies of the new drugs versus an appropriate comparator, and in an appropriate situation, were used. It was assumed that treatment of type 2 diabetes would start with lifestyle measures, principally diet, followed by metformin monotherapy then by the addition of a sulfonylurea. So the new drugs would be used in addition to metformin and sulfonylurea combination treatment, or as second-line therapy, particularly in those unable to tolerate adequate doses of those drugs. The main implication of this was that trials of the new drugs versus placebo, or as first-line monotherapy, or comparators not relevant to standard practice as laid down in CG 66, were excluded.

The outcomes of most interest for the GLP-1 analogues, DPP-4 inhibitors and the long-acting insulin analogues were:

- glycaemic control, as reflected by glycated haemoglobin (HbA_{1c}), and taken to be an indicator of the risk of long-term complications of diabetes
- hypoglycaemic episodes
- changes in weight
- adverse events
- quality of life (QoL)
- costs.

We did not expect to find any trials that were long enough to have microvascular or macrovascular events as end points.

For the glitazones, the main interest was safety, especially the risk of cardiovascular events.

Cost-effectiveness analysis

Modelling of the cost-effectiveness of the various regimes has used the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model, which models the first occurrence of a variety of downstream complications of diabetes, and estimates the cost and QoL impact of these. This was undertaken first for a representative male patient of body mass index (BMI) 30 kg/m², who was assumed to be reaching the 7.5% HbA_{1c} intensification threshold, but was repeated for males with BMI 35, and for females with BMIs 30 and 35.

The absolute HbA_{1c} impacts, weight impacts, cholesterol impacts and systolic blood pressure (SBP) impacts for the head-to-head comparisons, as identified within the clinical effectiveness section, were applied as first-line treatment and the UKPDS Outcomes Model was given an initial run to predict the evolution of HbA_{1c}. As treatment would be intensified again once the 7.5% HbA_{1c} intensification threshold was reached, for example intensification from first-line oral treatment to second-line basal insulin at the point the UKPDS Outcomes Model predicted the HbA_{1c} would rise above 7.5%, the effectiveness of the second-line treatment was applied. The UKPDS Outcomes Model was run a second time to predict the sawtooth evolution of HbA_{1c} for these first-line/second-line combination treatments. In a like manner, where a third-line intensification was possible, i.e. switching from second-line basal insulin to third-line basal bolus insulin, the procedure was undertaken once more, with the assumption of a 0.5% improvement in HbA_{1c} level on the switch to third-line basal bolus insulin.

Costs took into account the need for education and support on starting insulin, and the need for home blood glucose testing. This contrasts with exenatide, which has a fixed dose. The UKPDS Outcomes Model predicted the total cost and quality-adjusted life-years (QALYs) arising from routine care, and the microvascular and macrovascular complications of diabetes for each treatment sequence.

However, while the UKPDS Outcomes Model is well validated, it does not directly address aspects of the treatments under consideration, for example the direct utility effects from weight loss or weight gain, severe hypoglycaemic events and the fear of severe hypoglycaemic events. As a consequence, the survival curves of the UKPDS Outcomes Model were used to append these effects to the cost and QALY estimates of the UKPDS Outcomes Model.

Results – clinical effectiveness

GLP-1 analogue – exenatide

We looked first for trials in which exenatide was added to dual therapy with metformin and sulfonylurea, when that combination failed to achieve adequate glycaemia control. Comparators could be placebo, or a glitazone, or insulin.

There were five randomised controlled trials (RCTs) of reasonable quality which addressed our main questions. The main quality problems were insufficient reporting of methods (such as how randomisation was done) and lack of optimisation of other treatments (such as insulin dose). One trial was of exenatide versus insulin in people who were already on insulin. We added two other trials that did not meet our original criteria. One was added in order to provide more data on the insulin-versus-exenatide comparison; it was in patients who had failed only monotherapy with metformin. The other compared metformin monotherapy with metformin plus exenatide, and was added at the request of the NICE GDG to address the question of how to treat patients whose weight was of considerable concern, and in whom adding a sulfonylurea or a glitazone would cause undesirable further weight gain. All trials were sponsored by, and/or had co-authors from, the manufacturer.

HbA_{1c}

In patients with inadequate control on two oral glucose-lowering agents, the addition of exenatide led to a fall in HbA_{1c} level of about 1%.

In trials against insulins, results on HbA_{1c} level were comparable. In one trial in which insulin glargine or exenatide was added to the metformin-plus-sulfonylurea combination, HbA_{1c} level was reduced by 1.1% in both groups. In the trial in which exenatide or glargine was added when metformin monotherapy failed, both groups had a reduction of almost 1.4% in HbA_{1c} level.

Hypoglycaemia

Severe hypoglycaemic events were few in the trials. With oral combinations, most hypoglycaemic events seen with exenatide were when it was used in combination with a sulfonylurea.

Compared with insulin, there was less nocturnal hypoglycaemia with exenatide, but differences were not marked.

Weight

When exenatide is added to dual therapy, patients tend to lose weight – on average about 2 kg. In comparisons with insulin, patients on exenatide lost weight, whereas those on insulin tended to gain it, giving a difference that can be in the order of 5 kg.

Adverse effects

About half of the patients on exenatide suffer from nausea. This is usually more at the start of treatment, and is usually moderate or mild. Vomiting is quite common. In the trials, only a small proportion had to stop exenatide because of nausea. In some observational studies there were higher cessation rates. It is worth noting that the weight loss is not due only to nausea.

Issues

At present, exenatide has to be given by injection, twice daily. A long-acting form is under development, which can be given once weekly. It has been suggested, based on animal experiments, that the GLP-1 agonists may preserve beta-cell function. This is unproven in humans. Some studies show that the effect of exenatide wears off after it has been stopped, suggesting that there is no significant effect on beta-cell capacity.

Cases of pancreatitis have been reported in people taking exenatide. Most of the early reports were in people with other possible causes of pancreatitis, but with more cases being reported, it looks as if pancreatitis may be a real but rare side-effect of exenatide treatment. The FDA and the MHRA have asked for heightened vigilance and reporting, but have not suggested that exenatide should not be used. If the link is confirmed, the balance of

risks between occasional pancreatitis and poorly controlled diabetes will need to be considered.

Summary on exenatide

Exenatide is effective in improving glycaemic control by 1% or a little more, and has the added benefit of modest but useful weight loss. The downside is that it causes frequent nausea (although usually not major and tending to wear off with time), it has to be given by (at present) twice-daily injections, and there may be a small risk of pancreatitis.

DPP-4 inhibitors (gliptins)

The licences for these drugs at the time of the review were only for dual therapy with metformin, a glitazone, or (vildagliptin only) a sulfonylurea. However, we thought that triple therapy with a metformin, sulfonylurea and a gliptin would be a logical use of the drugs, and looked for trials of that as well. We also looked for trials in which a gliptin was used in combination therapy as an alternative to adding insulin to (usually) metformin.

Only four published trials met our inclusion criteria. All were sponsored by, and had co-authors from, the manufacturers. Two trials compared a gliptin plus metformin with a glitazone plus metformin. One trial examined the effect of adding sitagliptin to dual therapy with metformin and sulfonylurea (glimepiride or glipizide). The fourth trial took patients who were failing on metformin and added a gliptin or glipizide.

HbA_{1c}

In combination with metformin, the gliptins reduced HbA_{1c} level by similar amounts (about 0.8%) to a glitazone. When added to dual therapy with metformin and glimepiride, sitagliptin reduced HbA_{1c} level by about 0.8% compared with the placebo group. When compared with glipizide in dual therapy with metformin, both reduced HbA_{1c} level by 0.7%. Reductions are higher in those whose baseline HbA_{1c} level is higher, for example a drop of 1.3% in those with a baseline HbA_{1c} level of over 9%.

Hypoglycaemia

No severe hypoglycaemic episodes were reported in patients in the trials. In the wider Cochrane review, severe hypoglycaemia was not reported in any patient on sitagliptin or vildagliptin. Hypoglycaemia was rare in the dual therapy combinations.

Weight

The DPP-4 inhibitors did not seem to have the same weight loss effect as exenatide. In the trials against glitazones there was less weight gain in the DPP-4 groups, but that reflected weight gain on glitazones rather than loss on a DPP-4 inhibitor. However, absence of significant weight gain is a useful benefit, compared with sulfonylureas and glitazones.

Adverse events

In the short term, the gliptins were very well tolerated. Nausea was not increased. Longer-term data are needed to ensure that there are no adverse effects mediated by the immune system. Data from the Cochrane review show a statistically significant increase in infections with sitagliptin [relative risk (RR) 1.29, 95% confidence interval (CI) 1.1 to 1.5, $p = 0.003$] but not with vildagliptin (RR 1.04, 95% CI 0.87 to 1.24).

Other studies

The Cochrane review found 29 comparisons from 25 trials, most of which did not meet our inclusion criteria, usually because they were of gliptin monotherapy versus placebo, or against metformin monotherapy. However, these trials suggest that, compared with placebo, the gliptins reduce HbA_{1c} level by 0.6–0.7%. When compared with monotherapy with other agents, neither drug showed any advantage in HbA_{1c} level.

Summary

The gliptins are effective in glycaemia control, reducing HbA_{1c} level by about 0.8% in the included trials. Hypoglycaemia was not a problem, and nor was weight gain. Data are required on long-term safety.

Exenatide versus the gliptins

There are no published head-to-head trials comparing exenatide with either of the gliptins. The main differences are that the DPP-4 inhibitors are given orally, are less expensive, cause fewer side effects in the short-term, and are weight neutral rather than giving rise to the weight loss seen with exenatide. They may be a little less potent in lowering HbA_{1c} level, but that impression is based on indirect comparison and should be treated with caution.

Long-acting insulin analogues

Given the number of previous reviews, we started by identifying good-quality systematic reviews, and then looked for new trials published since the reviews. We drew on three good-quality reviews, which included 14 trials of glargine and two of

detemir. Three new trials were found, one of glargine and two of detemir. We combined the new trials with the relevant older ones in updated meta-analyses. We also noted one trial of glargine versus detemir.

HbA_{1c}

There was no difference in HbA_{1c} level between glargine and Neutral Protamine Hagedorn (NPH) insulin, and only a small non-significant difference in trials of detemir versus NPH (HbA_{1c} level was higher with detemir by 0.08%; 95% CI –0.03 to 0.19).

Hypoglycaemia

There were no differences in the frequency of severe hypoglycaemia between the analogues and NPH, but, overall, hypoglycaemia was less frequent with both glargine [odds ratio (OR) 0.74, 95% CI 0.63 to 0.89] and detemir (OR 0.51, 95% CI 0.35 to 0.76). Many of the hypoglycaemic episodes were nocturnal, and the ORs for those were 0.47 (95% CI 0.37 to 0.59) for glargine and 0.48 (95% CI 0.37 to 0.63) for detemir.

Weight

The meta-analyses showed that those on glargine gained slightly less weight than those on NPH (0.28 kg; 95% CI –0.72 to 0.15) but this was neither clinically nor statistically significant. On detemir, the difference was a little greater (1.2 kg; 95% CI –1.6 to –0.8). In the head-to-head trial of glargine versus detemir, those on glargine gained 3.5 kg on average, compared with a gain of 2.7 kg on detemir, but the difference of 0.8 kg is of doubtful clinical significance. The difference applied only to those on once-daily detemir; those on two injections daily gained 3.7 kg.

Insulin dose

In the head-to-head trial, the mean daily dose was higher for detemir (0.52 units/kg with once-daily injections; 1.0 units/kg with twice-daily injections) than for glargine (0.44 units/kg with once-daily injections).

Summary

Glargine and detemir are equivalent to NPH (and to each other) in terms of glycaemic control as reflected in HbA_{1c} level, but have modest advantages in terms of hypoglycaemia, especially nocturnal. There is little to choose between the two analogues. Detemir, when used only once daily, appears to have slightly less weight gain than glargine, but the difference in the head-to-head trial was under 1 kg and is probably not clinically significant. Detemir requires a slightly larger daily dose, at higher cost with present prices.

Glitazones

Little new information has emerged since the last guideline was produced. Pioglitazone and rosiglitazone appear to have similar effectiveness in controlling hyperglycaemia, and similar toxicity in terms of oedema, heart failure and fractures (in women only). However, the current evidence suggests that rosiglitazone increases the risk of heart attacks and cardiovascular mortality but that pioglitazone reduces it. The statistical significance of the increased risk for rosiglitazone is still debated. Most analyses show an increase in RR but some find that this is not statistically significant. This is partly because in most of the trials the absolute risk of cardiovascular events was low. Most trials were short-term, with HbA_{1c} level as the main outcome.

Most of the regulatory and prescribing advisory bodies have asked for warnings on rosiglitazone but have allowed its continued use. Some have suggested that, in future, pioglitazone be used in preference. Recent prescribing data from the USA shows a marked drop in the use of rosiglitazone, but suggest a shift to gliptins rather than a straight switch to pioglitazone.

Pioglitazone added to insulin

Pioglitazone is licensed for use with insulin when metformin is contraindicated or not tolerated. We included eight trials that examined the benefits of adding pioglitazone to an insulin regimen. In our meta-analysis, the mean reduction in HbA_{1c} level was 0.54% (95% CI -0.70 to -0.38). Hypoglycaemia was marginally more frequent in the pioglitazone arms (RR 1.27, 95% CI 0.99 to 1.63). In most studies, those on pioglitazone gained more weight than those who were not, with an average difference of almost 3 kg.

Results – costs and cost-effectiveness

The comparisons below are based on evidence from trials of direct comparisons, and so we are limited in what can be done. Costs were changing during the review. The analysis was bedevilled by very small differences in QALYs amongst the drugs, leading to fluctuations in incremental cost-effectiveness ratios (ICERs) even with 250,000 iterations. All costs given here will almost certainly be out of date by publication time.

In terms of annual acquisition costs, among the non-insulin regimes for a representative patient

with a BMI of around 30 kg/m² the gliptins are the cheapest of the new drugs, with costs of between £386 and £460. The glitazone costs are similar, with a total annual cost for pioglitazone of around £437 and for rosiglitazone of around £482 (although this is expected to fall shortly), but this situation may change as these drugs come off patent and generic varieties become available. Exenatide is somewhat more expensive, with an annual cost of around £830. Regimens containing insulin fall between the gliptins and exenatide in terms of their direct costs (including all costs), with a NPH-based regimen having an annual cost of around £468 for the representative patient, whereas the glargine and detemir regimens are considerably more expensive, at around £634 and £716, respectively. Also, insulin dose increases with patient weight, and, for a BMI of 35 kg/m², the annual cost of the NPH regime rises to £576, whereas the cost of glargine rises to £806. But it should be noted that this is for an insulin regime containing only basal insulin. As beta-cell function declines and control worsens, mealtime insulin will be required, increasing annual costs, for example, to around £617 for NPH and £783 for glargine for the representative patient with BMI of 30 kg/m².

For the comparison of exenatide with glargine it is anticipated that the net lifetime cost difference will be between a little over £1000 more costly for exenatide. (Note: It is assumed that patients will only stay on exenatide for a few years before insulin is required because of disease progression.) Given an anticipated QALY gain of around 0.057, this results in an estimated cost-effectiveness of around £20,000 per QALY. This improves to a cost-effectiveness estimate of around £1600 per QALY for a patient with a BMI of 35 kg/m², due mainly to the increased cost of the glargine regime. The dose of glargine increases with weight, whereas that of exenatide is fixed. However, these cost-effectiveness estimates are sensitive to the direct utility gain assumed for weight loss and weight gain, and if this effect is excluded, the anticipated cost-effectiveness of exenatide relative to glargine increases to between £9000 and £21,000 per QALY for the no-complications and with-complications scenarios, respectively. The term 'direct utility gain' refers to the fact that people feel happier if they lose weight, and is in contrast with the indirect gain achieved when weight loss favourably affects variables such as cholesterol or blood pressure. The UKPDS model already allows for indirect gains from weight loss.

So what this analysis is telling us is that over a lifetime there is little difference in costs of using

exenatide for a few years instead of going straight to insulin; there is a slight benefit in QALY terms, mostly due to the weight loss with exenatide. If patients did not lose sufficient weight, exenatide would not be cost-effective.

In summary, taking into account effects, side effects, costs and expected time to progression, and assuming sufficient weight is lost, then exenatide, when compared with glargine, appears to give ICERs within the range usually regarded as cost-effective. Provided that the effect of exenatide on BMI is reasonably consistent across the weight range, the cost-effectiveness of exenatide relative to glargine improves as BMI worsens, due in large part to the increasing cost of the required total glargine dose.

Comparing sitagliptin and rosiglitazone, the anticipated net QALY gain from sitagliptin is only 0.02–0.03, which is marginal and well within the bounds of error. However, sitagliptin is anticipated to be less expensive. If the direct utility effects of weight changes are excluded from this, sitagliptin is associated with a very small utility loss of –0.006 QALYs, although this does not affect the anticipated cost saving. Hence, the two drugs could be regarded as clinically equivalent but with sitagliptin marginally less costly at current prices.

For vildagliptin compared with pioglitazone the differences are again slight, with vildagliptin being associated with an insignificant QALY difference of between –0.011 and –0.007. Hence the two drugs could be regarded as clinically equivalent, but vildagliptin is anticipated to be around £600 less expensive than pioglitazone (at current prices – a fall of 22% in the cost of pioglitazone would equalise costs).

In summary, the gliptins and the glitazones appear roughly equivalent in glycaemic effect, but the former have an advantage in avoidance of weight gain, which, together with their lower (at present) costs, gives them an edge. However, given the uncertainties around the ICER estimate, it would be inappropriate to say that the glitazones were definitely less cost-effective than the gliptins. The cost-effectiveness hangs heavily on the benefits of weight differentials. This does not take into account the side effects of the glitazones. Both have problems with fractures (in women only) and heart failure, but rosiglitazone also appears to increase the risk of cardiovascular disease. However, until we have longer follow-up we will not know whether the gliptins have, as yet, unreported side effects.

For the comparison of glargine with NPH, the additional anticipated cost of around £1800

is associated with an insignificant QALY gain: yielding cost-effectiveness estimates of between £280,000 and £320,000 per QALY.

Within the comparison of detemir and NPH, the overall treatment costs from detemir are slightly higher, being between £2700 and £2600. QALY gains are again slight – about 0.015–0.006. Cost per QALY ranges from £188,000 to £412,000.

Hence on cost-effectiveness grounds, NPH should be the first-choice insulin in type 2 diabetes. However, some patients will have more trouble with hypoglycaemia than others and will potentially have more to gain.

In summary, as in CG 66, NPH should be preferred as first-line insulin, rather than a long-acting analogue. The analogues have modest advantages but, at present, much higher cost.

In some patients, the benefits of the analogues relative to NPH may be greater and cost-effectiveness correspondingly better.

Discussion

The main weaknesses in the evidence base at present are:

- long-term data on the safety of exenatide and the gliptins
- a lack of trials directly comparing exenatide and the gliptins
- lack of data on the effects of exenatide and the gliptins on cardiovascular outcomes
- a lack of head-to-head trials of exenatide and NPH.

Research needs

We need long-term follow-up studies of exenatide and the gliptins, although it is likely that exenatide will in future be used as the long-acting form, once weekly or even less often, and trials should use that form. Preliminary data from trials suggests that it will be more effective than the twice-daily form.

Data on combined insulin and exenatide treatment would be useful. The combination appears logical, but practice appears to be running ahead of evidence.

In routine care, how much does compliance fall off as complexity of regimens increases?

More economic analysis is required, undertaken independently of the manufacturers, including:

- looking at when it becomes cost-effective to switch from NPH to a long-acting analogue
- strengthening the evidence for the direct utility of weight gain, or of avoiding weight loss.

Conclusion

The new drugs – exenatide, the gliptins – and the ‘not so new’ detemir are all clinically effective.

In the authors’ opinion, the long-acting insulin analogues, glargine and detemir, have only slight clinical advantages over NPH, but have much

higher costs, and hence very high ICERs. They do not appear cost-effective as first-line insulins compared with NPH insulin in type 2 diabetes.

Exenatide, when used as third drug instead of progressing immediately to insulin therapy after failure of dual oral combination therapy, appears cost-effective relative to glargine, the current market leader, with most ICERs around £20,000, acceptable by current NICE standards. However, exenatide appears to be unlikely to be cost-effective compared with NPH.

The gliptins are comparable to the glitazones in glycaemic control and costs, but, at present, appear to have fewer long-term side effects.

Chapter I

Introduction

Type 2 diabetes

Diabetes mellitus is characterised by raised blood glucose levels. In non-diabetic people, the level of glucose in the blood is controlled by a balance of hormonal actions, principally insulin and glucagon, both of which are produced by specific types of cell in the pancreas, beta cells producing insulin and alpha cells producing glucagon. Insulin lowers blood glucose and glucagon raises it. In type 1 diabetes, the beta cells are lost because of an autoimmune process, little or no insulin is produced, and insulin treatment is required for survival. The cause, or causes, of type 1 diabetes are not known.

Type 2 diabetes is usually seen in people who are overweight or obese, particularly if inactive. They are usually insulin resistant, and therefore require higher levels of insulin in order to keep blood glucose within the normal range. The pancreatic beta cell is initially able to compensate for insulin resistance, by increasing production, thereby maintaining normal blood glucose levels. The higher than usual level of insulin is known as hyperinsulinaemia.

However, in most patients who may develop type 2 diabetes, the pancreatic beta-cell function progressively declines, leading to hyperglycaemia and clinical diabetes.¹ In the United Kingdom Prospective Diabetes Study (UKPDS),² beta-cell function was found to be impaired at diagnosis, especially in patients who were not overweight. Individuals with type 2 diabetes may have few or none of the classic clinical symptoms (such as thirst, passing abnormally large amounts of urine) of hyperglycaemia, and may be diagnosed incidentally as seen in the UKPDS,³ where 33% were found by incidental means (for example, urine testing for an insurance medical) and 53% via symptoms.

The difficulty in maintaining metabolic control over time may be related to several behavioural factors (for example, difficulties with healthy eating, exercise, medication regimens) but primarily reflects the underlying progressive decline in beta-cell function,⁴ so that control deteriorated over a 9-year follow-up period.⁵

Type 2 diabetes has traditionally been treated in a stepwise manner, starting with lifestyle modifications and encouragement of physical activity and, when necessary, pharmacotherapy with oral agents [National Institute for Health and Clinical Excellence (NICE) guideline, published May 2008].⁶ Several classes of oral agents are available. Until recently, these included:

- *Insulin secretagogues, which stimulate the pancreas to release more insulin, by binding to a sulfonylurea receptor* The main group is the sulfonylureas. There are seven of these in the *British National Formulary* (BNF), but older ones such as chlorpropamide are now little used. The ones most used in the UK are gliclazide, glipizide, glimepiride and glibenclamide (glyburide). A newer group of secretagogues is the meglitinide analogues, including nateglinide and repaglinide, but these are used far less than the sulfonylureas. They bind to the same receptor but are less potent than the sulfonylureas.⁷ They are shorter acting, and have been suggested for controlling postprandial hyperglycaemia, perhaps in combination with a long-acting insulin.
- *Insulin sensitizers, which make tissues such as the liver and the muscles more sensitive to insulin (i.e. they reduce the insulin resistance)* The commonest one in the UK is metformin, from the group of drugs called the biguanides. A newer group called the thiazolidinediones (TZDs), or glitazones, includes rosiglitazone and pioglitazone. The balance of actions on different tissues is different between the glitazones and metformin, and they are sometimes used in combination. Metformin increases insulin sensitivity in the liver by inhibiting hepatic gluconeogenesis and thereby reducing hepatic glucose production.⁸ Metformin may also increase peripheral insulin sensitivity by enhancing glucose uptake in the muscle. There have been concerns about the risk of lactic acidosis with metformin but the risk is probably much less than had been thought.⁹ The TZDs decrease insulin resistance in muscle and adipose tissue by activating the peroxisome proliferator-activated receptor-g (PPAR-g), which increases production of

proteins involved in glucose uptake. They also decrease hepatic glucose production by improving hepatic insulin sensitivity.

- *Drugs that delay the absorption of carbohydrates from the gastrointestinal tract, such as acarbose* Acarbose, and its related drug, miglitol, are alpha-glucosidase inhibitors. These drugs reduce especially postprandial elevations in plasma glucose (PG) levels. They do not significantly lower fasting plasma glucose (FPG) levels but cause a modest reduction in glycated haemoglobin (HbA_{1c}).¹⁰

The Prescribing Support Unit (PSU), in collaboration with the York and Humber Public Health Observatory (YHPHO), produces data on use of diabetes drugs. The most used drug is metformin, with about 10 million prescriptions a year in England.¹¹ Its use has been rising steadily. Second come the sulfonylureas, with around 5 million prescriptions a year, with little change over the last 5 years. Third come the glitazones, with about 2.4 million prescriptions per year. They are newer drugs, the use of which has increased over recent years. In terms of cost per annum, the glitazones are by far the most costly, being recently introduced drugs with no generic forms.

Insulin treatment comes in different forms:

- *Short acting*, with a rapid onset and short duration. There are two forms, the older soluble or 'regular' short-acting insulins, and the newer short-acting analogues (lispro, aspart, glulisine). These are used for mealtime injections (often called 'bolus', although the term is not universally popular).
- *Intermediate acting*, such as isophane [or Neutral Protamine Hagedorn (NPH)].
- *Long acting*, again with two types, the older forms such as ultralente, and the newer long-acting analogues, glargine and detemir. These are usually given once a day in type 2 diabetes.

Mixtures of short-acting and intermediate acting insulins are widely used. These can be mixed in the syringe by the patient prior to injection, but there are several premixed preparations available, which are more convenient. They are called biphasic.

The normal pancreas produces a little insulin throughout the 24 hours, with additional peaks of insulin after food. In recent years, in an attempt to mimic this physiological pattern, more use has been made of the combination of a long-acting insulin to provide the basal insulin with injections

of short-acting insulin at mealtimes – usually referred to as a basal bolus regimen.

In the UKPDS,⁵ insulin treatment started with a once-daily injection of long-acting ultralente. If that was insufficient, short-acting insulin was added – in effect a form of basal bolus.

The PSU/YHPHO prescribing data¹¹ show that the use of glargine increased very rapidly. In terms of number of prescriptions per annum, it overtook isophane insulin in the spring of 2004, and now runs at around 1 million per year, with isophane around 400,000 in the first quarter of 2007. Detemir was launched later than glargine but has now probably overtaken isophane in numbers.

Table 1 shows the range of costs of diabetes drugs.

NICE guideline

The purpose of this assessment report is to support an update of the NICE guideline on type 2 diabetes, released in May 2008.⁶ That guideline covers the full range of management of type 2 diabetes, whereas the update covers only the place of the new drugs. Some key recommendations and other aspects of the guidelines are listed below:

- Targets for control. An HbA_{1c} level of 6.5% or under was set for people with type 2 diabetes *in general*, but it was recommended that targets should be tailored to the needs of the individual, and might be higher than 6.5% (Recommendation 16).
- If HbA_{1c} levels were above target, but pre-meal levels were well controlled (< 7.0 mmol/l) then consideration should be given to reduction of postprandial glucose levels (Recommendation 18).
- It was recommended that treatment start with lifestyle measures, but it was accepted that these would fail in many or most cases.
- First-line therapy (algorithm, p. 99) should be metformin for people who are overweight or obese. A sulfonylurea to be considered in those who were not overweight.
- If monotherapy failed a sulfonylurea should be added to metformin, or vice versa. In some people, a meglitinide analogue might be considered instead of a sulfonylurea. Glitazones should be considered only if hypoglycaemia was expected to be a problem (though if it was a problem during a trial of the sulfonylurea, there could be a switch to a glitazone).

TABLE 1 Costs for selected drugs

Drug	Cost (£) per annum (insulins assume 40 IU/day) ^a
Metformin 500 mg × 4/day	39
Gliclazide 80 mg twice daily	25
Glibenclamide 5 mg twice daily	36
Glimepiride 2 mg once daily	69
Soluble insulin 10-ml vial	109
Isophane insulin 10-ml vial (including mixtures)	109
Metformin modified release 4 × 500-mg tablets/day	166
Biphasic insulins, cartridges	195–286
Insulin aspart 10-ml vial	286
Glargine or detemir 10-ml vial or glargine pre-filled device	379
Metformin/pioglitazone 2 × 850 mg + 15 mg/day	410
Sitagliptin 100 mg daily	432
Pioglitazone 45 mg once daily	480
Rosiglitazone 4 mg twice daily	643
Metformin/rosiglitazone combination	682
Exenatide 10 µg twice daily	828

IU, International Unit.
 a Costs are rounded to nearest whole number.
 Source: PSU/YHPHO.¹¹
 Caveat: Prices of all drugs fluctuate and some of the above may be out of date.

- If on dual therapy and HbA_{1c} remained above 7.5%, third-line treatment with a glitazone or insulin should be added. However, at this point treatment with exenatide could be considered.
 - Once insulin was started, metformin and the sulfonylurea would be continued but with reconsideration of the sulfonylurea if hypoglycaemia occurred.
 - If control deteriorated the insulin therapy would be intensified (and although not stated, it would be logical to withdraw the sulfonylurea).
 - As regards the type of insulin, Recommendation 52 stated that the first choice should be human NPH insulin, taken at bedtime or twice daily according to need. Glargine should be considered in certain situations for: those who required a carer to give the injections; those whose lifestyle is restricted by recurrent symptomatic hypoglycaemia; and those who would otherwise need twice-daily basal injections. These situations are the same as those for glargine in Technology Appraisal (TA) 53.¹² [Detemir was excluded from the Guideline Development Group (GDG) considerations because it was expected to be the subject of a technology appraisal.]
 - As regards choice of glitazone, the GDG noted concerns over cardiovascular risks with rosiglitazone, but concluded that: ‘On balance, despite reservations over rosiglitazone, it was felt not to be possible to unequivocally recommend a preference for pioglitazone in all circumstances, but rather to allow the choice of agent to rest with the person with diabetes and their advisor, taking account of the then current regulatory circumstances (which may yet change)’.⁶
- This is a little puzzling, as the risks appeared higher with rosiglitazone, and the economic analysis (p. 127) concluded that ‘pioglitazone was estimated to yield a greater quality-adjusted life-year (QALY) gain at lower cost than rosiglitazone’ and ‘rosiglitazone was consistently dominated by human insulin (both less effective and more expensive)’.

- On exenatide, the guideline concluded that, on the evidence then available (p. 135, section 10.4) 'human insulin is a consistently more cost-effective option in any patient in whom it is an acceptable form of treatment.' And Recommendation R44 said that 'Exenatide is not recommended for routine use in type diabetes.' But R45 identified a situation in which exenatide might be considered, if all of the following applied: a body mass index (BMI) of over 35; 'specific problems of a psychological, biochemical or physical nature arising from high body weight'; inadequate blood glucose control ($\text{HbA}_{1c} > 7.5\%$) with conventional oral agents after a trial of metformin and sulfonylurea; and other high-cost medication (such as a TZD or insulin injection therapy) would otherwise be started.

Figure 1 shows the flow chart from the NICE guideline. Please note that this may not be the final version.

Use of insulin treatment

In the UK there has been reluctance to switch to insulin in patients who are failing on oral agents. Two studies have used general practice databases to examine glycaemic control and treatment.

Calvert *et al.* (2007)¹³ used data from the DIN-LINK database, from the years 1995 to 2005. DIN-LINK has anonymised data from 154 general practices. Calvert *et al.* obtained data on patients with type 2 diabetes, including the treatment they were on and their HbA_{1c} levels. They were particularly interested in how long patients remained poorly controlled on oral agents before starting insulin. [The study was on behalf of Pfizer™ (Sandwich, Kent), to inform the NICE appraisal of inhaled insulin; Pfizer thought that one advantage of inhaled insulin would be to make it easier to persuade people to start insulin.]

Calvert *et al.* identified all patients with type 2 who were prescribed two or more types of oral agent, and looked at their HbA_{1c} levels before and after the addition of another drug. Adding a second drug reduced HbA_{1c} level by about 1% (95% CI 0.95 to 1.05). Adding a third reduced it by a further 0.48% (0.37 to 0.59). Adding a fourth drug gave no further benefit. [We should note that this was before the arrival of the glucagon-like peptide-1 (GLP-1) analogues and the dipeptidyl peptidase-4 (DPP-4) inhibitors.]

When insulin was prescribed for the first time to those with poor control on oral agents, the initial drop in HbA_{1c} was 1.3%, but 73% still had levels above the NICE target of 7.5% or less. The median time from addition of the last oral agent to the start of insulin therapy, for patients on two or more oral agents, was seven years. In those with poor glycaemic control following addition of the last oral drug, only 27% were prescribed insulin during the study. The implication is that many patients were left poorly controlled rather than being switched to insulin.

Rubino *et al.* (2007)¹⁴ used another British general practice database, The Health Improvement Network (THIN) database, to identify patients with type 2 diabetes who were poorly controlled (at two HbA_{1c} levels: $> 8\%$ and $> 9\%$) on oral agents, and who had not been treated with insulin. They then followed them to see how long it was before insulin was started.

Using the cut-off for poor control of HbA_{1c} levels of 8% or over, they found 2501 eligible patients, mostly aged 50–79 years, and with duration of diabetes usually at least 5 years. Most had been on oral glucose-lowering agents (OGLAs) for over 5 years. About 25% of these patients started insulin by 2 years, and 50% by 5 years. So transition was slow, and many were not transferred to insulin at all.

When OGLA failure was defined as HbA_{1c} level of 9% or over, they found 1691 patients who qualified. By 4.2 years, 50% had started insulin.

The presence of complications such as retinopathy, had little effect on the time to insulin treatment. Those with retinopathy started insulin at a median of 4.6 years, those without at 5 years.

This study was also funded by Pfizer.

Why is there reluctance to use insulin?

In a previous technology assessment report (TAR) for NICE, on inhaled insulins, we pondered upon why there should be reluctance.¹⁵ There seemed to be reluctance amongst both patients and physicians. *What follows is based on that TAR. Time did not permit a systematic review.*

The DAWN (Diabetes Attitude Wishes and Need) study found that 55% of patients who have never had insulin treatment are anxious about it being

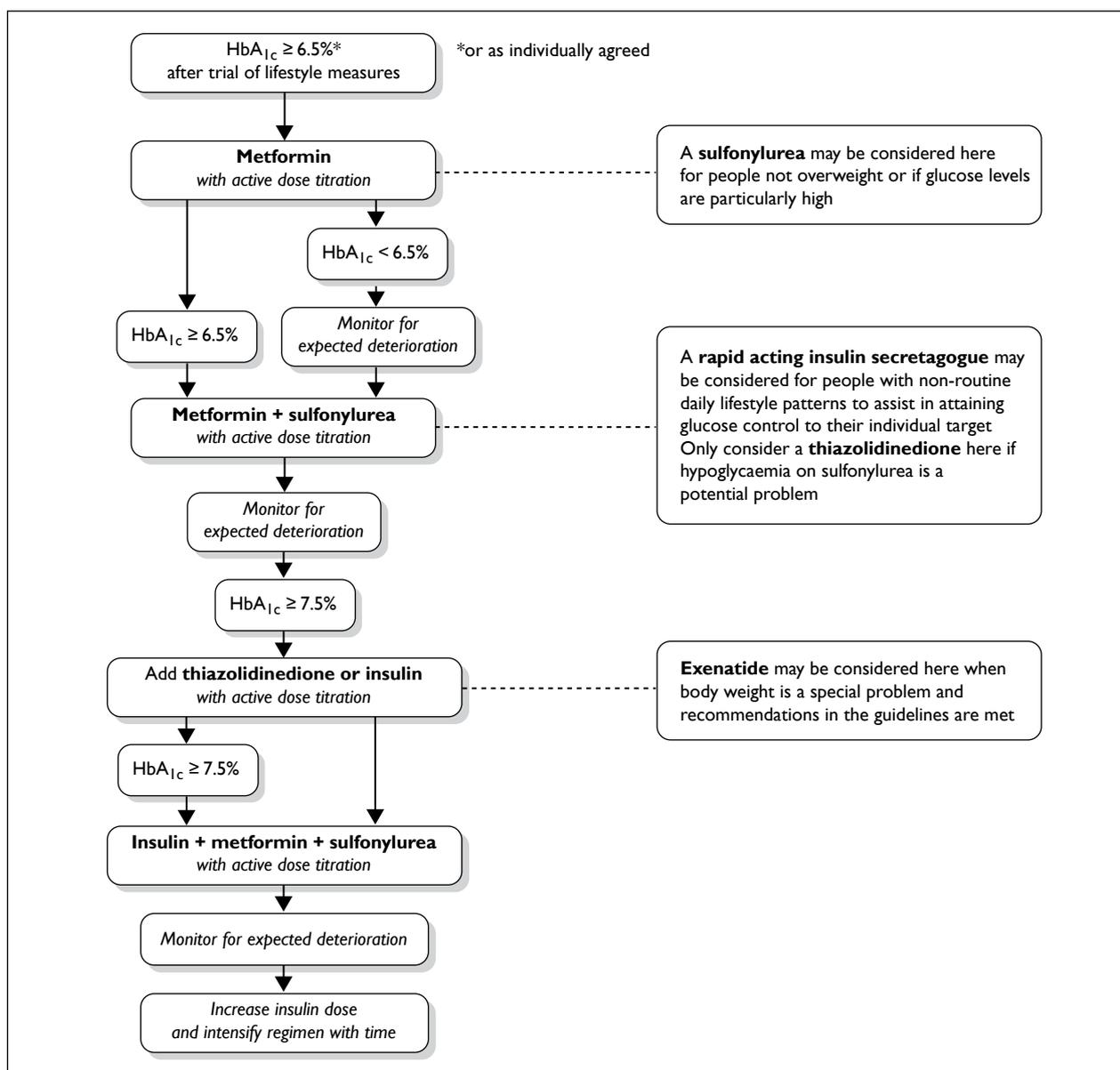


FIGURE 1 The National Institute for Health and Clinical Excellence guideline algorithm.

required. The authors, Peyrot *et al.* (2005)¹⁶ review previous studies of patient attitudes to insulin therapy. They note that these involve beliefs that 'taking insulin ... :

- leads to poor outcomes including hypoglycaemia, weight gain and complications
- means that the patient's diabetes is worse and that the patient has failed
- means life will be more restricted and people will treat the patient differently
- will not make diabetes easier to manage'.

It is important to note that insulin treatment is not just about injections, but a whole package of care, including dietary adjustments, home blood glucose

testing and self-adjustment of insulin doses. It is likely that, for most people, insulin injections are less troublesome than blood testing.

Changing to insulin does not mean that control will improve. Unpublished data from the Lothian audit show that the average HbA_{1c} in patients with type 2 diabetes on insulin is about 8.5% [J McKnight, presented at the Royal College of Physicians of Edinburgh (RCPE) conference, September 2005, personal communication]. The average for those with type 2 diabetes on OGLAs is 7.5%.

Similarly, a study from seven European countries¹⁷ found that only 9.5% of patients with type 2 diabetes, who were on insulin, had $HbA_{1c} < 6.5\%$;

another 44% had HbA_{1c} levels of 6.5–7.5%; and 47% had HbA_{1c} levels of over 7.6%.

One issue in insulin therapy is the provision of structured education programmes, such as DAFNE (Dose Adjustment For Normal Eating). Good education may reduce problems with insulin treatment.

What is the optimum treatment for people with type 2 diabetes inadequately controlled on oral agents?

It seems clear from the literature that there are differences of opinion on management of people with type 2 diabetes who are not adequately controlled on oral agents. A working group drawn from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) produced a consensus statement in 2006.¹⁸ Some extracts from this statement give an impression of the problems:

The availability of the newer agents has provided an increased number of choices for practitioners and patients and heightened uncertainty regarding the most appropriate means of treating this widespread disease. Although numerous reviews on the management of type 2 diabetes have been published in recent years, practitioners are often left without a clear pathway of therapy to follow.

The most appropriate target levels for blood glucose, on a day-to-day basis, and HbA_{1c}, as an index of chronic glycaemia, have not been systematically studied.

They noted the different target levels proposed by the various bodies, and reached a consensus that: ‘an HbA_{1c} of over 7% should serve as a call to action to initiate or change therapy’.

They recommended that insulin should be initiated with either bedtime intermediate-acting insulin or once-daily long-acting insulin; metformin should be continued.

Goudswaard *et al.* (2004),¹⁹ in a Cochrane review, concluded that combinations of insulin and oral hypoglycaemic agents should be the starting point for people with type 2 diabetes who required insulin. Their review preceded the studies on long-acting analogues, such as glargine and detemir.

The oral agents most commonly used in the trials they found were sulfonylureas; only 7% used metformin alone.

Douek *et al.* (2005)²⁰ from the Metformin Trial Group carried out a randomised controlled trial (RCT) of adding metformin or placebo in people with type 2 diabetes who had been switched to insulin because of poor control. Continuation of metformin resulted in less weight gain, lowered insulin requirement and improved glycaemic control.

Aviles-Santa *et al.* (1999)²¹ also showed that adding metformin to an insulin regimen in people with type 2 diabetes reduced HbA_{1c} by 0.9% compared with placebo. Insulin requirement was 29% lower, and the weight gain of 3.2 kg, seen in the placebo group, was much more than in the metformin group (0.5 kg).

Strowig and Raskin (2005)²² carried out a review of combination therapy with insulin and either metformin or a glitazone, or both. Details of methods are not given and it was probably not systematic. They also concluded that it was worthwhile continuing an insulin sensitiser in patients with type 2 diabetes who were switched to insulin. Because metformin and glitazones have different balances of sites of preferential action (acting on glucose production and glucose disposal), they also made the case that triple therapy should also be considered. Bailey (2005)²³ also supported combination therapy with metformin and a glitazone for reducing insulin resistance in type 2 diabetes.

Gerstein *et al.* (2006)²⁴ randomised poorly controlled (HbA_{1c} level 7.5–11%) patients to continue oral agents or to switch to glargine, in the Canadian INSIGHT (International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment) study. Those treated with glargine achieved lower HbA_{1c} and non-high-density lipoprotein (HDL) cholesterol, and greater satisfaction, but more weight gain. However, only 17.5% of patients on glargine reached the target of two or more consecutive HbA_{1c} levels of 6.5% or under. One weakness of the study was that at baseline about 17% of the patients had not been treated with any oral agent; another 40% were on oral monotherapy.

Hayward *et al.* (1997)²⁵ noted that results from trials of insulin therapy in type 2 diabetes showed it to be efficacious, but thought that these results might not

be replicated in routine care. In a very large study (8668 patients with type 2 diabetes) they found that 'insulin therapy was rarely effective in achieving tight glycaemic control'. Two years after starting insulin therapy, 60% still had HbA_{1c} levels of 8% or greater; 25% had levels between 8.0% and 8.9%, 20% between 9.0% and 9.9%, and 15% had levels over 10%. These are similar to the population-based audit from Lothian (J McKnight, personal communication).

The observation that starting insulin in routine care usually fails to give good control in people with type 2 diabetes failing on oral agents is presumably one reason why the physicians in the DAWN study¹⁶ showed considerable resistance to starting insulin therapy in type 2 diabetes – only about half of the physicians thought that insulin would be useful.

Yki-Järvinen *et al.* (2006)²⁶ came to similar conclusions in people with type 2 diabetes who were obese (defined in this study as BMI of over 28.1 kg/m²) – insulin did not improve control. In many of these patients, poor control is associated with overweight or obesity.

Aas *et al.* (2005)²⁷ tried another approach, randomising patients with poorly controlled type 2 diabetes to insulin or to a lifestyle intervention (exercise and diet counselling). Lifestyle intervention was as effective in glycaemic control but also resulted in weight loss. In a follow-up study in 2006, the authors also noted that lowering HbA_{1c} level by lifestyle measures had more beneficial effects on adipokine levels than when insulin therapy achieved the same lowering, which may result in a lower cardiovascular risk.²⁸ However, numbers in this study were small (38 in total), and the study needs to be replicated with larger numbers.

Beta-cell mass

As mentioned above, by the time of diagnosis of type 2 diabetes, beta-cell function is considerably impaired. An important issue is whether any treatments can preserve the remaining beta-cell function, or promote regeneration.

Conversely, it is important to know if any treatments might accelerate beta-cell decline. In

the ADOPT (A Diabetes Outcome Progression Trial) trial, patients were randomised to monotherapy with glibenclamide, metformin or rosiglitazone. Outcomes included failure of monotherapy. By 5 years, 34% of the glibenclamide group had failed, compared with 21% on metformin and 15% on rosiglitazone.²⁹ Aston-Mourney *et al.* (2008)³⁰ have argued, based on this trial and basic science studies, that it may be harmful to force the beta cell to produce more insulin, and that doing so may cause earlier beta-cell death. The implication might be that drugs that are insulin sensitisers, rather than insulin secretagogues, may help to preserve beta-cell function or mass, by reducing the pressure to produce more insulin. However, in the UKPDS⁴ the slopes of rises in blood glucose were similar for metformin and sulfonylureas, which does not support the sulfonylurea harm theory.

Meier (2008)³¹ has recently reviewed the evidence on beta-cell mass, and the hypothesis that 'resting' the beta cell would help, but concludes that: 'as yet, there is no direct evidence for the induction of beta cell apoptosis (death) by sulfonylurea drugs or for the preservation of beta cell mass by either metformin, glitazones or exogenous insulin in patients with type 2 diabetes.'

Decision issues

This TAR is being produced to assist the NICE Short GDG, whose task is to update the 2008 NICE Guidelines for the management of type 2 diabetes. The update is required because of a number of drug developments, namely:

- the GLP-1 analogues
- the dipeptidyl peptidase-4 (DPP-4) inhibitors
- the long-acting insulin analogues, which are not new, but where the current NICE guidance needs reviewed
- safety concerns over the glitazones.

The evidence on clinical effectiveness will be dealt with separately for each drug group, in Chapters 2–6. The literature on economic studies of new drugs for diabetes will be reviewed in Chapter 7, and the cost-effectiveness modelling of the new drugs will be in Chapter 8.

Chapter 2

The GLP-1 analogue: exenatide

The GLP-1 analogues are a new class of oral glucose-lowering drugs that mimic the endogenous hormone, glucagon-like peptide. GLP-1 is an incretin, a gastrointestinal hormone that is released into the circulation in response to ingested nutrients from food. The mechanism by which food stimulates GLP-1 release from intestinal endocrine cells is not known; however, it may be under the control of neuroendocrine pathways. The effect was discovered after it was noted that the stimulation of release of insulin from the pancreas was greater after oral glucose than after an equivalent amount given intravenously.³²

Endogenous GLP-1 has a number of actions.³³ It stimulates insulin secretion³⁴, but only in a glucose-dependent manner, so that insulin is not released if glucose is low. The incretin effect stops once the PG is down to 3 mmol/l.³² It also suppresses glucagon secretion, delays gastric emptying³⁵ and reduces appetite. It also increases insulin biosynthesis.^{36,37} Therefore, it controls PG level in a number of ways.³⁸ The reduction of glucagon secretion in type 2 diabetes is also glucose dependent.^{39,40}

Natural GLP-1 has been shown to affect PG levels when given by subcutaneous injection.⁴¹ However, it is rapidly broken down by the enzyme DPP-4, resulting in a half-life of 1–2 minutes.^{32,33,40} So, the endogenous form could only be used via a continuous infusion, and therefore would be impractical for treatment.

The GLP-1 analogues, of which only exenatide is currently available, have the same actions as GLP-1 but are resistant to breakdown by DPP-4. This gives them a much longer half-life than endogenous GLP-1. Other drugs are coming, with liraglutide expected to be licensed in 2009.

Exenatide has the following actions:^{42,43}

- increasing glucose-dependent insulin release
- suppressing glucagon secretion in situations where that is inappropriate, such as when glucose level is high

- slowing of gastric emptying (which will slow glucose absorption after meals)
- reducing appetite, and hence reduction of food intake
- restoring of first-phase insulin secretion in people with type 2 diabetes.

Given these actions, it was hoped that the GLP-1 analogues would not be associated with the weight gain that is seen with some other diabetes drugs. Early reports suggested that weight loss might occur.^{44,45}

Exenatide

Exenatide was originally isolated from the venom of the Gila lizard (Amylin Pharmaceuticals, San Diego, CA, USA). The peptide from the lizard had similarities with GLP-1, but had greater affinity with the receptor and was resistant to DPP-4.

Exenatide is produced synthetically. It has a short half-life of about 4 hours, and has to be given (by injection) twice daily at present. The drug has been developed for diabetes treatment under the trade name Byetta (Amylin Pharmaceuticals⁴⁵ and Eli Lilly,⁴⁶ Indianapolis, IN, USA). A longer-acting form, exenatide long-acting release (LAR) has been developed and is currently undergoing trials.^{45,47} It may have to be given only weekly.

The second GLP-1 analogue will be liraglutide, produced by Novo Nordisk (Crawley, UK).⁴⁸ It is based on human GLP-1 but has an amino acid substitution and an attached acyl chain, which fosters binding to serum albumin, thereby delaying renal excretion. It has a longer half-life, of about 11–13 hours, and so can be given once daily. (Note: Because the GLP-1 analogues are designed to act mainly at mealtimes, though they have some effect beyond those, they are not required during the night.) Again, being a digestible peptide, it has to be given by subcutaneous injection. Liraglutide has not yet received a licence for use in the UK, and will not be further discussed in this report.

Criteria for considering studies for this review

Types of evidence

For efficacy, RCTs are the gold standard. Open-label extension studies are useful to see if the effects persist, and for the development (or sometimes waning) of side effects. The dropout rate may also be a useful guide to tolerability.

For our purposes, we are interested mainly in trials that use standard UK practice as the comparator. Standard practice is set out in the current NICE guideline for type 2 diabetes (NICE 2008)⁶ and is shown in the flow chart in Chapter 1.

Types of interventions

Intervention consists of treatment for a minimum of 12 weeks with exenatide, exenatide long-acting or liraglutide. Twelve weeks is chosen because of the time it takes for glycaemic control to be reflected in HbA_{1c} level, but should be regarded as the minimum acceptable rather than satisfactory. Longer-duration studies would be better.

The 2008 NICE guideline on management of type 2 diabetes (see flow chart) stated that for individuals with a BMI of over 25 kg/m², the first choice in addition to diet was metformin, and, if that was insufficient, an insulin secretagogue should be added. In practice that would be a sulfonylurea; the other secretagogues, the meglitinide agonists, are little used in the UK.

So the most relevant comparisons are:

1. The addition of a GLP-1 analogue to standard combination therapy when that is insufficient to achieve good control, i.e. metformin + a sulfonylurea versus metformin + sulfonylurea + a GLP-1 analogue. A variant might use two insulin sensitisers: metformin + glitazone versus metformin + glitazone + GLP-1.
2. In those who cannot tolerate metformin, a glitazone might be used in combination therapy instead: sulfonylurea + a glitazone versus sulfonylurea + glitazone + GLP-1 analogue. One outcome of interest will be progression to insulin treatment.
3. Another option suggested in the NICE guideline was to add a glitazone to the metformin and sulfonylurea combination, i.e. triple therapy. If that fails, insulin

treatment is the next step, usually with a long-acting basal insulin, with metformin, and perhaps the other drugs, continued. So another possible comparison would be to try a GLP-1 agonist instead of insulin: metformin + sulfonylurea + glitazone + GLP-1 agonist versus basal

- insulin + metformin + sulfonylurea + glitazone.
4. In those who have started insulin recently there could be a case for stopping insulin and trying a GLP-1 analogue, so a further comparison is: insulin (with or without oral agents) versus oral agents + a GLP-1 analogue. This is not a licensed use. The Food and Drug Administration (FDA) patient information sheet⁴⁹ states that 'Byetta is not a substitute for insulin in patients whose diabetes requires insulin treatment'.
5. This comparison looks at adding exenatide to metformin monotherapy, and was included at the request of the GDG, which felt that there were some overweight patients in whom the further weight gain likely with the usual second-line combinations of adding a sulfonylurea (or a glitazone) was so undesirable that a GLP-1 agonist should be considered instead, given the likelihood of weight loss.

Ideally, the comparison would be of metformin + exenatide versus metformin + a gliptin but at the time of writing, no such trials had been done, so Comparison 5 is: metformin + exenatide versus metformin alone.

Licensed indications

The licensed indications vary a little between Europe and the USA. The European Medicines Evaluation Agency (EMA)-approved indications are: 'Byetta is indicated for the treatment of type 2 diabetes mellitus in combination with metformin, and/or sulfonylureas in patients who have not achieved adequate glycaemia control on maximally tolerated doses of these oral therapies'.

The FDA approval includes the glitazones:⁴⁹ 'Byetta is indicated as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, a TZD, a combination of metformin and a sulfonylurea, or a combination of metformin and a TZD, but have not achieved adequate glycemic control'.

Current evidence for effectiveness of GLP analogues in type 2 diabetes

Appendix 2 shows all of the trials. Most of the studies were parallel-group RCTs [Barnett *et al.* (2007)⁵⁰ was a crossover trial]. The majority of studies appear to have been conducted in North America and/or Europe, with the exception of one that was conducted entirely in Japan [Seino *et al.* (2007)⁵¹]. Four studies [Barnett *et al.* (2007),⁵⁰ Davis *et al.* (2007),⁵² Heine *et al.* (2006),⁵³ Nauck *et al.* (2007)⁵⁴] were reported as non-inferiority/equivalence trials.

Excluded studies

The studies in the *Table 2*, below, were excluded for the reasons given. Some of these trials provided useful information, for example showing that the GLP-1 agonists were effective in lowering PG compared with placebo, or were early dose-ranging studies, but were not relevant to our key comparisons.

Included studies

Seven trials were relevant for our purposes, and are listed below, under the relevant comparisons. The quality of the trials seems reasonable, although some details were not reported, and insulin, when a comparator, may not have been optimally used. *Table 3* gives the details.

Comparison 1

Comparison 1 involved the addition of GLP-1 analogue to dual combination therapy.

Kendall (2005)

Kendall *et al.*⁵⁹ recruited 733 people with type 2 diabetes whose control was inadequate (HbA_{1c} level

7.5–11%) on dual therapy with metformin and a sulfonylurea. Their average age was 55 years (range 22–77), and mean BMI was around 34 kg/m². They were recruited from 91 centres in the USA, with an average of eight recruits per centre. Most were Caucasian, with about 11% being black people and 16% Hispanic. Mean duration of diabetes was about 9 years.

There were three arms: placebo controls, exenatide 5 µg b.i.d. (twice a day) and exenatide 10 µg b.i.d. (after 4 weeks on 5 µg).

Zinman (2007)

Zinman *et al.*⁶⁰ recruited 233 patients whose control was inadequate on a glitazone with or without metformin, but about 80% were on metformin. They came from 49 centres in Canada, the USA and Spain, with an average of just under five patients per centre. Mean age was 56 (range 21–75) years, and their mean BMI was 34 kg/m².

These patients came from a larger group of 435 who were screened for entry. Discontinuation rates differed, with 71% of the exenatide group completing compared with 86% of the placebo group. The commonest reason for discontinuation was adverse events (19 out of 121 on exenatide versus 2 out of 112 on placebo). Exenatide was started at 5 µg twice daily for 4 weeks, and increased to 10 µg for the remaining 12 weeks.

Concerns about the study by Zinman *et al.* were raised by Malozowski (2007).⁶¹ These included:

- The representativeness of the included patients. Their control was inadequate, but many were not on maximal doses of other oral drugs. Also, 21% were not on any metformin, which should be first-line therapy.
- The lack of reinforcement of lifestyle interventions, such as diet; no details were

TABLE 2 Excluded GLP-1 trials

First author and year	Reason for exclusion
Exenatide trials	
Bunck (2007) ⁵⁵	Participants were on metformin monotherapy; in addition, it is not clear from the abstract whether they remained on metformin
Buse (2004) ⁵⁶	Participants had failed on sulfonylurea monotherapy
Trescoli-Serrano (2005) ⁵⁷	Abstract only and few details; does not say whether oral agents continued
Kim (2007) ⁴⁷ (exenatide LAR)	No details yet and not licensed

TABLE 3 Quality of included GLP-1 trials

Study	Method of randomisation	Allocation concealment	Blinding	ITT data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation
Barnett (2007) ⁵⁰ (crossover trial)	Computer-generated central randomisation table	Yes	Open	Yes	Exenatide/insulin glargine sequence: 80.9 Insulin glargine/exenatide sequence: 84.3	Yes (non-inferiority design)	Yes	Authors from Eli Lilly and Amylin Pharmaceuticals; funded by Eli Lilly
Davis (2007) ⁵²	Not reported	Not reported	Open	No	Exenatide: 57.6; insulin: 93.8	Yes	Yes	Authors from Eli Lilly and Amylin Pharmaceuticals
DeFronzo (2005) ⁵⁸	Not reported	Not reported	Triple blind	Yes	Exenatide (10 µg): 82.3; placebo: 78.8	Yes	Yes	Funded by Amylin Pharmaceuticals, Eli Lilly; authors from manufacturer
Heine (2005) ⁵³	Central randomisation table	Yes	Open	Yes	Exenatide: 80.9; glargine: 90.6	Yes (non-inferiority design)	Yes	Funded by Amylin Pharmaceuticals, Eli Lilly; authors from manufacturer
Kendall (2005) ⁵⁹	Not reported	Not reported	Double blind	Yes	Exenatide (5 µg): 84.1; exenatide (10 µg): 82.6; placebo: 76.1	Yes	Yes	Sponsorship from and author affiliation with Eli Lilly and Amylin Pharmaceuticals
Nauck (2007) ⁵⁴	Computer-generated randomisation table	Yes	Open	Yes	Exenatide: 78.7; biphasic insulin aspart: 89.9	Yes (non-inferiority design)	Yes	Some authors from Amylin Pharmaceuticals and Eli Lilly
Zinman (2007) ⁶⁰	Central randomisation table	Yes	Double blind	Yes	Exenatide: 71.1; placebo: 85.7	Yes	Yes	Sponsorship by Eli Lilly and Amylin Pharmaceuticals
ITT, intention to treat.								

given of educational input. (So care before starting exenatide does not appear to have been optimised.)

- There was a significant dropout rate, especially in the exenatide group which had 71% completing the trial.
- Full details of adverse events were not published, nor details of whether there were any subgroups more susceptible to the side effects (although with their relatively small numbers, Zinman *et al.* would not have the power to do much in the way of subgroup analysis).
- The study duration – 16 weeks – was too short for a chronic disease.

Comparison 2

- Comparison 2 involved patients who were intolerant of metformin, where a sulfonylurea plus glitazone combination was the standard arm comparator, versus that plus a GLP-1 analogue. No studies were found.

Comparison 3

- Comparison 3 consisted of insulin plus oral agents versus GLP-1 analogue plus oral agents.

Heine 2005

Heine *et al.*⁵³ recruited 551 patients in 82 centres in 13 countries, with an average of just under 7 patients per centre. Mean age was 59 (range 30–75) and mean duration of diabetes was 9.6 years. The recruits were less overweight than in some other studies, with a mean BMI of 31 kg/m². On dual therapy with metformin and sulfonylurea (at maximum doses), HbA_{1c} level was between 7% and 10%. Those with recent severe hypoglycaemia were excluded.

Patients were randomised to have glargine [starting at 10 units, titrated to achieve fasting blood glucose (FBG) < 5.6 mmol/l] or exenatide (10 µg b.i.d.) added to their oral agents. The dosage of the oral drugs was fixed unless hypoglycaemia was a problem, in which case the sulfonylurea dose was halved. Overall, 19% of the exenatide group and 10% of the glargine group withdrew from the study. The proportions withdrawing because of adverse events were 9.5% for exenatide and 0.7% for glargine.

Nauck 2007

Nauck *et al.*⁵⁴ compared twice-daily exenatide with twice-daily biphasic insulin (aspart 30:70) in 505 patients whose control was not good enough (mean HbA_{1c} level 8.6%; inclusion range 7–11%)

on dual therapy with optimal doses of metformin and sulfonylurea. Those with recent severe hypoglycaemia were excluded. The oral agents were continued in unchanged dosage, unless hypoglycaemia occurred, in which case the dose of sulfonylurea was halved in the exenatide group. (In the insulin group, the insulin was reduced.)

As in other studies, those randomised to exenatide started on 5 µg twice daily and increased to 10 µg (if tolerated – it was in 80%) after 4 weeks. The dosage of biphasic aspart was left to each investigator to adjust, according to glucose control and hypoglycaemia.

The study was carried out in 13 countries but the number of centres is not given. The trial was powered for equivalence, defined as a difference in HbA_{1c} level of not more than 0.4%. Of the 505 randomised, 199 (79%) of 253 on exenatide and 223 (90%) of the 248 on insulin completed the study. The difference was mainly due to withdrawals because of side effects – 20 withdrawals in the exenatide group and none in the insulin group.

Home (2007)⁶² had concerns about the study by Nauck *et al.*, including:

- The exenatide regimen was optimised but the biphasic insulin was not. The total daily insulin dose was lower than usually seen (it was 24 units/day at the end of 1 year).
- Blood glucose control was relatively poor in the insulin group, with a reduction of 0.9% in HbA_{1c} level, lower than seen in most recent treat-to-target studies of insulin in type 2 diabetes.
- Puzzlement about the use of an aspart product, from a rival manufacturer to the sponsor of the study (Eli Lilly), when they could have used their own similar product. Exenatide is made by Eli Lilly, who also produce the Humalog biphasic insulin.

The authors⁶³ mounted a reasonable defence against most of these points, but could not explain why insulin doses were not raised in pursuit of better control.

Barnett 2007

Strictly speaking, this study⁵⁰ does not meet our inclusion criteria, because it recruited patients with inadequate control on either metformin or a sulfonylurea, but we include it in order to have more than one trial against glargine, and hence

more data on relative effect size. The study was carried out in 26 places in six countries (not including the UK) and recruited 138 patients to a crossover trial of 10 µg exenatide twice daily or glargine titrated to achieve a satisfactory fasting glucose level. The baseline HbA_{1c} level was 9%. Mean age was 55 years, and baseline BMI was 31. It was funded by the manufacturer – Eli Lilly.

Comparison 4

This involved patients already on insulin, with replacement by GLP-1. This comparison is included for completeness and interest, but note that it is not currently a licensed indication.

Davis 2007

Davis *et al.*⁵² recruited 51 patients who were already on insulin (various forms, for about 3 years) in combination with oral agents (mostly metformin alone or with a sulfonylurea). Randomisation was 2:1 in favour of exenatide. Mean age was 53, mean BMI was 34 kg/m², and mean duration was 10 years. The study was carried out in five centres in the USA (average of 10 patients per centre).

There were more withdrawals in the exenatide group (14 out of 33) than in those remaining on insulin (1 out of 16). The commonest reason was loss of glycaemic control on exenatide.

An editorial by Rosenstock and Fonseca (2007)⁶⁴ made a number of criticisms, starting with the comment that ‘the scientific value is rather unclear, but the marketing appeal is obvious’. This may be a little harsh, as one aim of the study was to see if people with type 2 diabetes who had relatively recently started insulin could manage without it. More pertinent points were that insulin treatment was not optimised, and that the results were less successful than the paper implied: ‘this study raises issues about commercial bias in study design, interpretation and reporting by the pharmaceutical sponsors’.

Comparison 5

This concerned the addition of GLP-1 analogue to metformin monotherapy. DeFronzo *et al.* (2005)⁵⁸ carried out a three-armed trial (the Exenatide-112 trial), in 336 patients, aged 19–78 years (mean age 53), who had had diabetes for an average of about 6 years, in 82 sites in the USA. Baseline mean BMI was 34 and mean HbA_{1c} level was 8.2%. The three arms were metformin plus one of placebo, exenatide 10 µg b.i.d., and exenatide 5 µg b.i.d. Only the standard dose of 10 g b.i.d. is included here.

HbA_{1c} results

These are shown in *Tables 4A* and *4B* overleaf.

The trials show that in those whose control is not good enough on dual therapy, addition of exenatide improved HbA_{1c} by about 1% [Kendall (2005),⁵⁹ Zinman (2007)⁶⁰].

In the Kendall (2005)⁵⁹ trial, the changes in HbA_{1c} at 30 weeks were greater in those whose baseline level was higher.

When exenatide is compared with various insulin regimens, the results are similar, suggesting non-inferiority, although the issue of non-optimisation of the insulin treatment remains an issue.

Hypoglycaemia

Table 5 shows the frequency of hypoglycaemia.

Definitions of hypoglycaemia used in the included trials

- Barnett *et al.* (2007)⁵⁰ defined it as any sign or symptom due to hypoglycaemia, or a serum glucose concentration under 3.3 mmol/l. So, asymptomatic hypoglycaemic episodes were included.
- Davis *et al.* (2007)⁵² included any episode in which a patient felt that they were experiencing a sign or symptom of hypoglycaemia, or a blood glucose under 3.4 mmol/l, irrespective of whether any symptoms were associated.
- DeFronzo *et al.* (2005)⁵⁸ based recording on symptoms that were confirmed by a PG level of under 3.3 mmol/l.
- Heine *et al.* (2005)⁵³ included both symptomatic episodes and biochemical ones.
- Kendall *et al.* (2005)⁵⁹ used symptoms that ‘may have been documented by a PG under 3.33 mmol/l’.
- Nauck *et al.* (2007)⁵⁴ included both symptomatic episodes and instances of blood glucose level under 3.4 mmol/l during self-monitoring, whether or not the monitored episode was associated with any symptoms.
- Zinman *et al.* (2007)⁶⁰ also defined hypoglycaemia as either symptoms or self-monitoring readings.

As expected, the frequency of hypoglycaemia varied amongst studies. Severe hypoglycaemia was uncommon. There were no severe hypos in the Nauck *et al.* (2007)⁵⁴ and Zinman *et al.* (2007)⁶⁰

TABLE 4A HbA_{1c} results for GLP-1 trials

Study	Study arm and number randomised	HbA _{1c} (%) baseline	Change from baseline (%)	p-value from baseline	Difference between groups at end (exenatide-comparator 95% CI)	p-value between groups	Percentage of pts achieving HbA _{1c} level of ≤ 7%
Barnett (2007) ⁵⁰ (crossover trial)	Exenatide/insulin glargine treatment sequence + MET or SU (n = 68)	8.89 (SE 0.13)	-1.36 (SE 0.09)	p < 0.001	NS	NS	37.5 (exenatide-treated pts)
	Insulin glargine/exenatide treatment sequence + MET or SU (n = 70)	9.00 (SE 0.13)	-1.36 (SE 0.09)	p < 0.001			39.8 (glargine-treated pts)
Davis (2007) ⁵²	Exenatide + oral medications (n = 33)	8.0 (SD 1.2)	+0.3 (SE 1.5)	NS	0.4%	NS	
	Current insulin regimen + oral medications (n = 16)	8.3 (SD 0.9)	-0.1 (SE 0.7)	NS			
DeFronzo (2005) ³⁸	Exenatide (10 µg) + MET (n = 113)	8.18 (SD 1.0)	-0.78 (SE 0.1)			p < 0.002	46
	Placebo + MET (n = 113)	8.2 (SD 1.0)	+0.08 (SE 0.1)				13
Heine (2005) ⁵³	Exenatide + MET + SU (n = 282)	8.18	-1.11		0.017 (-0.123 to 0.157)	NS	46
	Insulin glargine + MET + SU (n = 267)	8.23	-1.11				48
Kendall (2005) ⁵⁹	Exenatide + MET + SU 5 µg (n = 245)	8.5 (SD 1.0)	-0.55 (SE 0.07)			p < 0.0001	24 ^a
	Exenatide + MET + SU 10 µg (n = 241)	8.5 (SD 1.1)	-0.77 (SE 0.08)				30 ^a
	Placebo + MET + SU (n = 247)	8.5 (SD 1.0)	+0.23 (SE 0.07)				7 ^a
Nauck (2007) ⁵⁴	Exenatide + MET + SU (n = 253)	8.6 (SD 1.0)	-1.04 (SE 0.07)	p < 0.001	-0.15 (-0.32 to 0.01)	NS (p = 0.067)	32 ^b
	Biphasic insulin aspart + MET + SU (n = 248)	8.6 (SD 1.1)	-0.89 (SE 0.06)	p < 0.001			24 ^b
Zinman (2007) ⁶⁰	Exenatide + MET + TZD (n = 121)	7.89 (SE 0.9)	-0.89		-0.98 (-1.21 to -0.74)	p < 0.001	62, 30 ^d
	Placebo + MET + TZD (n = 112)	7.91 (SE 0.8)	+0.09				30, 8 ^d

MET, metformin; NS, not significant; pts, patients; SE, standard error; SU, sulfonylurea.

a For intention-to-treat patients with HbA_{1c} level > 7% at baseline.

b Accounting for HbA_{1c} stratification at screening.

c For the per-protocol sample, with HbA_{1c} level > 7% at baseline.

d For the per-protocol sample who achieved a target HbA_{1c} level ≤ 6.5% (with HbA_{1c} level > 7% at baseline).

TABLE 4B Changes in HbA_{1c} at 30 weeks according to baseline level in Kendall et al.⁵⁹

	Exenatide 5 µg	Exenatide 10 µg	Placebo	Significance
Baseline A _{1c} < 9% (read from graph, figure 2C)	-0.40	-0.55	0.35	Compared with placebo (p < 0.0001)
Baseline A _{1c} ≥ 9% (read from graph, figure 2C)	-0.95	-1.40	0	Compared with placebo (p < 0.0002)

TABLE 5 Frequency of hypoglycaemic events in GLP-1 trials

Study	Study arm and number	Incidence of hypoglycaemia (%) (n)	Overall hypoglycaemia rates (events/patient-year)	Serious hypos	Nocturnal hypo events (events/patient-year)	Daytime hypos	Severe hypos
Barnett (2007) ⁵⁰ (crossover trial)	Exenatide + MET or SU	14.7	1.9 (95% CI 1.5% to 2.4%)	0	0.4 (95% CI 0.2% to 0.7%)		Zero episodes
	Insulin glargine + MET or SU	25.2	2.6 (95% CI 2.2% to 3.2%)	0	1.3 (95% CI 1.0% to 1.7%)		Eight episodes
Davis (2007) ⁵²	Exenatide + oral medications (n = 33)	39 (13)	1.72	0		11/13	One patient treated with exenatide + SU had three severe hypos
DeFronzo (2005) ⁵⁸	Current insulin regimen + oral medications (n = 16)	38 (6)	0.97	0		4/6	
	Exenatide (10 µg) + MET (n = 113)	5.3					0
Heine (2005) ⁵³	Placebo + MET (n = 113)	5.3					0
	Exenatide + MET + SU (n = 282)		7.3 ^a		0.9 ^b	6.6 ^c	Four pts
Kendall (2005) ⁵⁹	Insulin glargine + MET + SU (n = 267)		6.3		2.4	3.9	Four pts
	Exenatide + MET + SU 5 µg (n = 245)	19.2 (47)		One case			
Nauck (2007) ⁵⁴	Exenatide + MET + SU 10 µg (n = 241)	27.8 (67)					
	Placebo + MET + SU (n = 247)	12.6 (31)					
Zinman (2007) ⁶⁰	Exenatide + MET + SU (n = 253)		4.7 (SE 0.7)		17% (44) ^d		
	Biphasic insulin aspart + MET + SU (n = 248)		5.6 (SE 0.7)		25% (62)		
Zinman (2007) ⁶⁰	Exenatide + MET + TZD (n = 121)	10.7 (13) ^e					0
	Placebo + MET + TZD (n = 112)	7.1 (8)					0

hypo, severe hypoglycaemic episode; MET, metformin; NS, not significant; pts, patients; SE, standard error; SU, sulfonylurea.

a Difference (exenatide – glargine arms) = 1.1 (CI –1.3% to 3.4%) NS.

b Difference (exenatide – glargine arms) = –1.6 (CI –2.3% to –0.9%).

c Difference (exenatide – glargine arms) = 2.7 (CI 0.4% to 4.9%).

d $p < 0.038$.

e Difference between groups, 3.6% (CI –4.6% to 11.8%).

trials, and only one in the Kendall *et al.* (2005)⁵⁹ study.

In Barnett *et al.* (2007),⁵⁰ three patients experienced eight episodes of severe hypoglycaemia during insulin glargine treatment, whereas there were no episodes of severe hypoglycaemia during exenatide treatment.

Also exenatide-treated patients had significantly lower mean rates of overall hypoglycaemia ($p = 0.039$) and nocturnal hypoglycaemia ($p < 0.001$) than insulin glargine-treated patients. There were also no significant differences in rates of daytime hypoglycaemia between exenatide and insulin glargine treatment.

In the Davis *et al.* (2007)⁵² trial, most hypoglycaemia occurred during daytime. Of the 13 exenatide patients who reported hypoglycaemia, 10 were also taking a sulfonylurea. Overall hypoglycaemia rates were higher in those with good control (exenatide 2.5 events per patient-year, insulin 1.2 events per patient-year).

In the Heine *et al.* (2005)⁵³ trial, the overall frequencies of hypoglycaemia were similar, but nocturnal hypoglycaemia was less frequent in those on exenatide. In those who achieved good control (HbA_{1c} level of 7% or less at week 26), 61% of the exenatide group and 68% of the glargine group reported at least one symptomatic hypoglycaemic episode, and 21% of those on exenatide and 43% of those on glargine reported at least one episode of nocturnal hypoglycaemia.

Although the nocturnal hypoglycaemia rate in the Nauck *et al.* (2007)⁵⁴ study was significantly lower in the exenatide group (see *Table 5*), this was no longer statistically significant once adjusted for baseline HbA_{1c} level. Once the sulfonylurea doses were reduced, hypoglycaemia rates fell from 27 to 6 events per patient-year.

Weight

Most studies reported weight loss with exenatide treatment. Results are shown in *Table 6*.

Does nausea cause the weight loss?

Maggs *et al.* (2005)⁶⁵ carried out an analysis of patients in three trials [Buse *et al.* (2004),⁵⁶ DeFronzo *et al.* (2005),⁵⁸ Kendall *et al.* (2005)⁵⁹] to see if the weight loss with exenatide was related

to the nausea. Severe nausea was found in only 4%. They found little correlation between nausea and weight loss (or HbA_{1c} level). In the extension studies (to 52 weeks) the majority of patients had very little nausea, but lost the same amount of weight as the more nauseated subgroups.

Heine *et al.* (2005)⁵³ found that although the magnitude of weight reduction tended to be greater in patients taking exenatide who experienced longer durations of nausea, patients who did not report any episodes of nausea during the trial ($n = 120$) still demonstrated a mean weight change of -1.9 kg (CI -2.5 to -1.4).

Adverse events other than hypoglycaemia

Table 7 shows the most frequent side effects.

The most striking finding is the high frequency of nausea with exenatide, with vomiting not uncommon. However, the number who had to stop exenatide because of side effects was much lower. Most nausea was mild, and the frequency decreased over time. For example, Heine *et al.* (2005)⁵³ reported that 55% of patients reported nausea in the first 8 weeks, but only 13% did so in the last 8 weeks. However, 18 patients from the exenatide group withdrew because of nausea (compared with one patient in the insulin group). Heine *et al.* reported the frequencies of mild, moderate and severe nausea to be 33%, 20% and 5%, respectively.

Kendall *et al.* (2005)⁵⁹ also reported that the frequency of nausea diminished over time, and only 4% had to withdraw because of it.

Zinman *et al.* (2007)⁶⁰ reported that 9% of the exenatide group withdrew because of nausea, but that most nausea was mild (44%) or moderate (41%), and that it declined over time.

Cardiovascular risk factors

Three trials reported lipid and blood pressure data.

- DeFronzo (2005)⁵⁸ reported that exenatide treatment was not associated with an increased incidence of cardiovascular, hepatic, or renal adverse events. Also no changes in plasma lipids, laboratory safety parameters, heart rate, blood pressure, or electrocardiogram variables were observed between treatment arms.
- Nauck *et al.* (2007)⁵⁴ reported that HDL was higher by 0.04mmol/l with insulin, but that

TABLE 6 Weight changes in GLP-1 trials

Study	Study arm and number randomised	Weight in kg (SD) at baseline	Change in kg (SE) from baseline	p-value from baseline	Difference in kg between groups at end (exenatide-comparator 95% CI)	p-value between groups
Barnett (2007) ⁵⁰ (crossover trial)	Exenatide/insulin glargine treatment sequence + MET or SU (n=68)	85.6 (SE 2.0)	Exenatide treated -1.6 (SE 0.3)		-2.2 (SE 0.3), 95% CI -2.8 to -1.7	p<0.001
	Insulin/glargine/exenatide treatment sequence + MET or SU (n=70)	84.0 (SE 2.0)	Glargine treated +0.6 (SE 0.3)			
Davis (2007) ⁵²	Exenatide + oral medications (n=33)	95 (17)	-4.2 (3)	p<0.001		p<0.001
	Current insulin regimen + oral medications (n=16)	102 (19)	+0.5 (1.7)	p=NS		
DeFronzo (2005) ⁵⁸	Exenatide (10 µg) + MET (n=113)	101 (SE 2)	-2.8 (SE 0.5)			p≤0.001
	Placebo + MET (n=113)	100 (SE 2)	-0.3 (SE 0.3)			
Heine (2005) ⁵³	Exenatide + MET + SU (n=282)	87.5 (16.9)	-2.3		-4.1 (-4.6 to -3.5)	p<0.0001
	Insulin glargine + MET + SU (n=267)	88.3 (17.9)	+1.8			
Kendall (2005) ⁵⁹	Exenatide + MET + SU 5 µg (n=245)	97 (19)	-1.6 (0.2)			p≤0.01 vs placebo
	Exenatide + MET + SU 10 µg (n=241)	98 (21)	-1.6 (0.2)			
	Placebo + MET + SU (n=247)	99 (19)	-0.9 (0.2)			
Nauck (2007) ⁵⁴	Exenatide + MET + SU (n=253)	85.5 (15.7)	-2.5 (0.2)	p<0.01	-5.4 (-5.9 to -5.0)	p<0.001
	Biphasic insulin aspart + MET + SU (n=248)	83.4 (15.6)	2.9 (0.2)	p<0.01		
Zinman (2007) ⁶⁰	Exenatide + MET + TZD (n=121)	97.5 (18.8)	-1.75		-1.51 (-2.15 to -0.88)	p<0.001
	Placebo + MET + TZD (n=112)	96.9 (19)	-0.24			

MET, metformin; NS, not significant; SD, standard deviation; SE, standard error; SU, sulfonylurea.

TABLE 7 Most frequent side effects in GLP-1 trials

Study	Study arm and number randomised	Nausea	Vomiting	Diarrhoea	Any AE	Discontinuation due to AEs
Barnett (2007) ⁵⁰ (crossover trial)	Exenatide treatment Insulin glargine treatment	42.6% 3.1%	9.6% 3.1%		65.4% 52.8%	11 1
Davis (2007) ⁵²	Exenatide + oral medications (n = 33) Current insulin regimen + oral medications (n = 16)	48.5% 12.5%			79% 56%	Five pts Zero pts
DeFronzo (2005) ⁵⁸	Exenatide (10 µg) + MET (n = 113) Placebo + MET (n = 113)	45% 23%	12% 4%	16% 8%	2.7% (serious) (severe) 3.5% (serious) (severe)	7.1% 0.9%
Heine (2005) ⁵³	Exenatide + MET + SU (n = 282) Insulin glargine + MET + SU (n = 267)	161 (57.1%)* 23 (8.6%)	49 (17.4%)* 10 (3.7%)	24 (8.5%)** 8 (3.0%)		9.5% 0.7%
Kendall (2005) ⁵⁹	Exenatide + MET + SU 5 µg (n = 245) Exenatide + MET + SU 10 µg (n = 241) Placebo + MET + SU (n = 247)	96 (39.2%) 117 (48.5%) 51 (20.6%)	36 (14.7%) 33 (13.7%) 11 (4.5%)	25 (10.2) 42 (17.4) 16 (6.5%)		14 (5.7%) 22 (9.1%) 11 (4.5%)
Nauck (2007) ⁵⁴	Exenatide + MET + SU (n = 253) Biphasic insulin aspart + MET + SU (n = 248) Exenatide + MET + TZD (n = 121)	84 (33.2%) 1 (0.4%) 48 (39.7%) ^a	38 (15.0%) 8 (3.2%) 16 (13.2%) ^b	24 (9.5%) 5 (2.0%) 7 (5.8%) ^c	179 (70.8%) 123 (49.6%) 92 (76.0%) pts reporting ≥ 1 AE	Together, 5.1% of pts withdrew because of gastrointestinal-related AEs 19 (16%)
Zinman (2007) ⁶⁰	Placebo + MET + TZD (n = 112)	17 (15.2%)	1 (0.9%)	3 (2.7%)	73 (65.2%) pts reporting ≥ 1 AE	2 (2%)

AE, adverse event; MET, metformin; pts, patients; SU, sulfonylurea.

a The between-group difference in percentage of patients (exenatide minus placebo) was 24.5% (CI 12.7% to 36.3%).

b The between-group difference in percentage of patients (exenatide minus placebo) was 12.3% (CI 5.2% to 19.5%).

c The between-group difference in percentage of patients (exenatide minus placebo) was 3.1% (CI -2.9% to 9.1%).

*p < 0.001 compared with insulin glargine arm; **p = 0.006 compared with insulin glargine arm.

blood pressure fell with exenatide (systolic by 5 mmHg and diastolic by 2 mmHg), but did not change with insulin.

- Zinman *et al.* (2007)⁶⁰ found no significant differences in lipids and blood pressure.

Other outcomes

Patient-reported outcomes from the Barnett (2007)³⁸ trial were reported by Secnik *et al.* (2006)⁶⁶ in a poster presented at the International Diabetes Federation (IDF) in 2006. Responses to the following health outcome instruments were examined: the Psychological General Well-Being Index (PGWB), Diabetes Symptom Checklist-Revised (DSC-R), European Quality of Life-5 Dimensions (EQ-5D), Treatment Flexibility Scale (TFS) and Hypoglycaemia Fear Survey (HFS). No statistically significant between-group differences between twice-daily exenatide and glargine were found on any of these measured health outcomes.

Secnik *et al.* (2006)⁶⁷ reported some patient-reported outcomes from the Heine trial, including EQ-5D, the vitality scale of the Short Form questionnaire-36 items (SF-36) health survey, the Diabetes Symptom Checklist, and the Diabetes Treatment Satisfaction Questionnaire. No differences were found, suggesting that the greater number of injections with exenatide (twice daily versus once for glargine), and the frequent (at least initially) nausea was not enough to affect overall satisfaction, perhaps because those were balanced by weight loss on exenatide (on average, 2.3 kg) versus gain on insulin (mean 1.8 kg).

An abstract from the Nauck (2006) trial by Yurgin *et al.* (2006)⁶⁸ also reported EQ-5D and SF-36 data, stating that the exenatide group showed some improvement, whereas the biphasic aspart group showed no change.

Lower-dose exenatide

The standard dose of exenatide is 10 µg b.i.d., but there are some results on 5 µg b.i.d. from two of the trials. *Table 8* shows the results for comparison of low- and standard-dose results.

Hence those who can tolerate the starting dose but not the full one, still get some benefit. (Note: The cost appears to be the same, so the benefit–cost ratio is higher.)

Follow-up studies: open-label extensions

Klonoff *et al.* (2008)⁴² report results in people who had been on exenatide for at least 3 years. The participants were from the three 30-week studies [Buse *et al.* (2004),⁵⁶ DeFronzo *et al.* (2005),⁵⁸ Kendall *et al.* (2005)⁵⁹], only one of which met our inclusion criteria for this review. However, the pooled open-label follow-up can provide useful data on duration of efficacy and side effects.

The withdrawal rate was high. Of 527 eligible patients, 310 withdrew. The reasons for withdrawal included adverse events (11%), poor control (3%), and patient or investigator decision (41% – reasons not given).

Weight loss was maintained amongst the 41% (217) who stayed in the follow-up study. The mean weight loss at 3 years was 5.3 kg. Overall, 84% of patients lost weight. Reductions in HbA_{1c} level were also sustained (but this may be because those in whom it rose again left the study). Total cholesterol fell by 5% and triglycerides by 12%, presumably because of the weight loss, because there was a correlation between weight loss and cardiovascular risk factors.

The most frequent adverse effect (in 59%) was nausea, usually mild. Next came hypoglycaemia,

TABLE 8 Comparison of low- and standard-dose results

	5 µg b.i.d.	10 µg b.i.d.	Placebo
DeFronzo (2005)⁵⁸			
HbA _{1c} change (%)	–0.4	–0.8	–
Percentage reaching <7%	32	46	13
Weight (kg)	–1.6	–2.8	–0.3
Kendall (2005)⁵⁹			
HbA _{1c} change (%)	–0.55	–0.77	0.23
Percentage <7%	24	30	7

but only in those treated with a sulfonylurea. Upper respiratory infections were common (36%) but the significance of that cannot be assessed without a control group. There were no serious side effects other than a few severe hypoglycaemic episodes. So exenatide appears safe, but the high dropout rate reduces the value of the study.

Results from routine care

Rather different results were found in routine care by Wolfe and King (2007).⁶⁹ Two hundred consecutive exenatide-treated patients included 56 treated for 12 months. The nadir of weight occurred at 6 months. Few details are given of later weight loss in this ADA conference abstract, but the suggestion is that there was a plateau after 6 months.

Loh and Clement (ADA poster 2007)⁷⁰ reported a small follow-up study of 30 patients with type 2 diabetes who were treated with exenatide, some in addition of oral antidiabetic (OAD) drugs, others in addition to insulin. At 1 year, there was weight loss (mean 2 kg, $p = 0.0033$) but no significant reduction in HbA_{1c} level overall. Maximum weight loss occurred by 7 months, with most patients regaining weight over months 7–12. Half the patients had stopped exenatide by 12 months, because of therapeutic failure or side effects. Loh and Clement conclude that in the 'real world' exenatide may not give as good results as seen in trials.

Yoon *et al.* (2008)⁷¹ in a conference abstract (ADA 2008), reported use of exenatide added to insulin. In a case series of 226 patients who started exenatide, 34 (15%) stopped within 3 months due to adverse effects.⁷¹ Another 78 discontinued it later, mainly due to side effects or lack of efficacy. The final analysis of those who had used it for more than a year (116) showed weight loss of 6 kg, and a 20% reduction in insulin dosage. Eleven patients with an initial mean insulin dose of 17 units per day were able to stop insulin.

Another study from routine care, reported by Bhushan *et al.*⁷² at the ADA 2008 conference, followed 201 patients for 16 weeks; all received exenatide in addition to previous treatment (details of which not given). Weight loss was seen in 69%, and averaged about 2 kg. Total cholesterol fell by 6 mg/dl. Blood pressure was unchanged.

It seems logical that exenatide be combined with insulin, although this is not a currently licensed indication. In an abstract from the recent EASD,

Govindan *et al.*⁷³ presented a small case series from Wolverhampton, of 27 obese patients (mean BMI 43 at baseline), who were already on insulin but poorly controlled (mean HbA_{1c} level 8.8%). About half had nausea on exenatide, but only three had to stop it. The mean weight fell from 128 kg to 115 kg after 3 months; BMI from 43 to 40; and insulin dose from a mean of 170 to 36 units/day. The average insulin dose reduction comes about because 10 patients could stop it altogether, although mean HbA_{1c} level did not improve much (by only 0.3%; NS). Longer follow-up might show greater benefit, and it suggests that trials of combined exenatide and insulin therapy are justified.

Also from the EASD conference, Wintle *et al.* (from Amylin and Lilly)⁷⁴ presented data from diabetic care records from the General Electric database, on 2086 patients treated with exenatide for 6 months or more. Patients had previously been on metformin, sulfonylurea or glitazone monotherapy (about 30%), or on dual therapy (38%) or triple therapy (34%), but were not well controlled (mean HbA_{1c} level 8.4% and BMI 38.5).

Exenatide reduced HbA_{1c} level by 0.9% in those who had been on monotherapy, but by less (0.5–0.8%) in those who had been on combination treatment.

Kendall *et al.* (Amylin and Lilly)⁷⁵ reported a pooled analysis of 2 years of exenatide treatment. Patients were split into three groups according to pattern of weight loss: one group that lost none (they gained about 1 kg, but as their HbA_{1c} level fell by over 1%, they were presumably taking the exenatide, suggesting that compliance was not the issue); a second group (34%), which lost weight quite quickly (about 4 kg by week 12); and a third group (46%), which lost as much weight as the second group, but who did so more slowly. Groups 2 and 3 lost on average 6 kg by 2 years.

In the group that did not lose weight, HbA_{1c} level fell by about 1.2% but started rising again in the second year, to a drop of about 0.7% (from graph). In groups 2 and 3, the fall in HbA_{1c} level of about 1.5% was more sustained – about 1.5% reduction at 52 weeks and 1.3% at 104 weeks.

This finding might have implications if NICE recommended a stopping rule for exenatide, as it could be stopped in those in whom it was least effective (no weight loss), thereby improving the cost-effectiveness.

Exenatide LAR

The exenatide LAR formulation has been studied in a 15-week Phase II trial [Kim (2007)]⁴⁷ in patients with type 2 diabetes. The trial reported that a 2-mg dose of exenatide LAR showed a reduction in HbA_{1c} level of 1.4% (relative to placebo), which the authors say is approximately twice as great as that seen with twice-daily injections of conventional exenatide. Preliminary results have suggested that the LAR formulation is also better tolerated than the original formulation, with less nausea, and (in the 2-mg form) is associated with greater weight loss; however, patient numbers were small. Results from other trials are awaited. The Amylin website⁴⁵ reports an unpublished 30-week RCT of long-acting exenatide versus twice-daily Byetta, and states that 'results showed that exenatide once weekly demonstrated powerful glucose efficacy, complemented by striking weight loss'.

This trial is presumably the DURATION trial, recently described in two abstracts. The ADA abstract, Drucker *et al.* (2008),⁷⁶ reported the 30-week results in brief. They showed that once-weekly exenatide reduced HbA_{1c} level slightly more than twice daily: 1.9% versus 1.5%. Seventy-seven per cent of the once-weekly group achieved an HbA_{1c} level of less than 7.0%, compared with 61% for the twice daily. The trial recruited 295 patients who were poorly controlled (mean HbA_{1c} level 8.3%), but most were on no oral drugs (15%) or monotherapy (45%). Only the 40% on two oral agents are relevant to this review. However, the trial clearly suggests that the future lies with once-weekly exenatide. No details on cost are yet available, but some economies would be expected compared with twice-daily injections.

The second abstract is from EASD⁷⁷ and is a 22-week open-label follow-up of 241 of the DURATION patients by Buse *et al.* (2008)⁷⁷ [the same team as Drucker *et al.* (2008)⁷⁶]. Much of the abstract is about the patients who switched from twice-daily to weekly, but the 52-week HbA_{1c} level results in the original once-weekly group are reported in brief as being sustained – reduction at 52 weeks of 2% (1.9% at 30 weeks).

GLP-1 agonists and beta-cell function

Rodent studies have reported that liraglutide can increase beta-cell mass.

Gallwitz (2006)⁷⁸ has reviewed some of the animal and in vitro studies. The animal studies are mainly in rats, with a couple in mice. The evidence suggests that beta-cell growth is stimulated and that apoptosis is reduced. In isolated human islets, GLP-1 expands beta-cell mass. However, Gallwitz found no evidence regarding beta-cell mass in humans.

Xu *et al.* (1999)⁷⁹ reported that exenatide treatment improved diabetic control in rats that were made diabetic by partial pancreatectomy, and that this was related to an increase in beta-cell mass (assessed histologically). Interestingly, the improved control was seen even after exenatide was stopped after 10 days. Gedulin *et al.* (2005)⁸⁰ also reported an increase in beta-cell mass in rats after exenatide treatment.

Tourrel *et al.* (2001)⁸¹ treated newborn rats, made diabetic with streptozotocin, with exenatide and, again, noted an increase in beta-cell mass, which persisted (although the beta cells were less responsive to glucose).

If these findings are confirmed in humans, it would be of great importance, because it would suggest that the progressive nature of type 2 diabetes^{4,5} could be halted. Barnett (2007)³⁸ and Holst *et al.* (2008)⁸² both note that if the GLP-1 analogues could increase beta-cell mass there would be an argument for treatment early in the disease, before too many beta cells are lost.

However, there are few data on the effect in humans – some very short experiments on islet cells in vitro, reviewed by Wajchenberg (2007),⁸³ who concludes that there is, as yet, no clinical evidence that the GLP-1 analogues protect beta cells.

Bunck *et al.* (2008),⁸⁴ in an ADA abstract from their RCT of exenatide versus glargine,⁸⁵ reported that the beneficial effects seen on exenatide were not sustained – 5 weeks after stopping exenatide all of the improvements had gone, which may suggest that beta-cell function was not improved.

Further research is required, ideally with some means of determining at an early stage (2–3 years?) whether beta-cell mass is maintained in humans with type 2 diabetes.

Discussion

Barnett (2007)³⁸ comments that ‘The appeal of exenatide therapy is that it provides glycaemic control with concomitant weight loss (as opposed to rapid or short-acting insulins which tend to cause weight gain), and, when not used with a drug that increases circulating insulin levels, does not cause hypoglycaemia’.

The evidence to date shows that the GLP-1 analogues can provide a useful improvement in glucose control when added to dual treatment with oral drugs, and that, at least in the short term, they can be an alternative to starting insulin. How long this effect would last, is not known. If we assume that the disease will steadily progress, as shown in UKPDS 16,⁴ then some of the benefit will be lost, as the beta cells will no longer be there to release insulin. Other benefits, such as delayed gastric emptying, may continue, which may help control postprandial hyperglycaemia.

The glucose-dependent nature of the insulin release means that hypoglycaemia should be less of a problem, but the differences in the trials were not marked.

Weight loss is a useful feature in the trials, though perhaps seen less in routine care.

The drawbacks are the need for injections (twice daily with exenatide and once a day with liraglutide), the high rate of side effects (especially nausea) and the cost.

Injecting a foreign peptide could lead to antibody formation, but Barnett (2007)³⁸ notes that such antibodies were common by 30 weeks but did not appear to reduce efficacy.

A review by the well-respected Prescrire International group from France concluded that exenatide was an alternative to starting insulin in patients with poorly controlled type 2 diabetes but that there was no evidence, as yet, that it was better, and, given the much greater experience with insulin, that should be preferred.⁸⁶

The German Institute for Quality and Efficiency in Health Care [Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)] issued a report on exenatide in 2007.⁸⁷ Their review of exenatide addressed two questions:

- Is it worthwhile to add exenatide to therapy with metformin and/or a sulfonylurea?
- How does adding exenatide compare with other additional treatments?

The review identified five trials. These included the Kendall *et al.* (2005),⁵⁹ Nauck *et al.* (2007),⁵⁴ DeFronzo *et al.* (2005)⁵⁸ and Heine *et al.* (2005)⁵³ studies included in our TAR. The other one was Buse *et al.* (2004),⁵⁶ excluded from this TAR, because patients had failed on sulfonylurea monotherapy but not had metformin.

The IQWiG review concluded that:

- the reduction in HbA_{1c} level was comparable for exenatide and insulin
- no difference in the frequency of severe hypoglycaemia was shown in the trials against insulins
- patients on exenatide lost weight, but those on insulin gained weight
- the long-term benefits or harms of exenatide are unclear.

Postprandial hyperglycaemia

The slowing of gastric emptying by the incretin mimetics could, in theory, reduce postprandial hyperglycaemia.

Acute pancreatitis

There have been recent concerns about acute pancreatitis in people who have been treated with exenatide.⁸⁸ The FDA had (as at end of 2006) reviewed 30 reports of acute pancreatitis in patients on exenatide. Nearly all had other possible reasons for pancreatitis, including gallstones and alcohol use. Nearly all improved after exenatide was stopped, and a few in whom it was started again had a recurrence of symptoms. However, the improvement after the drug was stopped may be coincidental. The FDA has asked for a warning to be added to patient information and arranged enhanced monitoring, but has not restricted use.⁸⁹

The Medicines and Healthcare Products Regulatory Agency (MHRA) (Drug Safety Update May 2008)⁹⁰ has called for vigilance. It notes that by September 2007 there had been 89 reports of acute pancreatitis, with, curiously, 87 in the USA and two in Germany. One case has since been reported in the UK, after only 5 µg of the drug.

Summary

In patients with inadequate control, the addition of exenatide led to a fall in HbA_{1c} level of about 1.0%. In trials against insulins, the HbA_{1c} level results were comparable. There was less nocturnal hypoglycaemia with exenatide than with insulin. In trials against insulin, patients on exenatide lost

weight, whereas those on insulin gained weight. Nausea is very common, especially initially, but is not usually severe.

The need to inject exenatide twice daily may be a deterrent, but a long-acting once-weekly form is forthcoming.

Chapter 3

The DPP-4 inhibitors

This chapter draws on the recently published Cochrane review by Richter et al. (2008),⁹¹ but focuses on the comparisons that are relevant to this guideline.

As mentioned in the previous chapter, naturally occurring GLP-1 is broken down by the enzyme DPP-4. DPP-4 inhibitors, or 'gliptins', prevent GLP-1 degradation and prolong its half-life. Two inhibitors are currently on the market: – vildagliptin and sitagliptin – both for once-daily oral administration. A third, saxagliptin, is coming.⁹² The manufacturer has submitted a request for regulatory approval to the FDA.⁹³ A new drug application for a fourth drug, alogliptin (Takeda Pharmaceutical, Osaka, Japan), was submitted in 2007. However, Takeda Pharmaceutical has recently been notified by the FDA that the cardiovascular safety data that it is in the process of reviewing for alogliptin are 'insufficient'. The announcement is expected to delay approval of the drug.

Methods

For the review of the clinical effectiveness of the DPP-4 inhibitors, the primary sources of evidence were systematic reviews of RCTs, and recent RCTs, with other types of study such as open-label extensions being used only for data on duration of effect, side effects and continuation rates. Because the Cochrane review by Richter *et al.*⁹¹ is very recent, we searched only for studies that had been published after the searches for the Cochrane review were done.

Types of interventions

Treatment for a minimum of 12 weeks with DPP-4 inhibitors (sitagliptin or vildagliptin) in combination with meglitinide analogues, metformin, a sulfonylurea or a TZD.

As with the GLP-1 analogues, the comparisons of interest for this review are based on the licensed indications, and on the standard treatment of type 2 diabetes, as set out in the NICE guideline (2008),⁶ the algorithm that was reproduced in Chapter 1.

The licensed indications are as follows.⁹⁴

Sitagliptin

- In patients with type 2 diabetes, to improve glycaemic control in combination with metformin when diet and exercise plus metformin, do not provide adequate glycaemic control.
- In combination with a sulfonylurea, in patients who cannot tolerate metformin, or in whom metformin is inappropriate, when maximally tolerated dose of a sulfonylurea does not provide adequate control.
- For patients with type 2 diabetes in whom use of a TZD is appropriate, sitagliptin is indicated in combination with the peroxisome proliferator-activated receptor (PPAR) agonist when diet and exercise alone do not provide adequate glycaemic control.
- To improve glycaemic control in combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

This differs from the FDA approval,⁹⁵ which allows monotherapy as well.

Vildagliptin is indicated in the treatment of type 2 diabetes, as dual oral therapy in combination with:

- metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin
- a sulfonylurea, in patients with insufficient glycaemic control despite maximum tolerated dose of a sulfonylurea and in whom metformin is inappropriate due to contraindications or intolerance
- a TZD, in patients with insufficient glycaemic control and for whom the use of a TZD is appropriate.

The following comparisons are relevant to this review.

- *Comparison 1* When dual therapy with metformin (or a glitazone) and a sulfonylurea

have failed to achieve adequate control. The main comparisons will be:

- 1a. metformin + sulfonylurea *versus* metformin + either DPP-4 inhibitor
- 1b. sulfonylurea + glitazone *versus* sulfonylurea + either DPP-4 inhibitor
- 1c. sulfonylurea + glitazone *versus* glitazone + either DPP-4 inhibitor
- 1d. metformin + glitazone *versus* metformin + either DPP-4 inhibitor
- 1e. metformin + sulfonylurea *versus* metformin + sulfonylurea + sitagliptin.
- *Comparison 2* As an alternative to adding insulin to oral therapy. This would be in patients who have failed to achieve adequate control on dual or triple oral therapy. In those starting insulin, it is assumed that metformin would be continued, so the comparisons include:
 - 2a. metformin + long-acting insulin *versus* metformin + a DPP-4 inhibitor.
- *Comparison 3* There is evidence that in patients failing on standard combination therapy, an intensive lifestyle intervention (diet and supervised exercise) can be as good as starting insulin. So it may be that rather than start a DPP-4 inhibitor, an intensive lifestyle package could be tried:
 - 3. dual therapy + lifestyle *versus* dual therapy + a DPP-4 inhibitor.

Exclusions

- Trials of DPP-4 monotherapy versus placebo. These can show that the DPP-4 inhibitors are pharmacologically active, but are not relevant to standard practice.
- Trials of DPP-4 monotherapy versus monotherapy with other oral agents – not relevant to standard practice.
- Trials of DPP-4 inhibitors in combination with insulin (not licensed).

The Cochrane review of the DPP-4 inhibitors found 29 comparisons (some of the 25 trials had more than one arm), but these included:⁹¹

- six trials of sitagliptin monotherapy versus placebo
- two trials of sitagliptin monotherapy versus metformin or glipizide
- four trials of a sitagliptin combination versus metformin monotherapy
- one trial of a sitagliptin combination versus pioglitazone monotherapy

- one trial of a sitagliptin combination versus glimepiride monotherapy
- two trials of a sitagliptin combination versus alternative dual therapy
- six trials of vildagliptin monotherapy versus placebo
- three trials of vildagliptin monotherapy versus metformin, pioglitazone or rosiglitazone monotherapies
- two trials of vildagliptin and metformin versus metformin monotherapy
- two trials of vildagliptin and pioglitazone versus pioglitazone alone
- one trial of vildagliptin and insulin versus insulin alone
- one trial of vildagliptin and metformin versus pioglitazone and metformin.

About half of all of the vildagliptin trials were in patients who had never had an oral drug, but had been treated only with diet and exercise.

Most of these studies from the Cochrane review are not relevant to this review. *Table 9* shows which studies from the Cochrane review are exclusions for this HTA report, and the reasons for exclusion.

What do the excluded studies tell us?

Compared to placebo, sitagliptin and vildagliptin reduced HbA_{1c} level by around 0.7% and 0.6%, respectively. The sitagliptin versus placebo trials demonstrated substantial heterogeneity. (However, after eliminating a single study of Japanese patients only, Cochrane review noted that the heterogeneity decreased to an *I*²-value of 25%.) There was no weight loss advantage with the DPP-4 inhibitors.

Compared to monotherapy with other agents, neither drug showed any advantage.

There are no data on diabetic complications or mortality, but that is to be expected because of the short duration. Most included trials were 24 weeks' duration; three were for 52 weeks.

The trials gave no data on costs or quality of life (QoL).

Both drugs were well tolerated. No severe hypoglycaemia was reported.

TABLE 9 Trials, or arms of trials, of DPP-4 inhibitors excluded from this review

Study	Reason for exclusion
Ahren (2004) ⁹⁶	Compared with metformin monotherapy
Aschner (2006) ⁹⁷	Compared to placebo
Bosi (2008) ⁹⁸	Compared to metformin monotherapy
Charbonnel (2006) ⁹⁹	Compared to metformin monotherapy
Dejager (2007) ¹⁰⁰	Compared to placebo
Fonseca (2007) ¹⁰¹	Compared to metformin monotherapy
Garber (2007) ¹⁰²	Compared to pioglitazone monotherapy
Goldstein (2007) ¹⁰³	Compared to placebo
Goldstein (2007) ¹⁰³	Compared with metformin monotherapy
Hanefeld 2007 ¹⁰⁴	Compared to placebo
Mimori (2006) ¹⁰⁵	Compared to placebo
Nonaka (2008) ¹⁰⁶	Compared to placebo
Pan (2008) ¹⁰⁷	Compared to acarbose monotherapy
Pi-Sunyer (2007) ¹⁰⁸	Compared to placebo
Pratley (2006) ¹⁰⁹	Compared to placebo
Raz (2006) ¹¹⁰	Compared to placebo
Raz (2008) ¹¹¹	Compared with metformin monotherapy
Ristic (2005) ¹¹²	Compared to placebo
Rosenstock (2006) ¹¹³	Compared to pioglitazone monotherapy
Rosenstock (2007) ¹¹⁴	Compared to rosiglitazone monotherapy
Rosenstock (2007) ¹¹⁵	Compared to pioglitazone monotherapy
Rosenstock (2008) ¹¹⁶	Compared to placebo
Scherbaum (2008) ^{117,118}	Compared to placebo
Schweizer (2007) ¹¹⁹	Compared with metformin monotherapy
Scott (2007) ¹²⁰	Compared to placebo
Scott (2008) ¹²¹	Compared to placebo

Inclusions

A disappointingly small number of trials met our inclusion criteria – only four. All were funded by the manufacturers, and half or more of the authors were from the manufacturer.

The characteristics of the included trials are shown in Appendix 3.

There were no trials for Comparisons 1b and 1c.

Comparison 1a

Nauck (2007)¹²² – sitagliptin + metformin vs glipizide + metformin

This 52-week trial recruited 1172 patients, mean age 57 years and mean duration 6 years, whose control was unsatisfactory (HbA_{1c} 6.5–10%) on metformin alone. They had a period of dose titration on metformin first. They were randomised to sitagliptin (100 mg once daily) or glipizide (starting dose 5 mg/day). The latter was titrated up aiming at a target for pre-meal blood glucose of under 6.1 mmol/l, but could be reduced if hypoglycaemia was a problem. It was designed to confirm non-inferiority of sitagliptin to glipizide, and did so.

Comparison 1d

Bolli (2008)¹²³ – vildagliptin + metformin vs pioglitazone + metformin

This 24-week trial recruited 576 patients whose control was inadequate (HbA_{1c} 7.5–11%) on metformin alone, and randomised them to additional vildagliptin or additional pioglitazone, in a 24-week trial. Participants had poor control (HbA_{1c} 7.5–11%), were aged 18–77 (mean about 57 years), and had had diabetes for a mean of 6.4 years. It showed that vildagliptin was not inferior to pioglitazone.

Scott (2008)¹²¹ – sitagliptin + metformin vs rosiglitazone + metformin

This 18-week trial¹²¹ also recruited 273 patients whose control was inadequate on metformin monotherapy, and randomised them to dual therapy with either sitagliptin or rosiglitazone, or to a placebo group having metformin monotherapy. Patients were 18–75 years of age, taking at least 1500 mg of metformin each day. Inadequate control was defined as an HbA_{1c} level of 7% or over (but not more than 11%). The average duration of diabetes was 5 years (range 0.2–19 years). After 18 weeks, the mean HbA_{1c} levels decreased by 0.22% in the placebo arm, and by 0.73% and 0.79% in the sitagliptin and rosiglitazone arms, respectively. So the net gain in HbA_{1c} level from sitagliptin over placebo was 0.51%. There was weight gain with rosiglitazone (1.5 kg) but reductions with sitagliptin (0.4 kg) and placebo (0.9 kg).

Comparison 1e

Hermansen (2007)¹²⁴ – sitagliptin + glimepiride + metformin vs glimepiride + metformin

There were four arms and 441 patients in this 24 week trial¹²⁴ the two above, a glimepiride monotherapy arm, and a sitagliptin + glimepiride arm (a combination not currently licensed in Europe). The mean age at entry was around 57, and the mean duration of diabetes was around 8.5 years. They had inadequate control (HbA_{1c} level of 7.5% or over, up to 10.5%) on a sulfonylurea alone or with metformin. Mean baseline HbA_{1c} was 8.34%. Sitagliptin 100 mg once-daily reduced HbA_{1c} level by 0.89% compared with placebo, in patients also treated with both glimepiride and metformin.

There were no trials for Comparisons 2 and 3.

Quality of included trials

The quality of the included trials, as shown in *Table 10*, was good.

HbA_{1c} results

The results for HbA_{1c} in *Table 11* show that sitagliptin and vildagliptin have similar effects to a glitazone, but an improvement of 0.9% compared with placebo.

Weight change

Table 12 shows there was less weight gain than with the glitazones [Bolli (2008),¹²³ Scott (2007)¹²⁰] but that is mainly because people on glitazones gained weight – not because those on a DPP-4 inhibitor lost any. In the comparison with glipizide, the sitagliptin arm ended 2.6 kg lighter. In the Hermansen *et al.* trial (2007)¹²⁴ there was more weight gain with the DPP-4 inhibitor than in the placebo control arm.

The Cochrane review⁹¹ concluded (see tables 13 and 14 under ‘Additional tables’ for details) that in trials against placebo there was greater weight loss after placebo treatment than with sitagliptin and vildagliptin. The pooled estimate for sitagliptin studies was a weighted mean difference (WMD) of 0.7 kg (95% CI 0.3 to 1.1, $p = 0.0002$) in favour of placebo and 0.8 kg (95% CI 0.2 to 1.3, $p = 0.009$), for vildagliptin studies in favour of placebo. Most active hypoglycaemic comparators also resulted in more pronounced weight losses than sitagliptin or vildagliptin treatment.

So the DPP-4 drugs do not seem to have as great a weight reduction effect as exenatide, but in most cases there is no weight gain, which, compared with sulfonylureas and glitazones, is an advantage.

Adverse events

Table 13 shows selected adverse events.

For full details, see tables 15–27 of the Cochrane review by Richter *et al.* (2008).⁹¹ As mentioned above, the drugs were well tolerated. Discontinuation due to adverse effects did not differ significantly between sitagliptin or vildagliptin intervention and control arms. The risk ratios of serious adverse events also did not show statistically significant differences between groups.

In the Cochrane review, headache was reported more often with DPP-4 inhibitors, especially following vildagliptin therapy.

Hypoglycaemia

Bolli *et al.* (2008)¹²³ defined hypoglycaemia as symptoms that are suggestive of low blood glucose, confirmed by a self-monitored PG level of under 3.1 mmol/l. Hypoglycaemia was reported in only one patient in the Bolli study – in the vildagliptin group – and it was mild.

In the Hermansen *et al.* trial (2007),¹²⁴ any hypoglycaemia was reported in 16% of the sitagliptin group versus 0.9% of the control group. In the Scott *et al.* study (2007),¹²⁰ hypoglycaemia was reported in 1% of both groups. No severe hypoglycaemia was reported.

Nauck *et al.* (2007)⁵⁴ defined severe hypoglycaemia as requiring medical assistance, and had another category where non-medical assistance was sufficient. Any hypoglycaemia was reported in 32% in the glipizide arm and in 5% in the sitagliptin arm; severe hypoglycaemic attacks were reported in 1.2% and 0.2%, respectively. Hypoglycaemia of the ‘non-medical assistance needed’ category was reported in 1.4% (eight patients) and 0.2% (one patient).

In the wider Cochrane review by Richter *et al.* (2008),⁹¹ severe hypoglycaemia was not reported in patients taking sitagliptin or vildagliptin, and there were no statistically significant differences in hypoglycaemic episodes between sitagliptin/vildagliptin and comparator groups.

TABLE 10 Quality of DPP-4 studies

Study	Method of randomisation	Allocation concealment	Blinding	ITT analysis	Percentage completed	Power calculation	Similarity at baseline	Sponsorship by manufacturer
Bolli (2008) ¹²³	Not reported; 295 allocated to vildagliptin arm vs 281 to pioglitazone	Not reported	Double blind	Per protocol	89% and 87%	Yes	Good	Funded by Novartis and corresponding author from company
Hermansen (2007) ¹²⁴	Computer generated	Yes	Double blind	No	92/113 and 102/116	Yes	Good	Funded by Merck and 4/6 authors from company
Nauck (2007) ¹²²	Not reported	Not reported	Not blinded	No – per protocol	67% and 74%	Not clear	Good	Funded by Merck with four authors from company
Scott (2008) ¹²¹	Not reported	Not reported	Double blind	Per protocol	90% and 98%	Not clear	Good	Funded by Merck and 3/4 authors from company

TABLE 11 Summary of HbA_{1c} results in DPP-4 trials

Study	Study arm	HbA _{1c} (%) baseline	HbA _{1c} (%) end	Change from baseline (%)	Difference between groups at end (DPP-4 inhibitor-comparator)	p-value between groups	Percentage achieving HbA _{1c} <7%
Bolli (2008) ¹²³	Vildagliptin + metformin	8.4		-0.88 (±0.5 ^a)	0.10 (95% CI -0.05 to -0.26)		27
	Pioglitazone + metformin	8.4		-0.98 (±0.06 ^a)			36
Hermansen (2007) ¹²⁴	Sitagliptin + metformin + glimepiride	8.27		-0.59	-0.89	<0.001	22.6
	Metformin + glimepiride	8.26		+0.30			1.0
Nauck (2007) ¹²⁴	Sitagliptin + metformin	7.7% (all)	6.86 (PP)	-0.67	-0.02	NS	63
	Glipizide + metformin	7.6	6.84	-0.67			59
Scott (2007) ¹²⁰	Sitagliptin + metformin	7.8	7.01	-0.79	+0.07	NS	55
	Rosiglitazone + metformin	7.7	6.94	-0.76			63

NS, not significant; PP, per protocol.

^a Standard errors (SEs) as reported by authors. The different-sized SEs look odd. It may be the 0.5% for the vildagliptin group, which is wrong – it looks that way from the graph of HbA_{1c} in the paper. It should, perhaps, be 0.05%.

TABLE 12 Weight changes in DPP-4 trials

Study	Study arm	BMI baseline	Weight in kg (SD) at baseline	Change from baseline (kg)	Difference between groups at end (DPP-4 inhibitor-comparator)	p-value between groups
Bolli (2008) ¹²³	Vildagliptin + metformin	32.2	91.8 (18.5)	0.3	-1.6 kg	<0.001
	Pioglitazone + metformin	32.1	91.2 (16.9)	1.9		
Hermansen (2007) ¹²⁴	Sitagliptin + metformin + glimepiride	31.3	87.2 (19.7)	+0.4	+1.1 kg	<0.001
	Metformin + glimepiride	30.7	86.7 (21.1)	-0.7		
Nauck (2007) ⁵⁴	Sitagliptin + metformin	31.2	89.5	-1.5	-2.6 kg	<0.001
	Glipizide + metformin	31.3	89.7	+1.1		
Scott (2007) ¹²⁰	Sitagliptin + metformin	30.3	83.1 (17.1)	-0.4	-1.9 kg	(95% CI 1.3 to 2.5)
	Rosiglitazone + metformin	30.4	84.9 (18.5)	+1.5		

Infections

The Cochrane review by Richter *et al.* (2008)⁹¹ reported an increase in all-cause infections.

The Merck & Co responses to the consultation mentioned the analysis by Williams-Herman *et al.* (2008) (who are from Merck & Co),¹²⁵ and stated that this did not find any increase in infections.

There are three reviews that report infection rates in DPP-4 inhibitor trials:

- The Cochrane review by Richter *et al.* (2008)⁹¹ included all RCTs in adults with type 2 diabetes, with trial duration of at least 12 weeks. It included 25 trials: 11 sitagliptin, 14 vildagliptin. Study duration ranged from 12 to 52 weeks. Searches were carried out until January 2008. All-cause infections [for example, nasopharyngitis, upper respiratory tract infection, urinary tract infection (UTI)] showed a statistically significant increase after sitagliptin treatment [relative risk (RR) 1.29, 95% CI 1.09 to 1.52, $p = 0.003$] but did

TABLE 13 Adverse events in DPP-4 trials

Study	Study arm	Nausea (%)	Vomiting (%)	Diarrhoea (%)	Other GI (%)	Any AE (%)	Discontinuation due to side effects
Bolli (2008) ¹²³	Vildagliptin + metformin	NR	NR	3.4	3.1 (constipation)	2.0	3.1
	Pioglitazone + metformin	NR	NR	2.9	1.1 (constipation)	4.6	3.2
Hermansen (2007) ¹²⁴	Sitagliptin + metformin + glimepiride	0.9	1.7 (2 patients ex 116)	0.9	All GI AEs 4.3	18	1.7
	Metformin + glimepiride	0.9	0.9 (1 patient ex 113)	3.5	All GI AEs 7.1	7.1	1.8
Nauck (2007) ⁵⁴	Metformin + sitagliptin	2.6	0.4	5.8	2.7 (abdominal pain)	71	2.7
	Metformin + glipizide	2.7	1.5	5.5	2.1	76	3.6
Scott (2007) ¹²⁰	Sitagliptin + metformin	1	1	3	Any GI event 9	39	2
	Rosiglitazone + metformin	1	1	3	Any GI event 7	44	0

AE, adverse event; ex, excluded; GI, gastrointestinal; NR, not reported.

not reach statistical significance following vildagliptin therapy (RR 1.04, 95% CI 0.87 to 1.24, $p = 0.7$).

- A review by Amori *et al.* (2007)³² also included RCTs of at least 12 weeks' duration. Searches were until 20 May 2007. They found eight sitagliptin studies and 12 vildagliptin studies. They found a slightly increased risk of nasopharyngitis (6.4% for DPP-4 inhibitor versus 6.1% for comparator; RR 1.17; 95% CI 0.98 to 1.40), which was significant only for sitagliptin (RR 1.38, CI 1.06 to 1.81). The risk of UTI was increased by about 50% (3.2% for DPP-4 inhibitor versus 2.4% for comparator; RR 1.5; 95% CI 1.0 to 2.2), and this was seen with both DPP-4 inhibitors, although in the individual comparisons, confidence intervals (CIs) on risk ratios were wide and overlapped with unity. Amori *et al.* accepted that the relative risks were small, but commented: 'there are more than 20 million patients with diabetes in the United States who are both more likely to develop a urinary tract infection and are at higher risk of complications, including death from urosepsis. A relative risk of 1.5 increases the number of UTIs by 1 million new cases per year, placing a significant burden on the individual patient and the health-care system. Until more safety data are available, it may be prudent to avoid use of these agents in patients with a history of recurrent UTIs'.
- The analysis by Williams-Herman *et al.* (2008)¹²⁵ included only sitagliptin (100-mg dose). It pooled 12 large Phase IIb and Phase III RCTs, with duration at least 18 weeks (up to 2 years), based on data available in the industry database at November 2007. They reported that the only infection more common in the sitagliptin group was nasopharyngitis, with 7.1% in the sitagliptin group versus 5.9% in the comparators, but that the 95% CI for the difference overlapped with no difference (95% CI -0.1 to +2.4). They found no difference in the frequency of UTIs.

So we have two independent reports suggesting an increase in UTIs, and the manufacturer's analysis reporting no increase.

Table 14 shows the trials included in these reviews.

Quality of life

No publication provided data on health-related QoL.

Hypothetical adverse effects

In addition to reducing the breakdown of the incretins, GLP-1 and gastric inhibitory peptide, DPP-4 inhibitors also prolong the action of a number of neuropeptides, such as neuropeptide Y, growth hormone-releasing hormone and chemokines, such as stromal cell-derived factor 1 and macrophage-derived chemokine. Potential side effects include neurogenic inflammation, increase in blood pressure, enhanced inflammation and allergic reactions. DPP-4 contributes to T-cell activation, raising the possibility that these compounds compromise immune function.¹³⁰ Levels of tissue DPP-4 are reduced in nasal tissue of people with chronic rhinosinusitis, and DPP-4 inhibition seems to aggravate nasopharyngitis, as could be observed in clinical studies.

Therefore, the long-term safety of DPP-4 inhibitors merits further investigation, and it seems to be important to monitor DPP-4-treated patients for the development of inflammatory conditions, such as angioedema, rhinitis and urticaria.

Costs

Both of the sitagliptin trials used 100 mg daily, which, at a cost (BNF 55¹³¹) of £33.26 for 28 tablets, comes to £432 per year.

No cost is available for vildagliptin yet. The dose used by Bolli *et al.* (2008)¹²³ was also 100 mg daily.

Beta-cell function

A progressive reduction in beta-cell mass contributes significantly to gradual loss of glycaemic control in individuals with type 2 diabetes. A major goal of diabetes research is to restore the beta-cell mass typically lost during the natural progression of type 2 diabetes. Current treatments not only show no ability to reduce beta-cell loss, but also some, such as the sulfonylureas, have been shown to induce beta-cell apoptosis in cultured human islets.¹³² If the DPP-4 inhibitors can enhance beta-cell survival and stimulate beta-cell growth, they may provide a means to preserve or restore functional beta-cell mass in individuals with type 2 diabetes.

The Cochrane reviewers⁹¹ found few data on measurements of beta-cell function, especially for vildagliptin. The variety of methods used also made definite conclusions on the effects of DPP-4 inhibitors on beta-cell function difficult. Inspection

TABLE 14 Trials included in three reviews of DPP-4 inhibitors

Study ID	Reviews			DPP-4 inhibitor
	Richter (2008) ⁹¹	Amori (2007) ³²	Williams-Herman (2008) ¹²⁵	Vildagliptin (V) or sitagliptin (S)
Ahren (2004) ⁹⁶	✓	✓	NA	V
Aschner (2006) ⁹⁷	✓	✓	✓	S
Bolli (2008) ¹²³	✓	✗	NA	V
Bosi (2007) ⁹⁸	✓	✓	NA	V
Charbonnel (2006) ⁹⁹	✓	✓	✓	S
Dejager (2007) ¹⁰⁰	✓	✓	NA	V
Dobs (2008) ¹²⁶	✗	✗	✓	S
Fonseca (2007) ¹⁰¹	✓	✓	NA	V
Garber (2007) ¹⁰²	✓	✓	NA	V
Goldstein (2007) ¹⁰³	✓	✗	✓	S
Hanefeld (2005) ¹²⁷	✗	✓	✗	S
Hanefeld (2007) ¹⁰⁴	✓	✗	✓	S
Hermansen (2007) ¹²⁴	✓	✗	✓	S
Mimori (2006) ¹⁰⁵	✓	✓	NA	V
Nauck (2007) ¹²²	✓	✓	✓	S
Nonaka (2006, 2008) ^{106,128}	✓	✓	✗	S
Pi-Sunyer (2007) ¹⁰⁸	✓	✓	NA	V
Pratley (2006) ¹⁰⁹	✓	✓	NA	V
Raz (2006) ¹¹⁰	✓	✓	✗	S
Raz (2008) ¹¹¹	✗	✗	✓	S
Ristic (2005) ¹¹²	✓	✓	NA	V
Rosenstock (2006) ¹¹³	✓	✓	✓	S
Rosenstock (2007) ¹¹⁴	✓	✓	NA	V
Rosenstock (2007) ¹¹⁵	✓	✓	NA	V
Scherbaum (2008) ¹¹⁸	✓	✗	NA	V
Schweizer (2007) ¹¹⁹	✓	✓	NA	V
Scott (2007) ¹²⁰	✓	✓	✓	S
Scott (2008) ¹²¹	✓	✗	✗	S
Yang (2007) ¹²⁹	✗	✗	✓	S
P023 (Merck & Co, unpublished)	✗	✗	✓	S

NA, not applicable; ✓, trial included; ✗, trial not included.

of the sitagliptin homeostasis model assessment beta (HOMA-beta) data seems to indicate that sitagliptin, when compared with placebo, results in increased values of beta-cell function measurements, but the effect in comparison with other hypoglycaemic agents does not seem to be clear cut.

Most studies are quite short. An exception is the 2-year extension study by Scherbaum *et al.* (2008).¹¹⁷ This study (funded by Novartis, with the corresponding author from the company) was one of our exclusions because it compared vildagliptin with only placebo, but it does provide some data on a measure of beta-cell function, the insulin secretory rate relative to glucose level after meals.

This measure reflects the responsiveness of the beta cell to glucose, rather than absolute insulin production or plasma insulin level. The extension study was undertaken in under half of those who completed the original study (108 compared with 264). All of the original recruits had HbA_{1c} levels in the range of 6.2–7.5%. At recruitment the mean duration was 2 years.

Scherbaum *et al.* found that their measure of insulin secretory rate/glucose 'tended to increase' from the end of year 1 to the end of year 2, by which they mean that there was an increase that did not reach statistical significance. The implication is that there may be a steady improvement in beta-cell function. However, the mean HbA_{1c} level in the vildagliptin group fell after initiation, reached a nadir of about 6.2% by around 32 weeks, and then slowly rose to about 6.4% by 110 weeks. That rise suggests that vildagliptin is not having a dramatic effect on beta-cell function. It may be slowing the progression of the disease, which has been reported by the UKPDS (16 or 17);^{4,5} it is worth noting that the graph shows that mean HbA_{1c} level rose a little more steeply in the placebo group, whereas in UKPDS the lines were roughly parallel.

So far, no definite conclusions can be drawn on the effects of sitagliptin and vildagliptin on long-term beta-cell function. If beta-cell function does improve, and if that improvement is sustained over the long term (say 10–20 years), then that would be very important and there would be a case for early use, perhaps as the first drug to be used when diet fails. Or, given that diet usually fails, perhaps from the diagnosis of type 2 diabetes.

There could be an issue about the duration of diabetes at which any beta-cell preservation effect might be seen. The UKPDS study² reported that at diagnosis, about half of beta-cell function had been lost. If patients are then treated with incretin enhancers or mimetics after they had had diabetes for many years, it may be too late to see much effect. It would be interesting to assess effects on beta-cell function by duration of known diabetes, and perhaps also in people with impaired glucose tolerance (there is one trial of the effects of a DPP-4 inhibitor on people with impaired glucose tolerance¹¹⁶).

Emerging studies

Another third-line trial was reported at the ADA 2008 conference, in abstract only, by Dobs *et*

al. (2008)¹²⁶ It was an 18-week RCT of adding sitagliptin to metformin and rosiglitazone. HbA_{1c} level fell by 0.7% overall, but by 1.3% in those whose baseline HbA_{1c} level was over 9%.

At the same meeting, Krobot *et al.* (2008)¹³³ had an abstract from a second-line trial, of metformin and sitagliptin versus metformin and glipizide. The effects on HbA_{1c} level were similar, but hypoglycaemia was less frequent with sitagliptin (any hypoglycaemic event 5%) than the sulfonyleurea (32%).

At the September 2008 conference of the EASD three new gliptin trials were presented. One by Goodman *et al.* (2008)¹³⁴ was of vildagliptin versus placebo as an add-on to metformin, and would be an exclusion under our criteria. The other two are of interest. Arjona-Ferreira *et al.* (2008)¹³⁵ describe a Merck & Co-funded trial of adding sitagliptin in patients with inadequate control (HbA_{1c} level 7.5–11%) on metformin and rosiglitazone. Adding sitagliptin reduced HbA_{1c} level by 0.7% overall, but by 1.3% in those with baseline HbA_{1c} level of over 9%.

Braceras *et al.* (2008)¹³⁶ presented a Novartis trial comparing vildagliptin to a glitazone in patients not adequately controlled (initial HbA_{1c} level of over 7%) on metformin, and found them to be roughly equivalent. HbA_{1c} level fell by 0.68% on vildagliptin + metformin, and by 0.57% on glitazone + metformin.

Another new trial¹¹⁸ was published in full in August 2008, but is not relevant for our purposes. It compared vildagliptin and placebo in patients who had not previously had drug treatment. Their hyperglycaemia was mild (baseline HbA_{1c} level 6.2–7.5%). After 1 year on treatment, HbA_{1c} level fell by 0.3% in those receiving vildagliptin and rose by 0.15% in those on placebo, which was statistically significant, if not clinically so. It does provide a useful reminder that the size of reduction in HbA_{1c} level depends on baseline level.

Conclusions

Sitagliptin and vildagliptin are clinically effective in reducing blood glucose, do not cause problems with hypoglycaemia, and are well tolerated. However, we cannot yet say what the long-term effects on diabetes complications will be, nor what long-term adverse effects may appear.

Only indirect comparisons can be made with the GLP-1 analogues, because there have been no head-to-head trials. The main differences are that the DPP-4 inhibitors are given orally, are less expensive, cause fewer adverse events in the short

term (but may be slightly less potent in lowering blood glucose), and do not cause weight loss. They may not be so specific in action, and their effects on the immune system require monitoring.

Chapter 4

The long-acting insulin analogues

Objectives

In this chapter, we assess the effects of the new insulin analogues – glargine and detemir – with older long-acting (for example, ultralente) and intermediate-acting insulins (for example, NPH).

Background

An ideal basal insulin would have a flat action profile (i.e. the same level at all times of day) with no day-to-day variability in the same patient. Older long-acting insulins use a crystalline or amorphous suspension, that forms a slowly dissolving depot after subcutaneous injection. The newer long-acting analogues have adopted different approaches. Both have structural changes.

In glargine, these changes mean that it is soluble in the acidic (pH 4.0) solvent in which it is provided, but once injected into the neutral pH of the subcutaneous tissues, it forms stable hexamers which slowly release the insulin into the bloodstream.¹³⁷ In detemir, one amino acid is omitted and a long-chain (14-carbon) fatty acid, myristoyl, is attached. This facilitates binding of detemir to serum albumin. It has been suggested¹³⁸ that albumin binding may facilitate transport into the brain, and that this might cause slightly less weight gain than is seen with other insulins.¹³⁹

Methods

Inclusion criteria

Types of studies

A number of high-quality systematic reviews already exist in this area, so in the first instance, we reviewed systematic reviews of RCTs. The reviews had to include at least one RCT of at least 12 weeks' duration. We also considered any additional RCTs that were published after the last search of any relevant included review. The trials had to have a minimum duration of 12 weeks, although trials of at least 24 weeks' duration were preferred.

Types of participants

Patients of any age and gender with type 2 diabetes.

Types of interventions

In type 2 diabetes, treatment with insulin is started when control on a combination of oral drugs is unsatisfactory. Therefore, the comparators of glargine/detemir were other basal insulins, usually NPH but, occasionally, ultralente. Metformin will now usually be continued, and other oral therapies may be used. Some trials used insulin alone. So comparisons can include:

1. glargine + oral agents versus NPH + oral agents
2. detemir + oral agents versus NPH + oral agents
3. glargine + oral agents versus ultralente + oral agents
4. detemir + oral agents versus ultralente + oral agents
5. glargine versus detemir
6. glargine or detemir alone versus NPH alone.

Overweight people with type 2 diabetes often do not achieve good glycaemic control after switching to insulin, partly because it can cause further weight gain. We set out to review one other option (but did not identify any new relevant trials): metformin + sulfonylurea + insulin versus metformin + sulfonylurea + lifestyle interventions.

The trial by Aas *et al.* (2005)²⁷ (already described in Chapter 1) is relevant here.

There are trials of the long-acting analogues against short-acting insulins at mealtimes, for example once-daily glargine versus thrice-daily aspart. We excluded such trials, because they are comparing different approaches to glycaemic control, rather than the new and old basal insulins.

Types of outcomes

We planned to consider the following outcome measures:

- HbA_{1c}
- frequency of hypoglycaemia, especially if severe
- glycaemic excursions, including postprandial hyperglycaemia
- total daily dose of insulin
- weight gain or loss

- complication rates: retinopathy, nephropathy, myocardial infarction (MI), angina, heart failure, stroke, amputation, death
- adverse events
- health-related QoL.

Search strategy

Relevant literature was identified, and comprehensiveness checked, by:

- searches of bibliographic databases, MEDLINE, Cochrane Library and EMBASE
- checking reference lists of retrieved studies
- obtaining lists of published studies from manufacturers
- our peer review process.

Searches were also carried out to identify emerging evidence, from conference abstracts and trial registers. Studies available only in abstract were included in the assessment of clinical effectiveness if there was a paucity of studies published in full in peer-reviewed journals, but they were reported with appropriate caution. Our default position is for studies available only in abstract not to be used.

Authors of previous studies were not contacted.

Quality assessment of studies

The quality of systematic reviews was assessed using the following quality criteria, based on the NICE guidelines manual:

- appropriate and clearly focused question
- inclusion and exclusion criteria described
- literature search sufficiently rigorous to identify all relevant studies
- study selection described
- data extraction described
- study quality assessed and taken into account
- study flow shown
- study characteristics of individual studies described
- quality of individual studies given
- results of individual studies shown
- enough similarities between studies selected to make combining them reasonable.

Each of the items was rated as: well covered/adequately addressed/poorly addressed/not addressed/not reported/not applicable.

The overall quality of the review was rated as (+ +), (+) or (-).

Randomised controlled trials were assessed on the following criteria, based on the NICE guidelines manual:

- appropriate and clearly focused question
- method of randomisation
- allocation concealed
- participants blinded
- outcome assessors blinded
- all relevant outcomes measured in standard, valid, reliable way
- proportion of participants excluded/lost to follow-up
- handling of missing data
- intention-to-treat (ITT) analysis performed
- statistical analysis appropriate
- only difference between groups is treatment under investigation
- results in multicentre studies comparable for all sites
- groups comparable at baseline.

Again, overall quality of the trials was classified as (+ +), (+) or (-).

Data extraction

Data extraction was carried out by one researcher and checked by another. Any disagreements were resolved through discussion, involving a third person if necessary.

Data analysis

The clinical effectiveness, relative to the key comparators, was assessed, in terms of difference in effect size. (The key question for the cost-effectiveness analysis is not whether a drug is better than the comparator, but how much better.)

Data were summarised using tables and text. In addition, we performed a meta-analysis of all relevant trial data, combining data from the previous meta-analyses with newly identified trials. Data were summarised for continuous variables (for example, HbA_{1c}, weight change) as WMDs with 95% CIs using the inverse variance method and a random effects model. For dichotomous variables (hypoglycaemia), data were expressed as relative risks with 95% CIs (for patients with or without hypoglycaemia) and summarised using the Mantel-Haenzel method and a random effects model. For data already used in previous meta-analyses, data were generally used as given in the meta-analyses, although some double-checking was undertaken with the original papers. Where not given directly,

standard deviations (SDs) were either calculated from standard errors (SEs) or CIs, or in case of no measure of variability reported, the average of the SDs for the other studies for that outcome measure was used. If the SDs were missing for more than half of the studies, meta-analysis was considered not to be reliable and a statistical summary was not presented. Meta-analyses were generally done for end-of-study values except for weight change, as most studies reported data for weight change without giving baseline values. Heterogeneity was assessed using the chi-squared statistic.

We had set out to conduct sensitivity analyses to explore uncertainties in important parameters, and of the impact of hypoglycaemic episodes and the fear of hypoglycaemic episodes on QoL.

We did not include any indirect comparisons, for two main reasons. Firstly, such comparisons are prone to bias due to confounding variables, which may not all be apparent. Secondly, they are used mainly in technology appraisals, when seeking to decide which of two or more options is better or best. We do not expect the guideline development group will wish to make any recommendations of whether glargine should be used in preference to detemir, or vice versa, because such comparisons would be based partly on cost, which may change. Having two drugs available in each group encourages competition on price.

Systematic reviews

Search results

Fourteen papers were identified as potentially relevant systematic reviews. Of these, five fulfilled the inclusion criteria.^{140–144} Most of the remainder did not use systematic review methodology, and one was only a protocol for a systematic review (Table 15). Two further systematic reviews were identified after the completion of the present analysis and these will only be summarised briefly.^{145,146}

Description of reviews

The characteristics of the included reviews are shown in Appendix 4. Of the five included reviews, the reviews by Duckworth *et al.* (2007)¹⁴⁰ and Wang (2003)¹⁴³ had only a very limited description of methodology, the review by Horvath *et al.* (2007)¹⁴¹ was a Cochrane review, and the reviews by Warren *et al.* (2004)¹⁴⁴ and Tran *et al.* (2007)¹⁴² were Health Technology Assessments (one from

TABLE 15 Excluded reviews – long-acting insulin analogues

Study	Reason for exclusion
Dailey (2003) ¹⁴⁷	Not a systematic review, abstract only
Garber (2007) ¹⁴⁸	Not a systematic review
Glass (2008) ¹⁴⁹	Not a systematic review
Hemraj (2004) ¹⁵⁰	Not a systematic review
Mullins (2007) ¹⁵¹	Not a systematic review
Mullins (2007) ¹⁵²	Not a systematic review, abstract only
Rašlová (2007) ¹⁵³	Not a systematic review
Rosenstock (2005) ¹⁵⁴	Not a systematic review
Swinnen (2007) ¹⁵⁵	Protocol only, no full review

the UK and one from Canada). Four of the reviews had non-industrial funding, whereas the review by Duckworth *et al.* (2007)¹⁴⁰ was funded by Sanofi-aventis (New Jersey, NJ, USA).

Inclusion criteria

Only four out of the five reviews specified the study design of the studies to be included. The others included RCTs (or just ‘clinical trials’), where Warren *et al.* (2004)¹⁴⁴ specified a minimum duration of 4 weeks, Horvath *et al.* (2007)¹⁴¹ 24 weeks and Wang (2003)¹⁴³ specified a minimum number of participants of 100. Wang also included other designs to answer different parts of their review question, but only the clinical efficacy trials are considered here.

Both Health Technology Assessments and the review by Wang included both participants with type 1 and type 2 diabetes. The remaining two reviews were concerned only with participants with type 2 diabetes. The present review only summarises parts of the included reviews that describe patients with type 2 diabetes.

The reviews by Duckworth and Davis (2007),¹⁴⁰ Warren *et al.* (2004)¹⁴⁴ and Wang (2003)¹⁴³ focused on insulin glargine, whereas the reviews by Horvath *et al.* (2007)¹⁴¹ and Tran *et al.* (2007)¹⁴² reviewed the effects of both insulin glargine and insulin detemir. Comparison treatments were NPH insulin in the study by Duckworth and Davis, and Horvath *et al.*, another long-acting basal insulin in the review by Warren *et al.*, conventional human insulin or OAD agents in the review by Tran *et al.*, and comparison treatments were not specified in the review by Wang.

Outcomes that reviews set out to assess included glycaemic control (HbA_{1c}, FPG), hypoglycaemia (overall, severe and nocturnal), other adverse events, mortality, cardiovascular morbidity, diabetic late complications and health-related QoL.

Trials included in systematic reviews

General

The reviews included reports of 14 individual trials of insulin glargine and two trials of insulin detemir, as shown in *Table 16*.

There was one main trial of insulin glargine considering patients with previous insulin treatment [Rosenstock *et al.* (2001)¹⁵⁹], whereas the remainder of the glargine trials included previously insulin-naive patients who had been on oral

antihyperglycaemic agents (OHAs) before the trial and continued an oral regimen during the trial (either their previous treatment or a new treatment as specified by the trial). Of the remaining glargine trials in patients with previous insulin treatment, the trial by Fonseca *et al.* (2004)¹⁵⁸ was in fact a subgroup analysis of Rosenstock *et al.* (2001).¹⁵⁹ This trial included both patients using a once-daily and a twice-daily insulin regimen, and Fonseca *et al.* (2001)¹⁵⁷ considered only the subgroup on a once-daily insulin regimen. The trial by Yokoyama *et al.* (2006)¹⁶⁰ used two different insulin regimens – dose titration in the glargine group and an unchanged dose of NPH in the comparison group, which was considered to be an inappropriate comparison in the review by Horvath *et al.* (2007).¹⁴¹ Although the trial was included in their review, it was not considered in detail and it was not included in any analyses. Of the trials on insulin detemir, one

TABLE 16 Trials included in systematic reviews of long-acting insulin analogues

	Duckworth (2007) ¹⁴⁰	Wang (2003) ¹⁴³	Horvath (2007) ¹⁴¹	Tran (2007) ¹⁴²	Warren (2004) ¹⁴⁴
Previous insulin – glargine vs NPH insulin					
Fonseca (2004) ^{156–158} (subgroup analysis of Rosenstock 2001)	✓	✓	✓	✓	✓
Rosenstock (2001) ¹⁵⁹	✓	✓	✓	✓	✓
Yokoyama (2006) ¹⁶⁰			✓		
Insulin naive, oral antihyperglycaemic drugs – glargine vs NPH insulin					
Eliaschewitz (2006) ¹⁶¹			✓		
Fritsche (2003) ¹⁶²	✓	✓	✓	✓	
HOE 901/2004 Study Investigators Group (2003) ^{163,164}	✓	✓		✓	✓
Massi Benedetti (2003) ¹⁶⁵	✓		✓		
Meneghini (2005) ¹⁶⁶				✓	
Yki-Järvinen (2000) ¹³⁷	✓	✓		✓	✓
Yki-Järvinen (2006) ^{26,167}	✓		✓	✓	
Raskin (1998) ¹⁶⁸		✓			✓
Riddle (2003) ¹⁶⁹	✓	✓	✓	✓	
Rosenstock (2006) ¹⁷⁰				✓	
Previous insulin – insulin detemir					
Haak (2005) ¹⁷¹			✓	✓	
Insulin naive – insulin detemir					
Hermansen (2006) ¹⁷²			✓	✓	
Unclear					
Witthaus (2000) ¹⁷³		✓			

included patients previously on insulin and the other included insulin-naïve patients.

The individual reviews included between five and nine trials of insulin glargine versus NPH insulin, and two trials of insulin detemir versus NPH insulin. Both reviews assessing insulin detemir included the same trials, whereas only two trials of insulin glargine were included in all reviews. The reviews summarised data of between around 1400 and around 4700 patients in the included trials.

Design

All included trials were open-label RCTs and many were described as multicentre trials. Some trials had a non-inferiority or equivalence design. A number of trials were published as abstracts only (especially in the older reviews). Trial duration was between 4 and 52 weeks. Most trials came from Europe or North America, two also included data from South Africa, and one was conducted in participants from Latin America. A substantial number of trials were industry funded.

Trial quality

Trial quality was generally rated as rather poor. Blinding was considered difficult or impossible by most reviews, as insulins glargine and detemir exist as a clear solution, whereas NPH insulin has a milky appearance. The review by Horvath *et al.* (2007)¹⁴¹ stresses the bias that can be introduced by lack of blinding and especially the lack of blinding of outcome assessment, which does not seem to have been mentioned or considered by any of the trials. Horvath *et al.* considered all of their included trials to have been of insufficient methodological quality, with poor reporting of randomisation in most trials, adequate allocation concealment in five trials, discontinuation rates of between 1.6% and 10.2% and an ITT approach in all main analyses. The studies included in the review by Tran *et al.* (2007)¹⁴² had a mean Jadad score of 2.4 (out of 5, but blinding being impractical, a perfect score was not possible), with adequate allocation concealment in four trials and ITT analysis in 90%. Warren *et al.* (2004)¹⁴⁴ considered quality assessment to be possible for the two full publications included in their review, which both scored 2 on the Jadad score, with none of them specifying a blinded outcome assessment. The Wang review (2003)¹⁴³ did not present a formal quality assessment, but suggested that there was inconsistent reporting of mean or adjusted mean changes in primary and secondary efficacy end points within and between treatment groups, and that studies were generally statistically underpowered.

Participants

Patients with type 2 diabetes included in the reviews had a mean age of between 53 and 62 years. Where reported, between 36% and 49% of participants were female, patients had a mean BMI of between 27 and 35 kg/m², a diabetes duration of between 8 and 14 years, and a mean baseline HbA_{1c} value of between 7.9 to 9.7%.

Interventions

As mentioned above, there was one main trial of insulin glargine^{156–159} and one of insulin detemir¹⁷¹ in patients on previous insulin therapy without concomitant OHAs. In three trials of insulin-naïve patients using oral therapy,^{26,161,162} the patient's previous oral therapy was stopped and replaced by glimepiride^{161,162} or metformin.²⁶ In the other trials, the previous oral therapy was continued. OHAs included metformin, acarbose, pioglitazone, rosiglitazone, sulfonylurea or other insulin secretagogues or alpha-glucosidase inhibitors. One glargine trial included pre-meal regular insulin¹⁵⁹ and one detemir trial included pre-meal insulin aspart.¹⁷¹ Most glargine trials compared bedtime glargine with bedtime NPH, but one¹⁶² compared morning glargine with bedtime glargine and bedtime NPH, and in one,¹⁵⁹ patients received glargine at bedtime and NPH either once at bedtime or twice – at bedtime and in the morning. One of the detemir trials¹⁷¹ used detemir or NPH once daily at bedtime or twice daily at bedtime and in the morning, whereas the other¹⁷² used a twice-daily regimen of detemir or NPH. Trials used different dose titration targets, between 4.5 and 7.8 mmol/l for FBG, or of 7–7.5% for HbA_{1c} level.

Outcomes

Outcomes reported included HbA_{1c}, FPG, blood glucose profiles, hypoglycaemic episodes (overall, symptomatic, severe and nocturnal), the percentage of patients reaching the titration target, weight change, mortality, QoL and adverse events. None of the trials published diabetes secondary complication rates [although Horvath *et al.* (2007)⁴¹ retrieved some unpublished information], and there were no QoL data (one trial reported on patient satisfaction). Trials were underpowered to assess mortality. Weight change was not systematically reported.

Review quality

The review by Duckworth and Davis (2007)¹⁴⁰ was of poor quality. Its search strategy was restricted to a PubMed search and English articles only, and no information was given on other methodological

procedures such as study selection, quality assessment of trials, data extraction or data analysis. Inclusion criteria were briefly specified, but only for participants, interventions and outcomes, not for study design.

Both the Cochrane review by Horvath *et al.* (2007)⁴¹ and the Canadian HTA Assessment by Tran *et al.* (2007)¹⁴² were of good quality. Inclusion criteria were well described, as was study selection, quality assessment of trials, data extraction, and data analysis. A comprehensive search was carried out and described in detail. Study flow was shown. Both reviews included a meta-analysis.

The UK HTA Assessment by Warren *et al.* (2004)¹⁴⁴ appears good but had some reporting omissions. Inclusion criteria were well described and the search strategy was very comprehensive. However,

it is unclear whether study selection and quality assessment were done in duplicate and data extraction was only done by one reviewer. Study flow was not shown.

The review by Wang (2003)¹⁴³ was of poor quality. Inclusion criteria were described and the search strategy was adequate. However, study selection, quality assessment, data extraction and data analysis were not described, nor was study flow shown. Although no details of quality assessment methodology were given, some comments on study quality were made.

Results

Main results are shown in *Table 17* and subgroup analyses in *Table 18*.

TABLE 17 Main results reported in reviews of long-acting insulin analogues

Study	Outcome	n (studies)	Results – magnitude of change/difference	Statistical significance
All studies – glargine vs NPH insulin				
<i>HbA_{1c}</i>				
Horvath (2007) ¹⁴¹	HbA _{1c} (%) (studies with available data)	4	WMD 0.1% (95% CI –0.1 to 0.2)	p = NS
	HbA _{1c} (%) (all studies, pooled SD)	6	WMD 0.00% (95% CI –0.1 to 0.1)	p = NS
Tran (2007) ¹⁴²	HbA _{1c} (%)	7	Meta-analysis, WMD 0.05 (95% CI –0.07 to 0.16)	p = NS; no significant difference for analysis by different cointerventions
<i>Hypoglycaemia</i>				
Horvath (2007) ¹⁴¹	Severe hypoglycaemia	4	Meta-analysis, 6-month studies only, Peto OR 0.70 (95% CI 0.40 to 1.23)	p = NS; no significant difference or no statistical information for remaining three studies
	Symptomatic hypoglycaemia	3	Meta-analysis, 6-month studies only, RR 0.84 (95% CI 0.75 to 0.95)	Significantly fewer with glargine, p = 0.005; for remaining four studies: three studies no significant difference, one significant in favour of glargine (p < 0.02)
	Overall hypoglycaemia	1	Morning glargine: 74% Evening glargine: 68% Evening NPH insulin: 75%	p = NS
	Nocturnal hypoglycaemia	3	Meta-analysis, 6-month studies only, RR 0.66 (95% CI 0.55 to 0.80)	Significantly fewer with glargine, p < 0.0001; also significant results for the three studies not included in the meta-analysis but reporting on nocturnal hypoglycaemia
Tran (2007) ¹⁴²	Overall hypoglycaemia	6	Meta-analysis, RR 0.89 (95% CI 0.83 to 0.96), NNT 14 (95% CI 9 to 33)	p = 0.002; no significant difference for analysis by different cointerventions
	Severe hypoglycaemia	4	Meta-analysis, RR 1.09 (95% CI 0.56 to 2.12)	p = NS; no significant difference for analysis by different cointerventions

TABLE 17 Main results reported in reviews of long-acting insulin analogues (continued)

Study	Outcome	n (studies)	Results – magnitude of change/difference	Statistical significance
	Nocturnal hypoglycaemia	5	Meta-analysis, RR 0.57 (95% CI 0.44 to 0.74), NNT 8 (95% CI 6 to 11)	$p < 0.0001$; no significant difference for analysis by different cointerventions
<i>Glycaemic excursions</i>				
Tran (2007) ¹⁴²	Eight-point blood glucose profiles	3		Generally no statistically significant difference between glucose profiles for glargine vs NPH; pre-dinner values lower in two studies for glargine, and in one study for morning (but not evening) glargine vs evening NPH
<i>Total daily dose – not reported</i>				
<i>Weight change – not reported</i>				
<i>Complication rates</i>				
Horvath (2007) ¹⁴¹	Mortality	3	Small numbers, no study adequately powered to assess this parameter	
	New development of non-proliferative retinopathy	1	Glargine: 8.4% NPH insulin: 14%	p -value not reported
	Development of clinically significant macular oedema (of people with no retinopathy)	1	Glargine: 1.8% NPH insulin: 2.4%	p -value not reported
	Progression of retinopathy by more than three stages	2	Glargine: 5.9–7.5% NPH insulin: 2.7–9.1%	p -value not reported for one study, significantly more with glargine in the other study, $p = 0.028$
	Development of clinically significant macular oedema	1	Glargine: 11.2% NPH insulin: 6.5%	$p = NS$
Tran (2007) ¹⁴²	Mortality	4		None of reported deaths thought to be related to study medication
<i>Adverse events</i>				
Horvath (2007) ¹⁴¹	Overall AEs	4		Numbers comparable between groups
	Serious AEs	2		Numbers comparable between groups
	AEs possibly related to treatment	4		Numbers comparable between groups
	Patients withdrawing due to AEs	6		Numbers comparable between groups
Tran (2007) ¹⁴²	AEs	10		No significant differences in AEs between glargine and NPH
<i>Health-related QoL</i>				
Horvath (2007) ¹⁴¹	Diabetes Treatment and Satisfaction Questionnaire	1	More pronounced improvement of treatment satisfaction reported with glargine vs NPH	$p < 0.05$

continued

TABLE 17 Main results reported in reviews of long-acting insulin analogues (continued)

Study	Outcome	n (studies)	Results – magnitude of change/difference	Statistical significance
Previous insulin – glargine vs NPH insulin				
<i>HbA_{1c}</i>				
Duckworth (2007) ¹⁴⁰	HbA _{1c} (%)	2	Glargine: -0.41% NPH insulin: -0.46% to -0.59%	Change in HbA _{1c} similar between groups
	Target reached (HbA _{1c} ≤ 7.0 to ≤ 7.5; FBG ≤ 6.7 mmol/l)	2	HbA _{1c} Glargine: 18% NPH insulin: 18% FBG Glargine: 29.6% to 34% NPH insulin: 24% to 27.1%	Similar between groups for both studies
Wang (2003) ¹⁴³	HbA _{1c} (%)	2	Glargine: -0.35% to -0.41% NPH insulin: -0.44% to -0.59%	p = NS in one study, not reported for the other
Warren (2004) ¹⁴⁴	HbA _{1c} (%)	2	Glargine: -0.35% NPH insulin: -0.44%	p = NS for both
	Patients reaching target FBG	1	Glargine: 29.6% NPH insulin: 27.1%	p = NS
<i>Hypoglycaemia</i>				
Duckworth (2007) ¹⁴¹	Overall symptomatic hypoglycaemia	2	Glargine: 46% to 61.4% NPH insulin: 60% to 66.8%	p < 0.05 in one study, p = NS in the other
	Severe hypoglycaemia	2	Glargine: 0% to 0.4% NPH insulin: 2.0% to 2.3%	p = NS
	Nocturnal hypoglycaemia	2	Glargine: 15% to 26.5% NPH insulin: 27 to 35.5%	p < 0.05 in one study, p = NS in the other
Wang (2003) ¹⁴³	≥ 1 episode of hypoglycaemia	1	Glargine: 46.2% NPH insulin: 60.4%	p = 0.048
	Reported nocturnal hypoglycaemic events	2	Glargine: 15.4% to 31.3% NPH insulin: 27.1% to 40.2%	p = NS in one study, p = 0.014 in other study
	Symptomatic hypoglycaemia	2	Glargine: 17.3% to 61.4% NPH insulin: 31.3% to 66.8%	p = NS in 1 study, p = 0.002 in the other
	Episodes of severe hypoglycaemia	1	Glargine: 6.6% (-0.4%) NPH insulin: 10.4% (-2.3%)	p = NS
Warren (2004) ¹⁴⁴	Symptomatic hypoglycaemia	2	Glargine: 6.6% to 17.3% NPH insulin: 10.4% to 31.3%	p = NS in one study, p < 0.05 in the other study
	Nocturnal hypoglycaemia	2	Glargine: 15.4% to 35% NPH insulin: 27.1% to 43.7%	p = NS in one study, p < 0.05 in the other study
	Severe hypoglycaemia	2	Not reported separately	

TABLE 17 Main results reported in reviews of long-acting insulin analogues (continued)

Study	Outcome	n (studies)	Results – magnitude of change/difference	Statistical significance
<i>Glycaemic excursions – not reported</i>				
<i>Total daily dose</i>				
Warren (2004) ¹⁴⁴	Insulin use	1	For patients on pre-trial once-daily NPH, slightly more insulin used at trial end than at baseline (no data presented) For patients on pre-trial more than once-daily NPH, people on glargine used slightly less at trial end (reduced by 4.4 U/day) and patients treated with NPH used about the same (no more data presented)	Unclear
<i>Weight change</i>				
Wang (2003) ¹⁴³	Weight gain	1	Glargine: +0.4 kg NPH insulin: +1.4 kg $p < 0.001$, CIs not reported	
<i>Complication rates – not reported</i>				
<i>Adverse events</i>				
Wang (2003) ¹⁴³	Injection site pain	1	28 weeks Greater number of patients reported injection site pain with insulin glargine compared with NPH insulin (pain usually mild and did not result in discontinuation of treatment)	
Warren (2004) ¹⁴⁴	Injection site pain	1	Glargine: 10.4% NPH insulin: 7.7%	Unclear, probably $p < 0.05$; but mild and no dropouts as a result
	Insulin antibodies	1	No increases in either comparison group	
<i>Health-related QoL – not reported</i>				
Insulin-naive, oral antihyperglycaemics – glargine vs NPH insulin				
<i>HbA_{1c}</i>				
Duckworth (2007) ¹⁴¹	HbA _{1c} (%)	5	Glargine: -0.46% to -2.36% NPH insulin: -0.38% to -2.44%	Four trials HbA _{1c} similar between groups, one trial significantly more HbA _{1c} reduction with morning glargine than bedtime NPH ($p < 0.001$) and with morning glargine vs bedtime glargine ($p = 0.009$)
	Target reached (HbA _{1c} ≤ 7.0 to ≤ 7.5 ; FBG ≤ 6.7 mmol/l)	4	HbA _{1c} Glargine: 33% to 58% NPH insulin: 32% to 57.3% FBG Glargine: 40.7% to 42% NPH insulin: 35.1% to 44%	Three trials no significant difference, one trial significantly more patients reaching target with morning glargine than with bedtime glargine or NPH ($p < 0.05$)

continued

TABLE 17 Main results reported in reviews of long-acting insulin analogues (continued)

Study	Outcome	n (studies)	Results – magnitude of change/difference	Statistical significance
Wang (2003) ¹⁴³	HbA _{1c} (%)	4	Glargine: -0.76% to -1.64% NPH insulin: -0.66% to -1.63%	Three trials no significant difference between glargine and NPH, one trial significantly more HbA _{1c} reduction with morning glargine than bedtime NPH ($p < 0.001$) and with morning glargine vs bedtime glargine ($p = 0.009$)
	Target reached ($\leq 7.0\%$ to $< 8.0\%$)	2	Glargine: 53.8 to 57.9% NPH insulin: 43.9 to 57%	One study $p = NS$, one study unclear
Warren (2004) ¹⁴⁴	HbA _{1c} (%)	3	Glargine: -0.8% NPH insulin: -0.8%	$p = NS$ for all studies
	Patients reaching target FBG	1	Numbers only reported for one Glargine: 7.7% NPH insulin: 7.6%	$p = NS$
<i>Hypoglycaemia</i>				
Duckworth (2007) ¹⁴⁰	Overall symptomatic hypoglycaemia	6	Glargine: 18.8% to 56%, 5.5 to 13.9 events/patient-year NPH insulin: 32.4% to 58%, 8.0 to 17.7 events/patient-year	$p < 0.05$ in four studies, $p = NS$ in two studies
	Severe hypoglycaemia	2	Glargine: 0% to 2.5% NPH insulin: 0% to 1.8%	$p = NS$
	Nocturnal hypoglycaemia	5	Glargine: 7.3% to 23%, 4.0 events/patient-year NPH insulin: 19.1% to 38%, 6.9 events/patient-year	$p < 0.05$ in all studies
Wang (2003) ¹⁴³	Hypoglycaemic episodes (%)	2	Glargine: 7.3% to 33% NPH insulin: 19.1% to 43%	$p < 0.05$ for both studies
	Nocturnal hypoglycaemia	3	Glargine: 9.9% to 47% NPH insulin: 24% to 55%	$p < 0.05$ for all studies
	Achieving HbA _{1c} $\leq 7.0\%$ without nocturnal hypoglycaemia	1	Glargine: 33% NPH insulin: 27%	$p < 0.05$
	Severe hypoglycaemia	1	Glargine: 2.5% NPH insulin: 2.3%	$p = NS$
Warren (2004) ¹⁴⁴	Symptomatic hypoglycaemia	2	Glargine: 7.3% NPH insulin: 19.1%	$p < 0.05$ for both
	Nocturnal hypoglycaemia	1	Numbers only for one trial No numbers reported in trial	Significantly fewer in glargine group, $p = 0.0001$
	Severe hypoglycaemia	0	Not reported by studies	
<i>Glycaemic excursions</i>				
Wang (2003) ¹⁴³		1	Change in FPG levels significantly greater both before and after dinner with insulin glargine ($p = 0.035$, no details); FPG levels at 3.00 a.m. similar between groups (glargine: 133, SE 3.6 mg/dl; NPH: 131.4, SE 3.6 mg/dl)	

TABLE 17 Main results reported in reviews of long-acting insulin analogues (continued)

Study	Outcome	n (studies)	Results – magnitude of change/difference	Statistical significance
<i>Total daily dose</i>				
Warren (2004) ¹⁴⁴	Insulin use	1	Glargine: 23 U/day NPH insulin: 21 U/day	Unclear
<i>Weight change</i>				
Wang (2003) ¹⁴³		2	Glargine: no change to +2.57 kg NPH insulin: no change to +2.34 kg	$p = \text{NS}$ for both studies
<i>Complication rates – not reported</i>				
<i>Adverse events</i>				
Wang (2003) ¹⁴³	Injection site pain	1	Greater number of patients reported injection site pain with insulin glargine compared with NPH insulin (pain usually mild and did not result in discontinuation of treatment)	
Warren (2004) ¹⁴⁴	Insulin antibodies	1	No increases in either comparison group	
<i>Health-related QoL</i>				
Wang (2003) ¹⁴³	Diabetes Treatment Satisfaction Well-Being Questionnaire	1	No numeric data reported; increases in treatment satisfaction significantly greater for insulin glargine than NPH insulin at week 36 ($p = 0.033$); small increase in the perceived frequency of hypoglycaemia in both groups, but no significant difference between groups	
<i>FPG (where HbA_{1c} not reported)</i>				
Duckworth (2007) ¹⁴⁰	FPG	1	Not reported for groups separately, decrease from baseline -3.10 to -3.49 mmol/l	Similar between groups
Wang (2003) ¹⁴³	FPG	1	Glargine with 30 µg/ml of zinc: -2.8 mmol/l Glargine with 80 µg/ml of zinc: -2.6 mmol/l NPH insulin: -2.3 mmol/l	p -value not reported
All studies – detemir vs NPH insulin				
<i>HbA_{1c}</i>				
Horvath (2007) ¹⁴¹	HbA _{1c} (%)	2	Meta-analysis using different ways of estimating missing SDs, WMD 0.12% (95% CI 0.01 to 0.23), WMD with pooled SD 0.15% (95% CI -0.02 to 0.32)	First calculation yields significant result ($p = 0.03$) in favour of NPH, but well within predefined non-inferiority margin of 0.4% HbA _{1c} ; second calculation, $p = \text{NS}$
Tran (2007) ¹⁴²	HbA _{1c} (%)	2	Meta-analysis, WMD 0.11% (95% CI -0.03 to 0.26)	$p = \text{NS}$; no significant difference for analysis by different cointerventions

continued

TABLE 17 Main results reported in reviews of long-acting insulin analogues (continued)

Study	Outcome	n (studies)	Results – magnitude of change/difference	Statistical significance
<i>Hypoglycaemia</i>				
Horvath (2007) ¹⁴¹	Severe hypoglycaemia	2	Meta-analysis Peto OR 0.5 (95% CI 0.18 to 1.38)	$p = \text{NS}$
	Symptomatic hypoglycaemia	1	Detemir: 4.9 events/patient-year NPH insulin: 9.7 events/patient-year Relative risk 0.56 (95% CI 0.42 to 0.74)	$p < 0.001$
	Overall hypoglycaemia	2	Meta-analysis, RR 0.82 (95% CI 0.74 to 0.90)	$p < 0.0001$
	Nocturnal hypoglycaemia	2	Meta-analysis, RR 0.63 (95% CI 0.52 to 0.76)	$p < 0.00001$
Tran (2007) ¹⁴²	Overall hypoglycaemia	1	Relative risk 0.91 (95% CI 0.75 to 1.11)	$p = \text{NS}$
	Nocturnal hypoglycaemia	1	Relative risk 0.66 (95% CI 0.45 to 0.96)	$p < 0.05$
<i>Glycaemic excursions</i>				
Tran (2007) ¹⁴²	Eight-point blood glucose profiles	2		Glucose profiles similar for detemir vs NPH; no difference depending on cointervention (insulin aspart or OHAs)
<i>Total daily dose – not reported</i>				
<i>Weight change</i>				
Horvath (2007) ¹⁴¹	Weight change	2	Difference in weight gain between detemir and NPH –0.8 to –1.6 kg	$p < 0.05$
<i>Complication rates</i>				
Horvath (2007) ¹⁴¹	Mortality	1	Small numbers, no study adequately powered to assess this parameter	
	Cardiovascular morbidity	1	Very small numbers, no conclusions can be drawn	
	Diabetic late complications	1	Very small numbers, no conclusions can be drawn	
Tran (2007) ¹⁴²	Mortality	1		None of reported deaths thought to be related to study medication
<i>Adverse events</i>				
Horvath (2007) ¹⁴¹	AEs	2	No difference in frequency of AEs	
Tran (2007) ¹⁴²	AEs	1		No significant differences in AEs between detemir and NPH
<i>Health-related QoL – not reported</i>				
AE, adverse event; NNT, number needed to treat; NS, not significant; OR, odds ratio.				

TABLE 18 Reviews of long-acting insulin analogues – subgroup/sensitivity analyses

Study	Outcome	Factor	n (studies)	Results [of meta-analysis (95% CI) or narrative]	Statistical significance
All studies – glargine vs NPH insulin					
<i>HbA_{1c}</i>					
Horvath (2007) ¹⁴¹	HbA _{1c} (%)	Morning glargine vs evening glargine or NPH	1	Greater reduction in HbA _{1c} from baseline in the morning group than in evening groups	<i>p</i> < 0.05
		Insulin-naive patients	1	No significant difference	<i>p</i> = NS
		Patients applying insulin only once daily	1	No significant difference	<i>p</i> = NS
<i>Hypoglycaemia</i>					
Horvath (2007) ¹⁴¹	At least one episode of symptomatic hypoglycaemia	Insulin-naive patients	1	Glargine: 33% NPH insulin: 43%	<i>p</i> = 0.04
	At least one episode of symptomatic hypoglycaemia	Patients applying insulin only, once daily	1	Glargine: 17% NPH insulin: 31%	<i>p</i> < 0.002 [wrong numbers in Horvath (2007) ¹⁴¹]
	Nocturnal hypoglycaemia	Insulin-naive patients	1	Glargine: 10% NPH insulin: 24%	<i>p</i> = 0.0001
	Nocturnal hypoglycaemia	Patients applying insulin only, once daily	1	Glargine: 15% NPH insulin: 27%	<i>p</i> = NS
Complication rates					
Horvath (2007) ¹⁴¹	Development of clinically significant macular oedema	Patients without insulin pretreatment vs patients with insulin pretreatment	1	<i>Without insulin pretreatment</i> Glargine: 14% NPH insulin: 4% <i>With insulin pretreatment</i> Glargine: 1.9% NPH insulin: 12.7%	<i>p</i> -value not reported
Insulin-naive, oral antihyperglycaemics – glargine vs NPH insulin					
Duckworth (2007) ¹⁴⁰	HbA _{1c}	BMI > 28 kg/m ²	1	<i>Change from baseline</i> Glargine: -0.42% NPH insulin: -0.11%	<i>p</i> = 0.0237
Wang (2003) ¹⁴³	Nocturnal hypoglycaemia	Patients reaching/not reaching FPG target (≤ 120 mg/dl)	1	<i>52 weeks</i> <i>Target reached</i> Glargine: 12.6% NPH insulin: 28.8% <i>Target not reached</i> Glargine: 9.0% NPH insulin: 21.4%	<i>p</i> < 0.05 for both subgroups glargine vs NPH
NS, not significant.					

Glycaemic control

Trials generally showed a reduction in HbA_{1c} level from baseline to end of study, but without any difference between comparison groups. Horvath *et al.* (2007)¹⁴¹ carried out two meta-analyses regarding HbA_{1c} results for insulin glargine versus NPH insulin, one including only the four for which SDs were available or could be calculated, and the other including studies where this was not the case and where a pooled SD was used (two extra studies, i.e. six in the meta-analysis). In both analyses, there was no significant difference between glargine and NPH in end-of-study level of HbA_{1c}, with a WMD between groups of around 0 (for all six studies WMD 0.0, 95% CI -0.01, 0.1). Similarly, Tran *et al.* (2007)¹⁴² in their meta-analysis of seven studies found no significant difference in HbA_{1c} values between glargine and NPH (WMD 0.05, 95% CI -0.07 to 0.16). For the remaining reviews, results were presented according to whether patients had received previous insulin treatment without oral treatment or were previously insulin naive with concomitant oral treatment. For the two trials (or rather one with subgroup analysis) of people with previous insulin treatment, HbA_{1c} level at the end of study was similar between the glargine and NPH groups (reduction from baseline between -0.35 and -0.6%). For the trials in insulin-naive patients using concomitant oral therapy, most trials showed no significant difference between glargine and NPH at the end of the study either, except in the study by Fritsche (2003),¹⁶² where, after 24 weeks of treatment HbA_{1c} level was significantly more reduced with morning glargine than with evening glargine or evening NPH (-1.24% versus -0.96% and -0.84%, respectively). Subgroup analyses in two trials, one of insulin-naive patients and one of patients applying insulin once rather than twice daily also showed no difference in HbA_{1c} values between groups. However, one study found a significant effect for HbA_{1c} in favour of glargine in a subgroup analysis of patients with a BMI of more than 28 kg/m² (HbA_{1c} change from baseline -0.42% with glargine and -0.11% with NPH, *p* = 0.024). There was no significant difference in end-of-study HbA_{1c} values in the two studies of insulin detemir versus NPH, irrespective of previous treatment and cointerventions.

Where reported, the percentages of patients reaching the FPG or HbA_{1c} targets were also similar between insulin glargine and NPH insulin, except in the study by Fritsche (2003),¹⁶² where significantly more patients reached the target with morning glargine than with evening glargine or evening NPH.

Hypoglycaemia

Severe hypoglycaemia

In their meta-analysis of studies of glargine versus NPH, Horvath *et al.* (2007)¹⁴¹ summarised four studies of 6 months' duration (to avoid imbalance due to different study durations) and found no significant difference in the frequency of severe hypoglycaemia between glargine and NPH [Peto odds ratio (OR) 0.70, 95% CI 0.40 to 1.23]. There was no significant difference – or no statistical information available – for the remaining three studies assessing severe hypoglycaemia that were not included in the meta-analysis. Similarly, Tran *et al.* (2007)¹⁴² did a meta-analysis of severe hypoglycaemia in four studies and found no significant difference between glargine and NPH (RR 1.09, 95% CI 0.56 to 2.12) and no significant difference when analysing trials depending on their cointerventions. In the remaining reviews, no significant differences in severe hypoglycaemia were reported for patients on previous insulin therapy or for previously insulin-naive patients on oral antihyperglycaemic therapy (and continuing oral therapy). Similarly, no significant difference was found for severe hypoglycaemia for the two trials of insulin detemir versus NPH insulin.

Overall and symptomatic hypoglycaemia

Definition of 'overall' and 'symptomatic' hypoglycaemia varied, with some reviews summarising under 'overall' hypoglycaemia 'overall symptomatic hypoglycaemia' and some referring to 'any hypoglycaemic event'. Results for this outcome were inconclusive. In their meta-analysis of three 6-month studies of glargine versus NPH, Horvath *et al.* (2007)¹⁴¹ found significantly fewer symptomatic hypoglycaemic episodes with glargine than with NPH (RR 0.84, 95% CI 0.75 to 0.95), but only one of the remaining four studies reporting this outcome found a significant effect in favour of glargine. Similarly, the one study reporting overall hypoglycaemia found no significant difference between glargine (morning or evening) and NPH.

Tran *et al.* (2007)¹⁴² included six trials in their meta-analysis of overall hypoglycaemia and found a significant difference in favour of glargine (RR 0.89, 95% CI 0.83 to 0.96). Considering studies in patients previously on insulin separately, the trial by Rosenstock *et al.* (2001)¹⁵⁹ found no significant effect on overall symptomatic hypoglycaemia in favour of glargine, whereas the subgroup analysis of that study including patients on once daily insulin did (46.2% versus 60.4% of patients with one or more episodes). In the analyses of insulin-naive patients on oral therapy, Duckworth

and Davis (2007)¹⁴⁰ summarised data for overall symptomatic hypoglycaemia in six studies and found a significant effect in favour of glargine versus NPH in four of these (where between 10% and 13% fewer patients had symptomatic hypoglycaemias in the glargine groups, or between 2.5 and 3.8 fewer events occurred per patient-year). Warren *et al.* (2004)¹⁴⁴ and Wang (2003)¹⁴³ included two studies in their analyses and found significant differences in favour of glargine for both of them for hypoglycaemic episodes/symptomatic hypoglycaemia (10 or more per cent less with glargine). For insulin detemir, Horvath *et al.* (2007)¹⁴¹ found a significant difference in favour of detemir in one study for symptomatic hypoglycaemia (not reported by the other study) (4.9 versus 9.7 events per patient-year), and for overall hypoglycaemia the meta-analysis of the two included studies gave a significant result (RR 0.82, 95% CI 0.74 to 0.90, $p < 0.0001$).

Nocturnal hypoglycaemia

Results for nocturnal hypoglycaemias were clearly in favour of the long-acting insulin analogues. In their meta-analysis of three 6-month studies of glargine versus NPH, Horvath *et al.* (2007)¹⁴¹ obtained a RR of 0.66 (95% CI 0.55 to 0.80, $p < 0.0001$). The three studies not included in the meta-analysis, but reporting on nocturnal hypoglycaemia, also all found a significant result in favour of glargine. Tran *et al.* (2007)¹⁴² included five studies in their meta-analysis and obtained a RR for nocturnal hypoglycaemias of 0.57 (95% CI 0.44 to 0.74) in favour of glargine. Considering studies in patients previously on insulin separately, the trial by Rosenstock *et al.* (2001)¹⁵⁹ found a significant effect on nocturnal hypoglycaemia (31.3 versus 40.2%, with at least one episode of nocturnal hypoglycaemia, $p = 0.016$), whereas the subgroup analysis of that study including patients on once-daily insulin did not. All trials of previously insulin-naïve patients on oral therapy found significantly fewer nocturnal hypoglycaemias with insulin glargine than with NPH insulin (between ~10% to 20% fewer patients with nocturnal hypoglycaemias with glargine). One trial also reported that significantly more patients using glargine reached the HbA_{1c} target of 7% or less without nocturnal hypoglycaemias (33% versus 27% using NPH, $p < 0.05$). With respect to insulin detemir, the meta-analysis of nocturnal hypoglycaemia in the two trials by Horvath *et al.* (2007)¹⁴¹ obtained a RR of 0.63 (95% CI 0.52 to 0.76, $p < 0.00001$) in favour of detemir [similar relative risk in the review by Tran *et al.* (2007),¹⁴² which reported data from only one trial].

Glycaemic excursions

Data on glycaemic excursions were only systematically summarised by the review by Tran *et al.* (2007),¹⁴² who reported data from three studies that had measured eight-point glucose profiles. There was generally no statistically significant difference between glucose profiles for glargine versus NPH with the exception of two trials. One study showed significantly lower pre-dinner glucose levels for glargine, and the other reported significant values for morning (but not evening) glargine in comparison with evening NPH. For insulin detemir, eight-point glucose profiles were similar in comparison to NPH, irrespective of the cointervention.

Total daily insulin dose

Total daily insulin dose was not systematically reported by the systematic reviews. Warren *et al.* (2004)¹⁴⁴ reported for one trial of patients with previous insulin use, that patients on pre-trial once-daily NPH used slightly more insulin at trial end than at baseline, and patients on more than once-daily NPH pre-trial used slightly less insulin in the glargine group at the end of the trial (reduced by 4.4 U/day) than patients treated with NPH, who used about the same (no more data presented). For one trial of previously insulin-naïve patients on oral therapy, Warren *et al.* (2004)¹⁴⁴ reported similar insulin consumption of 23 U/day for glargine and 21 U/day for NPH, but statistical information was not provided. Insulin daily doses were not provided for the trials using insulin detemir.

Weight change

Weight change was not systematically reported by the systematic reviews. Wang (2003)¹⁴³ reported a significant change in weight gain for a trial of patients previously treated with insulin, with patients receiving insulin glargine gaining significantly less weight than patients on NPH insulin (+0.4 kg versus +1.4 kg, $p < 0.001$). In two other trials of previously insulin-naïve patients on oral therapy, no significant difference in weight change was seen between the glargine and NPH insulin groups (total changes between no change and +2.6 kg). Horvath *et al.* (2007)¹⁴¹ reported significantly less weight gain with insulin detemir than NPH insulin with a weight difference of between 0.8 and 1.6 kg between the comparison groups ($p < 0.05$).

Diabetic complications

Data on diabetic complications were not systematically reported by the reviews – and were generally not available in the trials (and trials were underpowered for assessing such outcome parameters). Several reviews – and trials – reported mortality data, but numbers were generally small and deaths were considered to be unrelated to the trial interventions. No data on diabetic late complications were included in any of the reviews, but Horvath *et al.* (2007)¹⁴¹ found some information on diabetic retinopathy for one trial of patients with previous insulin treatment and for one trial of patients on oral therapy (some of whom had been insulin pretreated). In the trial including oral therapy, 8.4% of patients in the insulin glargine group and 14% of patients in the NPH insulin group who had had no retinopathy at baseline developed non-proliferative retinopathy, and 1.8% and 2.4%, respectively, developed clinically significant macular oedema. Progression of retinopathy by more than three stages was seen in 5.9% of patients on glargine and 9.1% of patients on NPH (no significance values reported). In the study of patients on previous insulin treatment without oral therapy, significantly more patients on glargine had a progression of retinopathy by three or more stages than with NPH (7.5 versus 2.7%, $p = 0.028$). In the study of patients on concomitant oral therapy, no significant difference in development of clinically significant macular oedema was seen between glargine and NPH (11.2% with glargine, 6.5% with NPH, $p = \text{NS}$). However, there was a marked difference in this outcome between previously insulin-naive patients and patients pretreated with insulin. In insulin-naive patients, the development of clinically significant macular oedema in 14% in the glargine group and 4% in the NPH group. In contrast, patients previously treated with insulin had incidences of 1.9% and 12.7% (no significance reported). Numbers of diabetic late complications occurring in one of the trials of insulin detemir were too small to draw any conclusions.

Adverse events

No significant differences in adverse events, number of patients with adverse events, severe adverse events, or withdrawals because of adverse events were generally seen between insulin glargine or detemir and NPH insulin. There was some indication in some trials that a greater number of patients on insulin glargine reported injection site pain than patients on NPH insulin, but pain was usually mild and did not result in discontinuation

of treatment. Where reported, no differences in insulin antibodies were seen between study groups. None of the studies was long enough to assess any longer-term effects.

Health-related QoL

No data were reported on health-related QoL. Wang (2003)¹⁴³ and Horvath *et al.* (2007)¹⁴¹ reported on one study each, and it was suggested that there was a significantly greater improvement of treatment satisfaction with insulin glargine than with NPH insulin.

Additional reviews identified after completion of this review

Two systematic reviews, both including meta-analyses, were identified after completion of the main analyses for this review. The review by Bazzano *et al.* (2008)¹⁴⁵ focused on the safety and efficacy of glargine compared with NPH insulin in type 2 diabetes, whereas the review by Monami *et al.* (2008)¹⁴⁶ considered both glargine and detemir compared with NPH insulin in type 2 diabetes. Bazzano *et al.* included 12 RCTs and Monami *et al.* included 11 RCTs of glargine versus NPH insulin and three RCTs of detemir versus NPH insulin. All of the RCTs included in the two reviews have been considered by the present review.

The review by Bazzano *et al.* was of good quality. The search strategy was thorough, inclusion criteria were described, as was data extraction, quality assessment and data analysis. Study flow was shown. Descriptive and quality data were given for each included RCT. The review by Monami *et al.* was also of good quality. Inclusion criteria, search strategies, data extraction, quality assessment and data analysis were described. Study flow was shown and descriptive and quality data were shown for each trial.

Both reviews suggested that there was no significant difference between glargine or detemir and NPH insulin for glycaemic control. Bazzano *et al.* reported slightly less patient-reported hypoglycaemia with glargine than with NPH insulin, and Monami *et al.* reported less symptomatic and nocturnal hypoglycaemia with glargine or detemir versus NPH. Bazzano *et al.* reported slightly less weight gain with NPH than with glargine, whereas Monami *et al.* reported no differences in BMI when comparing glargine and NPH, but a lower BMI with detemir than with NPH insulin.

Review conclusions and research recommendations

Review conclusions and recommendations are shown in *Table 19*.

Although there were some differences in assessment of the data between reviews, all reviews essentially came to the same conclusions. All

reviews concluded that insulin glargine – and insulin detemir where assessed – led to a glycaemic control equivalent to that when using NPH insulin.

Regarding the occurrence of hypoglycaemia, all reviews concluded that insulin glargine – and where assessed, probably also insulin detemir – were more effective at reducing nocturnal

TABLE 19 Conclusion and recommendations – reviews of long-acting insulin analogues

Study	Conclusions (medical effectiveness)	Recommendations for research	Comments
Bazzano (2008) ¹⁴⁵	<p><i>HbA_{1c}</i>: Results indicate that there is no difference in glycaemic control between glargine and NPH insulin</p> <p><i>Hypoglycaemia</i>: Results indicate that there is less patient-reported hypoglycaemia with glargine than NPH in patients with type 2 diabetes (absolute differences small but significant for all types, symptomatic and nocturnal hypoglycaemia; not significant for rates of hypoglycaemia)</p> <p><i>Glycaemic excursions</i>: No relevant trial data reported</p> <p><i>Total daily dose</i>: No significant difference between groups</p> <p><i>Weight change</i>: Patients on NPH insulin gained slightly less weight than patients on glargine</p> <p><i>Complication rates</i>: No relevant trial data reported</p> <p><i>Adverse events</i>: No relevant trial data reported</p> <p><i>Health-related QoL</i>: No relevant trial data reported</p>		Review financially supported by Eli Lilly and Company
Duckworth (2007) ¹⁴⁰	<p><i>HbA_{1c}</i>: Review suggests that insulin glargine and NPH insulin are similarly effective with respect to achieving and maintaining glucose control</p> <p><i>Hypoglycaemia</i>: Insulin glargine is associated with a significantly lower risk of hypoglycaemia, particularly nocturnal hypoglycaemia, than NPH insulin</p> <p><i>Glycaemic excursions</i>: No relevant trial data reported</p> <p><i>Total daily dose</i>: No relevant trial data reported</p> <p><i>Weight change</i>: No relevant trial data reported</p> <p><i>Complication rates</i>: No relevant trial data reported</p> <p><i>Adverse events</i>: No Relevant trial data reported</p> <p><i>Health-related QoL</i>: No relevant trial data reported</p>	None explicit; suggested that QoL research would be useful in eliciting which insulin patients prefer	
Horvath (2007) ¹⁴¹	<p><i>HbA_{1c}</i>: No significant difference between insulin glargine or insulin detemir and NPH insulin (statistically significant but clinically unimportant superiority for detemir vs NPH)</p> <p><i>Hypoglycaemia</i>: No significant difference for severe hypoglycaemia; rate of overall, symptomatic and nocturnal hypoglycaemia significantly lower with glargine or detemir than with NPH, but authors suggest that there is only a minor clinical effect</p> <p><i>Glycaemic excursions</i>: No relevant trial data reported</p> <p><i>Total daily dose</i>: No relevant trial data reported</p> <p><i>Weight change</i>: No conclusions given</p> <p><i>Complication rates</i>: Only limited information available</p>	<p>Long-term follow-up data needed to assess effectiveness in terms of diabetes late complications and safety issues</p> <p>Studies in young and old patients (i.e. younger and older than the age range of 55–62 years in the included studies)</p>	

continued

TABLE 19 Conclusion and recommendations – reviews of long-acting insulin analogues (continued)

Study	Conclusions (medical effectiveness)	Recommendations for research	Comments
Monami (2008) ¹⁷⁴	<p><i>Adverse events:</i> No significant difference between glargine or detemir and NPH insulin</p> <p><i>Health-related QoL:</i> No relevant trial data reported; limited data suggesting more treatment satisfaction with glargine than NPH insulin (but only one study and data potentially unreliable)</p> <p><i>HbA_{1c}:</i> The use of long-acting insulin analogues in patients with type 2 diabetes does not seem to provide a better glycaemic control in comparison with NPH insulin</p> <p><i>Hypoglycaemia:</i> Treatment with long-acting insulin analogues in comparison with NPH reduces the risk of nocturnal and symptomatic hypoglycaemia</p> <p><i>Glycaemic excursions:</i> No relevant trial data reported</p> <p><i>Total daily dose:</i> No relevant trial data reported</p> <p><i>Weight change:</i> Detemir, but not glargine, could be associated with smaller weight gain than NPH insulin</p> <p><i>Complication rates:</i> No relevant trial data reported</p> <p><i>Adverse events:</i> No relevant trial data reported</p> <p><i>Health-related QoL:</i> No relevant trial data reported</p>	<p>More uniform and rigorous reporting of results; including definitions of different types of hypoglycaemia</p> <p>Longer-term data are needed to assess the clinical relevance of differences in the effects on weight gain of glargine/detemir</p>	
Tran (2007) ¹⁴²	<p><i>HbA_{1c}:</i> No significant difference in HbA_{1c} levels with insulin glargine or detemir in comparison with NPH</p> <p><i>Hypoglycaemia:</i> Risk of nocturnal hypoglycaemia significantly reduced with insulin glargine compared with NPH, probably also with insulin detemir</p> <p><i>Glycaemic excursions:</i> No evidence for significant difference in eight-point blood glucose profiles when comparing insulin glargine or detemir with NPH</p> <p><i>Total daily dose:</i> No relevant trial data reported</p> <p><i>Weight change:</i> Some trials reported increases in weight, but no differences between comparison groups were quoted</p> <p><i>Complication rates:</i> No deaths in trials related to study medication</p> <p><i>Adverse events:</i> No significant differences between comparison groups reported</p> <p><i>Health-related QoL:</i> No relevant information identified</p>	None	Six trials in patients with type 2 diabetes were identified after the completion of the assessment; the authors conclude that the results of those trials were unlikely to change the conclusions of the review; only three of the extra trials are valid comparisons of long-acting insulin analogues with NPH and two are included in the review by Horvath (2007); ¹⁴¹ the third is presented below
Wang (2003) ¹⁴³	<p><i>HbA_{1c}:</i> Insulin glargine appears to have equal clinical efficacy as NPH insulin</p> <p><i>Hypoglycaemia:</i> Insulin glargine is associated with significant reductions in nocturnal hypoglycaemia compared with NPH insulin</p> <p><i>Glycaemic excursions:</i> Insulin glargine is associated with lower FPG and FBG levels than NPH insulin</p> <p><i>Total daily dose:</i> No relevant trial data reported</p> <p><i>Weight change:</i> No conclusions given</p> <p><i>Complication rates:</i> No relevant trial data reported</p> <p><i>Adverse events:</i> Insulin glargine was associated with greater pain at the injection site than NPH insulin</p> <p><i>Health-related QoL:</i> Greater treatment satisfaction has been reported with insulin glargine than with NPH insulin</p>	None (only indirect – see Comments)	The authors comment that the place of insulin glargine in routine clinical practice remains to be determined; studies were limited by their open-label design, inadequate sample sizes, use of individual dose titration to achieve FPG ≤ 120 mg/dl, lack of information on cointerventions; use should be limited in patients with type 2 diabetes to those taking multiple daily injections of basal/bolus regimens who

TABLE 19 Conclusion and recommendations – reviews of long-acting insulin analogues (continued)

Study	Conclusions (medical effectiveness)	Recommendations for research	Comments
Warren (2004) ¹⁴⁴	<p><i>HbA_{1c}</i>: Insulin glargine does not appear to improve long-term glycaemic control compared with NPH insulin</p> <p><i>Hypoglycaemia</i>: Insulin glargine is effective in reducing the number of nocturnal hypoglycaemic episodes, especially when compared to once-daily NPH; equivocal evidence regarding control of symptomatic hypoglycaemia; no evidence of improvement on severe hypoglycaemia</p> <p><i>Glycaemic excursions</i>: No relevant trial data reported</p> <p><i>Total daily dose</i>: There are insufficient data to make reliable conclusions regarding insulin dose</p> <p><i>Weight change</i>: No conclusions given</p> <p><i>Complication rates</i>: No relevant trial data reported</p> <p><i>Adverse events</i>: Most common adverse event was injection site pain; where reported, no significant increases in insulin antibodies in either comparison group</p> <p><i>Health-related QoL</i>: No relevant trial data reported</p>	Studies of QoL required focusing on assessing both the short-term immediate impact of acute episodes of hypoglycaemia and the longer-term impact of living with a reduced fear of hypoglycaemia	<p>have not achieved optimal glycaemic control with NPH insulin who have episodes of symptomatic hypoglycaemia; in insulin-naïve patients taking OAD agents, use of insulin glargine should be limited to those who continue to have elevated morning blood glucose levels and episodes of nocturnal hypoglycaemia while taking a combination of oral agents or a combination of bedtime NPH insulin with OAD agents</p> <p>Clinical relevance unclear, as trial patients may have used different regimens than patients in usual clinical practice</p>

hypoglycaemias than NPH insulin. In addition, there was no between group differences for severe hypoglycaemias, and the evidence was inconclusive regarding overall/symptomatic hypoglycaemias (with some reviews being more optimistic than others). However, the review by Horvath *et al.* (2007)¹⁴¹ suggested that even the effect on nocturnal hypoglycaemias was only minor. Only Tran *et al.* (2007)¹⁴² systematically assessed glycaemic excursions and concluded that, overall, there was no significant difference in glucose profiles between glargine or detemir and NPH insulin. None of the studies came to any firm conclusions regarding total insulin dose or weight change. Not enough trial information was available to make any conclusions about diabetic secondary

complications or health-related QoL. Overall, reviews concluded that there were no significant differences in adverse events between glargine or detemir than with NPH insulin (although there may be slightly more injection site pain with glargine, as reported by some reviews).

In some of the reviews, it was suggested that the clinical relevance of the findings was unclear: trials were thought to have major design flaws (for example, all being open label, giving limited information on important factors such as cointerventions, etc.). In addition, Warren *et al.* (2004)¹⁴⁴ suggested that trial patients may have used different regimens than patients in usual clinical practice.

Not all of the reviews included clear recommendations for research; where given, research recommendations included the need for:

- long-term follow-up data to assess effectiveness in terms of diabetes late complications and safety issues
- studies in young and old patients (i.e. younger and older than the age range of 55–62 years in the included studies)
- more uniform and rigorous study design and reporting of results; including definitions of different types of hypoglycaemia
- studies of QoL, focusing on assessing both the short-term immediate impact of acute episodes of hypoglycaemia and the longer-term impact of living with a reduced fear of hypoglycaemia; and other aspects of the impact of the different insulin on patients' QoL.

Randomised controlled trials

Search results

Fourteen papers were identified as potentially relevant RCTs. Of these, six fulfilled the inclusion criteria, but one¹⁷⁵ turned out to refer to a trial [Hermansen *et al.* (2006)¹⁷²], already included in the review by Horvath *et al.* (2007).¹⁴¹ One abstract and one full publication referred to the same trial^{176,177} of insulin glargine versus insulin detemir. Full data extraction was undertaken for five trials.^{143,177–180} Table 20 shows the excluded trials. Trials were excluded because they did not include the comparisons of interest (for example, no comparison with another basal insulin), because data were inadequate or because no outcomes of interest were investigated.

Description of trials

Characteristics of the included trials are shown in Appendix 5.

Design

All five trials were parallel, open-label RCTs, sponsored by industry (where reported). Trial duration was between 12 and 52 weeks. The LEAD (Liraglutide Effect and Action in Diabetes) trial by Pan *et al.* (2007)¹⁷⁹ was carried out in China, Korea and France; the trial by Wang *et al.* (2007)¹⁸⁵ was carried out in China; the PREDICTIVE-BMI trial reported by Montanana *et al.* (2007)¹⁷⁸ was carried out in Spain, and the trials by Philis-Tsimikas *et al.* (2006)¹⁸⁰ and Rosenstock *et al.* (2008)¹⁷⁷ were carried out in various European countries and the USA.

Participants

The trials included between 24 and 582 participants, with between 8 and 291 in each comparison group. The total number of participants was 1818. The LEAD trial (2007)¹⁷⁹ was carried out using only Asian participants, and the trial by Wang *et al.* (2007)¹⁸⁵ in Chinese participants. The LEAD trial, and the trials by Philis-Tsimikas *et al.* (2006),¹⁸⁰ Wang *et al.* (2007)¹⁸⁵ and Rosenstock *et al.* (2008)¹⁷⁷ were carried out in insulin-naïve patients with concomitant OHAs, whereas the PREDICTIVE-BMI trial (2007)¹⁷⁸ was undertaken in participants who had been on insulin (two daily doses, at least one pre-mix) for 3 months or more. The LEAD trial did not detail any required specific previous oral therapy, while the trial by Wang *et al.* required previous treatment with sulfonylurea or combination treatment. The trial by Philis-Tsimikas *et al.* specified that previous oral therapy had to have been with metformin, an insulin secretagogue or a combination of the two; at US centres, concomitant treatment with TZDs was permitted throughout the study period, whereas at European centres TZD was to be discontinued before initiation of insulin treatment; use of an alpha-glucosidase inhibitor was permitted but only in combination with another oral agent. The trial by Rosenstock *et al.* required previous treatment with one or two oral agents (metformin, insulin secretagogues, alpha-

TABLE 20 Table of excluded trials – long-acting insulin analogues

Study	Reason for exclusion
Holman (2007) ¹⁸¹	Not compared with other basal
Hermansen (2007) ¹⁸²	Not compared with other basal
Klein (2006) ¹⁸³	Very short duration and no outcomes of interest
Kolendorf (2005) ¹⁸⁴	Inadequate data
Rosenstock (2006) ¹⁷⁰	Not one of the comparisons specified in protocol

glucosidase inhibitors). The PREDICTIVE-BMI trial included patients who were already overweight (BMI of between 25 and 40 kg/m²). Further details of inclusion and exclusion criteria of the trials can be found in Appendix 5. Trial participants had a mean age of between 56 and 62 years. Between 41% and 62% of women took part in the trials. Ethnicity was reported for the Asians in the LEAD trial, who came from 10 different countries of origin (the largest groups from China and South Korea); 99% of participants in the PREDICTIVE-BMI trial were white people, and between 86% and 90% of participants in the trial by Rosenstock *et al.* (2008) were white people. Mean diabetes duration was between 9 and 16 years. Details of previous diabetes medication for the two trials are shown in Appendix 5. Baseline BMI was between 25 kg/m² and 32 kg/m².

Interventions

The trial by Philis-Tsimikas *et al.* (2006)¹⁸⁰ compared three intervention groups, whereas the other trials compared two groups. In the LEAD trial (2007),¹⁷⁹ insulin glargine once daily at bedtime plus once-daily glimepiride (3 mg) in the morning was compared with NPH insulin at bedtime plus 3 mg glimepiride once daily in the morning. In both arms, insulin was titrated to a target FBG ≤ 6.7 mmol/l, starting at insulin dose of 0.15 U/kg/day. The trial included a screening phase of 3–4 weeks in which oral treatments were standardised to 3 mg of glimepiride, and patients were given training in self-administration of insulin and self-monitoring of blood glucose levels.

Wang *et al.* (2007)¹⁸⁵ compared insulin glargine plus extended-release glipizide with NPH insulin plus extended-release glipizide. Glargine or NPH were injected at bedtime with an initial dose of 0.15 IU/kg/day and then titrated to reach a FBG value of < 6.7 mmol/l. Glipizide was given before breakfast (5 mg/day). During a 2-week screening phase, previous oral medication was stopped and patients were initiated on 5 mg/day extended-release glipizide. They also received diabetes education.

In the PREDICTIVE-BMI trial (2007),¹⁷⁸ once-daily evening insulin detemir was compared with once-daily evening NPH insulin. In both groups, basal insulin was continually and individually titrated, aiming for pre-breakfast PG levels of ≤ 6.1 mmol/l without levels of hypoglycaemia considered unacceptable to the patient. In addition, all patients received insulin aspart at the main meals

(individually titrated aiming for postprandial glucose levels of ≤ 10.0 mmol/l); concomitant treatment with metformin was also allowed (used by $\sim 50\%$ of patients on detemir and $\sim 58\%$ of patients on NPH).

In the trial by Philis-Tsimikas *et al.* (2006),¹⁸⁰ insulin detemir once daily before breakfast was compared with insulin detemir once daily in the evening, as well as to human NPH insulin once daily in the evening. The initial dose of treatment was 10 IU, doses were titrated at clinic visits or by telephone at least once every 4 weeks based on the mean of three PG levels measured on three consecutive days; in patients receiving detemir in the morning, the dose was titrated to aim for pre-dinner PG concentration of ≤ 6.0 mmol/l; in patients receiving detemir or NPH in the evening, titration was aimed to achieve pre-breakfast PG concentration of ≤ 6.0 mmol/l. Oral antihyperglycaemic therapy and dose was to remain unchanged.

In the trial by Rosenstock *et al.* (2008),¹⁷⁷ detemir was compared with glargine. The detemir group received an injection once daily in the evening or twice daily (morning and evening). Glargine was injected once daily in the evening. In both groups, basal insulin was initiated at once daily (evening) 12 IU and titrated according to a structured treatment algorithm; people on detemir were allowed to receive an additional morning dose, i.e. pre-dinner PG was > 7.0 mmol/l, but only if pre-breakfast PG was < 7.0 mmol/l or nocturnal hypoglycaemia (major episode or PG ≤ 4.0 mmol/l) precluded the achievement of the FPG target. Insulin was injected using a pen-injector. The FPG was ≤ 6.0 mmol/l in the absence of hypoglycaemia. Oral glucose-lowering therapy, diet and physical activity recommended to remain stable during the study; no mealtime insulin was allowed.

Outcomes

In the LEAD trial (2007),¹⁷⁹ the trial by Philis-Tsimikas *et al.* (2006),¹⁸⁰ and the trial by Rosenstock *et al.* (2008)¹⁷⁷ the primary outcome measure was HbA_{1c} level. No primary outcome measure was specified the trial by Wang *et al.* (2007).¹⁸⁵ The primary outcome in the PREDICTIVE-BMI (2007)¹⁷⁸ trial was weight change. All trials reported outcomes related to HbA_{1c} level, hypoglycaemia and weight change. Blood glucose profiles, total daily insulin dose, and adverse events were also reported by most of the trials. None of the trials reported health-related QoL or diabetic secondary complications.

TABLE 21 Quality of included trials – long-acting insulin analogues

	Pan (2007) ¹⁷⁹	Wang (2007) ¹⁸⁵	Montanana (2007) ¹⁷⁸	Philis-Tsimikas (2006) ¹⁸⁰	Rosenstock (2008) ¹⁷⁷
Appropriate and clearly focused question	Yes	Yes	Yes	Yes	Yes
Method of randomisation	Not described	Not described	Described, adequate	Described, adequate	Described, adequate
Allocation concealed	Not reported	Not reported	Yes	Unclear	Yes
Participants blinded	No	Not reported	No	No	No
Outcome assessors blinded	No	Not reported	Not reported	No	Unclear
All relevant outcomes measured in standard, valid, reliable way	Yes	Yes	Yes	Yes	Yes
Proportion of participants excluded/lost to follow-up	Four patients withdrew consent after randomisation and received no study medication; one received medication but provided no outcome measures; 49 were excluded for major protocol violations; no further details	Not reported (no dropouts/withdrawals?)	Seven withdrawals in detemir group, 12 withdrawals in NPH group, reasons listed, no significant difference between groups	18, 16 and 17 in morning detemir, evening detemir and evening NPH groups, respectively; reasons listed, no significant difference between groups	60 withdrawn in detemir group (23 adverse events, three ineffective therapy, 10 non-compliant, 24 other reasons); 39 withdrawn in glargine group (11 adverse events, two ineffective therapy, 15 non-compliant, 11 other reasons)
Handling of missing data	Not reported	Not reported	Last observation carried forward	Last observation carried forward	Last observation carried forward
ITT analysis performed	Yes	Not reported	Yes	Yes	Yes
Statistical analysis appropriate	Yes	Yes	Yes	Yes, non-inferiority analysis	Yes, non-inferiority analysis

	Pan (2007) ¹⁷⁹	Wang (2007) ¹⁸⁵	Montanana (2007) ¹⁷⁸	Philis-Tsimikas (2006) ¹⁸⁰	Rosenstock (2008) ¹⁷⁷
Only difference between groups is treatment under investigation	Yes	Yes	Yes	Yes	Yes, although detemir was dosed twice daily in some patients
Results in multicentre studies comparable for all sites	Not reported	Not applicable	Not reported	Not reported	Unclear
Groups comparable at baseline	Yes	Yes	Yes	Yes	Yes
Summary					
How well was study done to minimise bias (++)/+/–)?	(–)	(–)	(+)	(+)	(+)
What is the likely direction in which bias might affect study results?	Positive effects of study drug exaggerated	Positive effects of study drug exaggerated			
Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Probably	Probably	Yes	Yes	Yes
Are the results of this study directly applicable to the patient group targeted by this guideline?	No (Asian patients only)	No (Chinese study)	Yes	Yes	Yes

Trial quality

Details of the quality assessment of the trials are shown in *Table 21*.

The LEAD trial (2007)¹⁷⁹ and the trial by Wang *et al.* (2007)¹⁸⁵ had a number of quality deficits, whereas the trials by Philis-Tsimikas *et al.* (2006)¹⁸⁰ and Rosenstock *et al.* (2008)¹⁷⁷ and the PREDICTIVE-BMI trial (2007)¹⁷⁸ were of better quality.

In the LEAD trial (2007),¹⁷⁹ the method of randomisation was not described, nor was allocation concealment. Participants and outcome assessors were not blinded. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. The proportion of participants excluded/lost to follow-up was only reported for the whole study group, but not for comparison groups separately, with five patients (1%) withdrawing before receiving treatment or not providing any outcomes, and 49 excluded due to major protocol violations (11%). ITT analysis was performed, but handling of missing data was not reported. The comparison groups were comparable at baseline. The study population was 100% Asian.

The trial by Wang *et al.* (2007)¹⁸⁵ was underpowered (only 24 participants); randomisation and allocation concealment were not described, and neither was blinding. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. Withdrawals or dropouts were not mentioned, and handling of missing data and ITT analysis were not reported. The study groups were comparable at baseline.

The PREDICTIVE-BMI (2007)¹⁷⁸ trial had adequate randomisation and allocation concealment. Participants were not blinded, blinding of outcome assessors was not reported. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. The proportion of participants excluded/lost to follow-up was reported with reasons for each comparison group separately, with no significant differences between study groups (7% withdrawals/losses to follow-up). ITT analysis was performed, and handling of missing data was by last observation carried forward. The comparison groups were comparable at baseline.

In the trial by Philis-Tsimikas *et al.* (2006),¹⁸⁰ the method of randomisation was described and adequate, but allocation concealment was

uncertain. Participants and outcome assessors were not blinded. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. The proportion of participants excluded/lost to follow-up was reported with reasons for each comparison group separately, with no significant differences between study groups (11% withdrawals/losses to follow-up). ITT analysis was performed, and handling of missing data was by last observation carried forward. The comparison groups were comparable at baseline.

The trial by Rosenstock *et al.* (2008)¹⁷⁷ had adequate randomisation and allocation concealment. Participants were not blinded, blinding of outcome assessors was not reported. As far as reported, all relevant outcomes were measured in a standard, valid, reliable way. The proportion of participants excluded/lost to follow-up was reported with reasons for each comparison group separately, with no significant differences between study groups (10% withdrawals/losses to follow-up). ITT analysis was performed, and handling of missing data was by last observation carried forward. The data were analysed in a non-inferiority analysis. The comparison groups were comparable at baseline.

Results

Results for the five trials are shown in *Table 22*.

Glycaemic control

None of the trials found any significant difference in HbA_{1c} values between insulins glargine or detemir and NPH insulin at study end. Levels of HbA_{1c} decreased by between 0.92% and 1.74% from baseline to study end. No significant difference between glargine and NPH was seen in the LEAD trial (2007)¹⁷⁹ for patients reaching the HbA_{1c} target (< 7.5%: 38% for glargine, 30% for NPH) or the FBG target (≤ 6.7 mmol/l: 62% for glargine, 59% for NPH). There was a significant difference in the proportion of patients reaching the HbA_{1c} target (< 7.5%) without nocturnal hypoglycaemia in favour of glargine (23% for glargine, 14% for NPH, $p = 0.017$). There was no significant difference between detemir and NPH for patients reaching HbA_{1c} $\leq 7.0\%$ in the PREDICTIVE-BMI trial (2007)¹⁷⁸ (27% of patients in each group).

The results of the meta-analysis are shown in *Figure 2* for insulin glargine and in *Figure 3* for insulin detemir. Baseline HbA_{1c} values in the trials

TABLE 22 Main results of included trials – long-acting insulin analogues

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
Insulin-naïve, oral antihyperglycaemics – glargine vs NPH insulin					
<i>HbA_{1c}</i>					
Pan (2007) ¹⁷⁹ (LEAD study)	HbA _{1c} (%)	Glargine: 9.02, SD 0.88% NPH insulin: 9.05 SD, 0.84%	Glargine: 8.03% NPH insulin: 8.28%	Glargine: -0.99% NPH insulin: -0.77% Difference in ITT population 0.22 (95% CI 0.02 to 0.42)	p = NS for per-protocol population, p = 0.0319 for ITT population
	Patients achieving target HbA _{1c} (<7.5%) (%)		Glargine: 38.1% NPH insulin: 30.3%		p = NS
	Patients achieving target HbA _{1c} (<7.5%) without nocturnal hypoglycaemia (%)		Glargine: 22.9% NPH insulin: 14.0%		p = 0.017
	Patients achieving target FBG (≤ 120 mg/dl) (%)		Glargine: 62.3% NPH insulin: 58.7%		p = NS
Wang (2007) ¹⁸⁵	HbA _{1c} (%)	Glargine: 8.77, SD 1.18% NPH insulin: 8.75, SD 1.24%	Glargine: 7.62, SD 0.98% NPH insulin: 7.43, SD 0.73%		p = NS
<i>Hypoglycaemia</i>					
Pan (2007) ¹⁷⁹ (LEAD study)	Number of hypoglycaemic episodes		Glargine: 682 NPH insulin: 1019		p < 0.004
	Symptomatic hypoglycaemia		Glargine: 515 NPH insulin: 908		p < 0.0003
	Severe hypoglycaemia		Glargine: 5 NPH insulin: 28		p < 0.03
	Nocturnal hypoglycaemic episodes		Glargine: 221 NPH insulin: 620		p < 0.001
Wang (2007) ¹⁸⁵	All hypoglycaemic events		Glargine: 2 in 2 patients NPH insulin: 6 in 4 patients		p = NS
	Nocturnal hypoglycaemic events		Glargine: 1 in 1 patient NPH insulin: 4 in 4 patients		p = 0.028

continued

TABLE 22 Main results of included trials – long-acting insulin analogues (continued)

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
<i>Glycaemic excursions</i>					
Pan (2007) ¹⁷⁹ (LEAD study)	Eight-point blood glucose profiles			Eight-point blood glucose profiles similar between groups at study end, except for post dinner, where blood glucose concentration in glargine group was significantly lower than in NPH group (236 mg/dl vs 249 mg/dl; $p=0.044$)	$p=0.044$
Wang (2007) ¹⁸⁵ (continuous glucose monitoring system)	Average blood glucose		Glargine: 8.2, SD 1.2 mmol/l NPH insulin: 8.0, SD 2.0 mmol/l		$p=NS$
	SD of blood glucose		Glargine: 1.4, SD 0.4 mmol/l NPH insulin: 2.3, SD 0.5 mmol/l		$p<0.05$
	SD of FPG		Glargine: 0.7, SD 0.4 mmol/l NPH insulin: 1.5, SD 0.7 mmol/l		$p<0.05$
	SD of bedtime PG		Glargine: 1.2, SD 0.4 mmol/l NPH insulin: 2.0, SD 0.7 mmol/l		$p<0.05$
	Blood glucose – pre-breakfast		Glargine: 5.5, SD 0.8 mmol/l NPH insulin: 5.8, SD 1.5 mmol/l		$p=NS$
	Blood glucose – 2 hours post breakfast		Glargine: 9.8, SD 2.6 mmol/l NPH insulin: 10.4, SD 1.9 mmol/l		$p=NS$
	Blood glucose – pre-lunch		Glargine: 5.9, SD 1.0 mmol/l NPH insulin: 6.6, SD 1.2 mmol/l		$p=NS$
	Blood glucose – 2 hours post lunch		Glargine: 9.8, SD 1.5 mmol/l NPH insulin: 10.2, SD 1.8 mmol/l		$p=NS$
	Blood glucose – pre-supper		Glargine: 6.0, SD 0.7 mmol/l NPH insulin: 7.1, SD 1.0 mmol/l		$p<0.05$
	Blood glucose – 2 hours post supper		Glargine: 10.8, SD 1.6 mmol/l NPH insulin: 11.7, SD 1.4 mmol/l		$p=NS$
	Blood glucose – bedtime		Glargine: 7.8, SD 1.2 mmol/l NPH insulin: 9.2, SD 2.0 mmol/l		$p<0.05$
	Blood glucose – 3.00 a.m.		Glargine: 5.1, SD 0.8 mmol/l NPH insulin: 4.2, SD 1.4 mmol/l		$p<0.05$

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
<i>Total daily dose</i>					
Pan (2007) ¹⁷⁹ (LEAD study)	Daily insulin dose	Glargine: 9.6, SD 1.5 IU NPH insulin: 9.8, SD 1.9 IU	Glargine: 32.1, SD 17.6 IU NPH insulin: 32.8, SD 18.9 IU		p = NS
Wang (2007) ¹⁸⁵	Daily insulin dose		Glargine: 18.5, SD 7.5 IU NPH insulin: 19.0, SD 8.4 IU		p = NS
<i>Weight change</i>					
Pan (2007) ¹⁷⁹ (LEAD study)	BMI	Glargine: 24.8, SD 3.1 kg/m ² NPH insulin: 25.1, SD 3.3 kg/m ²		Glargine: +1.40 kg/m ² NPH insulin: +1.29 kg/m ²	p = NS
Wang (2007) ¹⁸⁵	Weight			Glargine: +1.47, SD 1.04 kg NPH insulin: +1.20, SD 1.17 kg	p = NS
<i>Complication rates – not reported</i>					
<i>Adverse events</i>					
Pan (2007) ¹⁷⁹ (LEAD study)	Treatment-emergent adverse events that were possibly treatment related (66 events in 45 patients)		Glargine: 22 patients NPH insulin: 23 patients, majority related to injection-site reactions (45 events in 31 patients)		p-value not reported
	Serious adverse events			No significant difference between groups, none of the events was considered unusual for the demographic group studied	p = NS
<i>Health-related QoL – not reported</i>					
Previous insulin – detemir vs NPH insulin					
HbA _{1c}					
Montanana (2007) ¹⁷⁸ (PREDICTIVE-BMI)	HbA _{1c}	Detemir: 8.9, SD 0.9% NPH: 8.8, SD 1.0%	Detemir: 7.8, SD 1.1% NPH: 7.8, SD 1.0%		p = NS
	Percentage reaching HbA _{1c} ≤ 7.0% without hypoglycaemia		Detemir: 27% NPH: 27%		p = NS

continued

TABLE 22 Main results of included trials – long-acting insulin analogues (continued)

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
<i>Hypoglycaemia</i>					
Montanana (2007) ¹⁷⁸ (PREDICTIVE-BMI)	All hypoglycaemic events	Not reported	26 weeks Detemir: 256 NPH: 481	Significantly less in detemir group, RR 0.62	$p < 0.0001$
	Patients reporting any hypoglycaemic events		26 weeks Detemir: 34.7% NPH: 65.3%		
	Nocturnal hypoglycaemic events	Not reported	26 weeks Detemir: 46 NPH: 107	Significantly less in detemir group, RR 0.43	$p < 0.0001$
	Patients reporting nocturnal hypoglycaemia		26 weeks Detemir: 30.1% NPH: 69.9%		
	Severe hypoglycaemic episodes		26 weeks Detemir: 0 NPH: 3		
<i>Glycaemic excursions – not reported</i>					
<i>Total daily dose</i>					
Montanana (2007) ¹⁷⁸ (PREDICTIVE-BMI)	Insulin dose (IU/kg) – total (basal + bolus)	Detemir: 0.64, SD 0.21 IU/kg NPH: 0.59, SD 0.18 IU/kg	Detemir: 1.05, SD 0.40 IU/kg NPH: 0.85, SD 0.29 IU/kg		p-value not reported
	Insulin dose (IU/kg) – basal	Detemir: 0.30, SD 0.11 IU/kg NPH: 0.28, SD 0.09 IU/kg	Detemir: 0.59, SD 0.25 IU/kg NPH: 0.47, SD 0.18 IU/kg		p-value not reported
<i>Weight change</i>					
Montanana (2007) ¹⁷⁸ (PREDICTIVE-BMI)	Weight change	Detemir: 79.5 kg NPH: 82.2 kg	26 weeks Detemir: +0.4 kg NPH: +1.9 kg	Baseline-adjusted difference 1.5 kg (95% CI 0.8 to 2.8)	$p < 0.0001$
	BMI	Detemir: 31.6 kg/m ² NPH: 32.2 kg/m ²	26 weeks Detemir: +0.17 kg/m ² NPH: +0.77 kg/m ²	Baseline-adjusted difference 0.6 kg/m ²	$p < 0.0001$
	Percentage with no change or loss of weight		26 weeks Detemir: 46.4% NPH: 22.6%		p-value not reported

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
<i>Complication rates – not reported</i>					
<i>Adverse events</i>					
Montanana (2007) ⁷⁸ (PREDICTIVE-BMI)	All adverse events		26 weeks Detemir: 91 NPH: 73		
	Serious adverse events		26 weeks Detemir: 6 NPH: 4		All thought to be unlikely to be related to basal insulin
	Withdrawals because of adverse events		Detemir: 3 NPH: 0		
<i>Health-related QoL – not reported</i>					
Insulin-naïve, oral antihyperglycaemics – detemir vs NPH insulin					
HbA _{1c}					
Philis-Tsimikas (2006) ¹⁸⁰	HbA _{1c} (%)	Morning detemir: 9.08, SD 0.97% Evening detemir: 8.88, SD 0.95% NPH insulin: 9.15, SD 1.0%	Morning detemir: 7.50, SD 0.96% Evening detemir: 7.40, SD 0.77% NPH insulin: 7.35, SD 0.93%	Morning detemir: -1.58, SD 1.07% Evening detemir: -1.48, SD 1.01% NPH insulin: -1.74, SD 1.08%	p = NS
<i>Hypoglycaemia</i>					
Philis-Tsimikas (2006) ¹⁸⁰	Major episodes		Morning detemir: 0 Evening detemir: 2 events in 2 (1.2%) patients NPH insulin: 0		Too few events for statistical analysis
	All confirmed episodes		Morning detemir: 91 events in 32 (19.4%) patients Evening detemir: 82 events in 27 (16.0%) patients NPH insulin: 153 events in 53 (32.3%) patients	Relative risk Morning vs evening detemir: 1.43 Morning detemir vs evening NPH: 0.68 Evening detemir vs evening NPH: 0.47	Morning detemir vs evening detemir or NPH p = NS Evening detemir vs evening NPH p = 0.019

continued

TABLE 22 Main results of included trials – long-acting insulin analogues (continued)

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
Glycaemic excursions Philis-Tsimikas (2006) ¹⁸⁰	Nocturnal episodes		Morning detemir: 6 events in 4 (2.4%) patients Evening detemir: 19 events in 8 (4.7%) patients NPH insulin: 47 events in 22 (13.4%) patients (no major episodes occurred)	Relative risk Morning vs evening detemir: 0.35 Morning detemir vs evening NPH: 0.13 Evening detemir vs evening NPH: 0.35	Morning detemir vs evening detemir $p = NS$ Morning detemir vs evening NPH $p < 0.001$ Evening detemir vs evening NPH $p = 0.031$
	Pre-breakfast self-measured PG (mmol/l)		Morning detemir: 7.97, SD 1.23 mmol/l Evening detemir: 6.50, SD 1.28 mmol/l NPH insulin: 6.78, SD 1.26 mmol/l		$p < 0.001$, morning detemir vs evening detemir and evening NPH
Pre-dinner self-measured PG (mmol/l)			Morning detemir: 7.11, SD 1.91 mmol/l Evening detemir: 7.76, SD 1.84 mmol/l NPH insulin: 7.95, SD 1.98 mmol/l		$p = 0.005$, morning detemir vs evening detemir; $p < 0.001$, morning detemir vs evening NPH
	Nine-point self-measured PG profile				Similar for two evening insulin groups, mean profile of morning insulin detemir group was characterised by lower glycaemic values in the daytime and higher values overnight; $p < 0.001$
Total daily dose Philis-Tsimikas (2006) ¹⁸⁰	Mean insulin dose		Morning detemir: 0.5, SD 0.3 IU/kg Evening detemir: 0.4, SD 0.2 IU/kg NPH insulin: 0.4, SD 0.2 IU/kg		$p = NS$

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
Weight change Philis-Tsimikas (2006) ¹⁸⁰	Weight gain			Morning detemir: +1.2 kg Evening detemir: +0.7 kg NPH insulin: +1.6 kg	Morning detemir vs evening detemir or NPH: $p = NS$ Evening detemir vs evening NPH: $p = 0.005$
Complication rates – not reported					
Adverse events					
Philis-Tsimikas (2006) ¹⁸⁰	Withdrawals due to adverse events		Morning detemir: 2.4% Evening detemir: 2.4% NPH insulin: 2.4%		
	Overall profiles of adverse events		Morning detemir: 123 AEs in 70 patients Evening detemir: 150 AEs in 67 patients NPH insulin: 144 AEs in 82 patients		Statistically similar, mostly considered unrelated to study insulins; all serious adverse events unrelated to insulins
	Injection site reactions		Morning detemir: 2 events in 2 patients Evening detemir: 7 events in 6 patients NPH insulin: 2 events in 2 patients		$p = NS$
	Potential allergic reactions		Morning detemir: 2 events in 2 patients Evening detemir: 5 events in 5 patients NPH insulin: 1 event in 1 patient		$p = NS$
	Health-related QoL – not reported				

AE, adverse event; NS, not significant.

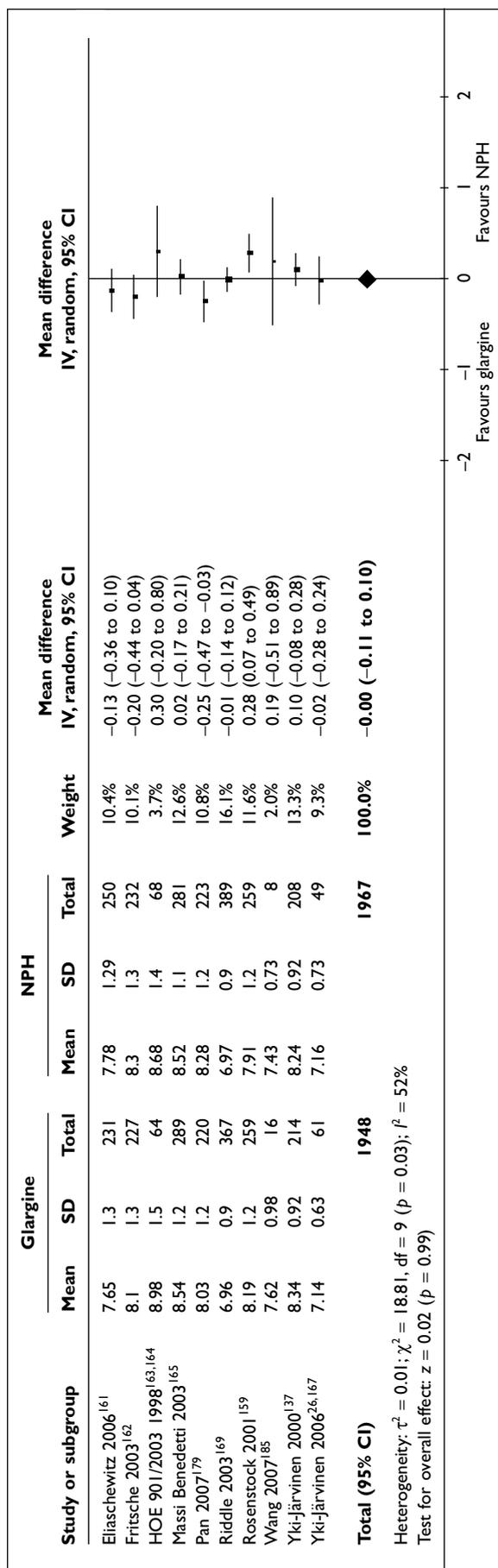


FIGURE 2 HbA_{1c} glargine versus Neutral Protamine Hagedorn.

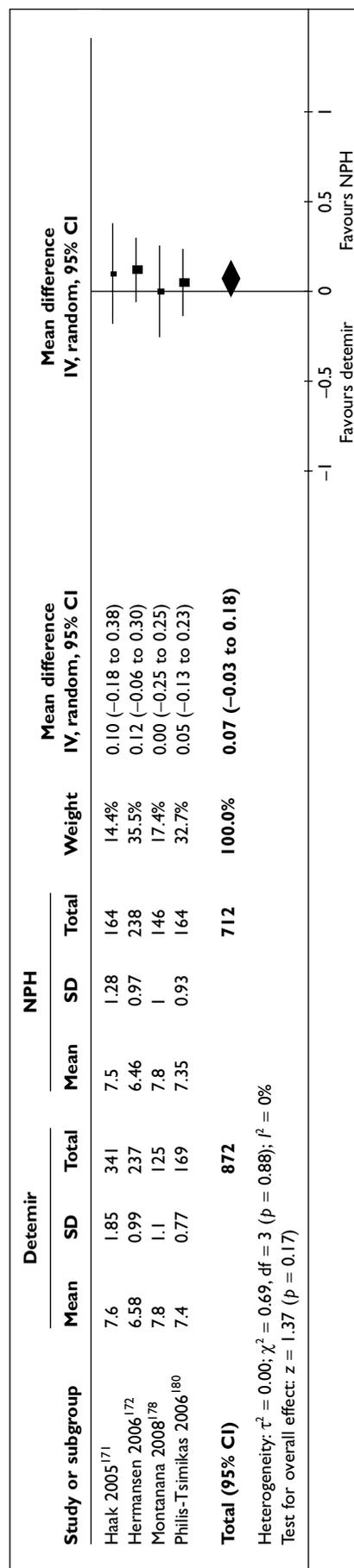


FIGURE 3 HbA_{1c} detemir versus Neutral Protamine Hagedorn.

included in the meta-analysis were between 8.5% and 9.7% in the glargine versus NPH trials, and between 7.8% and 9.2% in the detemir versus NPH trials. None of the meta-analyses showed a significant effect for insulin glargine (nine studies) or insulin detemir (four studies) versus NPH for HbA_{1c} level. The WMD was 0.00% (95% CI -0.11 to 0.10) for glargine and 0.07% (95% CI -0.03 to 0.18) for detemir. There was significant heterogeneity for the results for insulin glargine which disappeared when the only study of patients on previous insulin therapy [Rosenstock *et al.* (2001)]¹⁵⁹ was excluded.

Hypoglycaemia

The LEAD trial (2007)¹⁷⁹ and the PREDICTIVE-BMI trial (2007)¹⁷⁸ found significant results in favour of glargine and detemir respectively in comparison with NPH for all hypoglycaemia-related outcomes reported. The trial by Wang *et al.* (2007)¹⁸⁵ found significantly fewer episodes of nocturnal hypoglycaemia with glargine compared with NPH, but no significant difference for all hypoglycaemic events. The trial by Philis-Tsimikas *et al.* (2006)¹⁸⁰ found significant effects in favour of detemir for all comparisons of evening detemir versus evening NPH, but not for some of the other comparisons.

In the LEAD trial (2007)¹⁷⁹ there were 682 hypoglycaemic episodes in the glargine group compared with 1019 in the NPH group ($p < 0.004$). There were 515 episodes of symptomatic hypoglycaemia in the glargine group compared with 908 in the NPH group ($p < 0.0003$), five of severe hypoglycaemia in the glargine group compared with 28 in the NPH group ($p < 0.03$), and 221 episodes of nocturnal hypoglycaemia in the glargine group compared with 620 in the NPH group ($p < 0.001$).

In the trial by Wang *et al.* (2007),¹⁸⁵ there were two hypoglycaemic events in two patients in the glargine group and six hypoglycaemic events in four patients in the NPH group ($p = \text{NS}$). There was one nocturnal hypoglycaemic event in one patient in the glargine group and four nocturnal hypoglycaemic events in four patients in the NPH group ($p = 0.028$).

The PREDICTIVE-BMI trial (2007)¹⁷⁸ reported significantly fewer hypoglycaemic events with detemir than with NPH (256 versus 481, RR 0.62; $p < 0.0001$) and also significantly less nocturnal hypoglycaemia (46 versus 107, RR 0.43, $p < 0.0001$).

In the trial by Philis-Tsimikas *et al.* (2006)¹⁸⁰ there were too few major hypoglycaemic episodes for statistical analysis (only two events in the evening detemir group). For all confirmed hypoglycaemic episodes, there were 91 events in 32 patients on morning detemir, 82 events in 27 patients on evening detemir, and 153 events in 53 patients on evening NPH, with a significant difference in favour of evening detemir versus evening NPH, but not of morning detemir versus evening detemir or NPH. For nocturnal hypoglycaemia, there were six events in four patients on morning detemir, 19 events in eight patients on evening detemir, and 47 events in 22 patients on evening NPH, with a significant difference in favour of either detemir group versus evening NPH, but not of morning detemir versus evening detemir.

The meta-analyses for severe hypoglycaemia (Figures 4 and 5) included six studies (reporting the number of patients with severe hypoglycaemia) for insulin glargine versus NPH and four studies for insulin detemir versus NPH. There was no significant difference in the number of patients with severe hypoglycaemia in the glargine or detemir groups compared with NPH insulin [RR 0.82 (95% CI 0.45 to 1.49) for glargine and RR 0.59 (95% CI 0.15 to 2.24) for detemir]. There was no significant heterogeneity.

The meta-analysis for overall hypoglycaemia (Figures 6 and 7) included seven studies (reporting the number of patients with any hypoglycaemia) for insulin glargine versus NPH, and four studies for insulin detemir versus NPH. There was a significant difference in the number of patients reporting any hypoglycaemia in favour of the glargine and detemir groups compared with NPH insulin [RR 0.89 (95% CI 0.83 to 0.96, $p = 0.002$) for glargine, and RR 0.68 (95% CI 0.54 to 0.86, $p = 0.001$) for detemir]. There was no significant heterogeneity for glargine versus NPH but there was for detemir versus NPH ($p = 0.002$).

The meta-analysis for symptomatic hypoglycaemia (Figure 8) included four studies (reporting the number of patients with symptomatic hypoglycaemia) for insulin glargine versus NPH. There was a significant difference in the number of patients reporting symptomatic hypoglycaemia in favour of the glargine groups compared with NPH insulin [RR 0.80 (95% CI 0.68, 0.93, $p < 0.004$)]. There was significant heterogeneity ($p = 0.04$).

The meta-analysis for nocturnal hypoglycaemia (Figures 9 and 10) included seven studies (reporting the number of patients with nocturnal

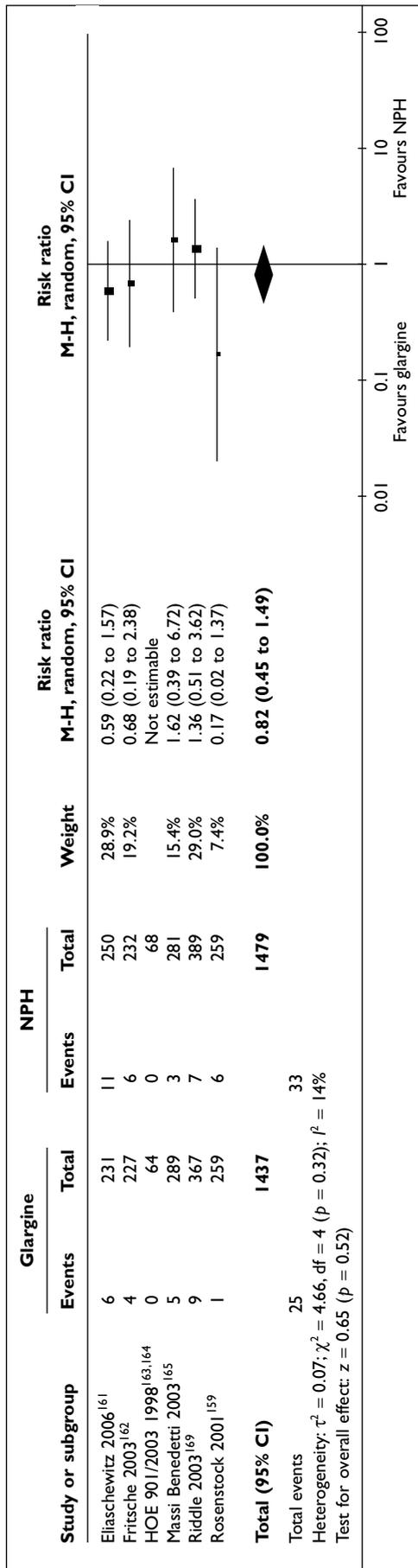


FIGURE 4 Severe hypoglycaemia glargine versus Neutral Protamine Hagedorn.

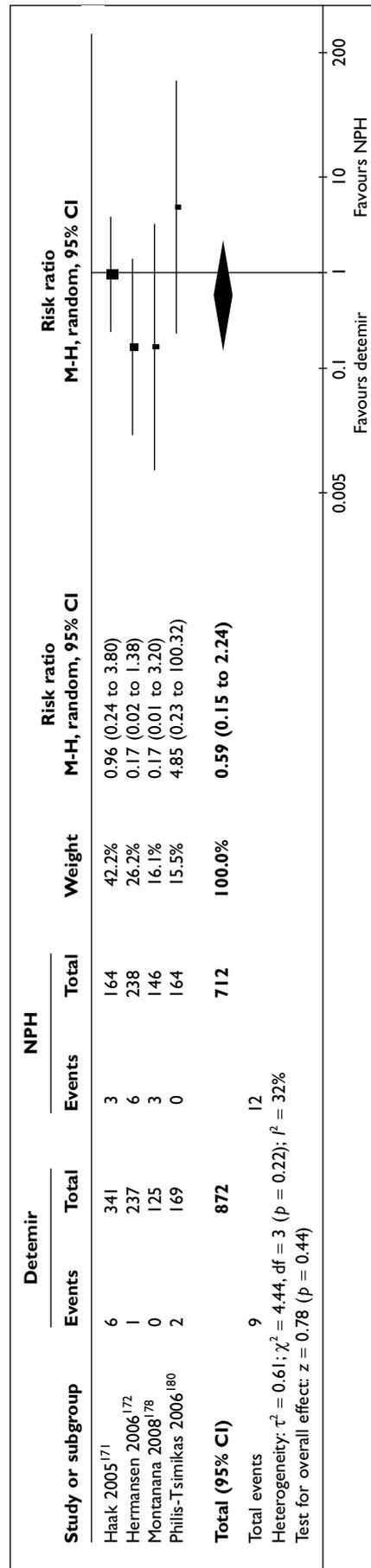


FIGURE 5 Severe hypoglycaemia detemir versus Neutral Protamine Hagedorn.

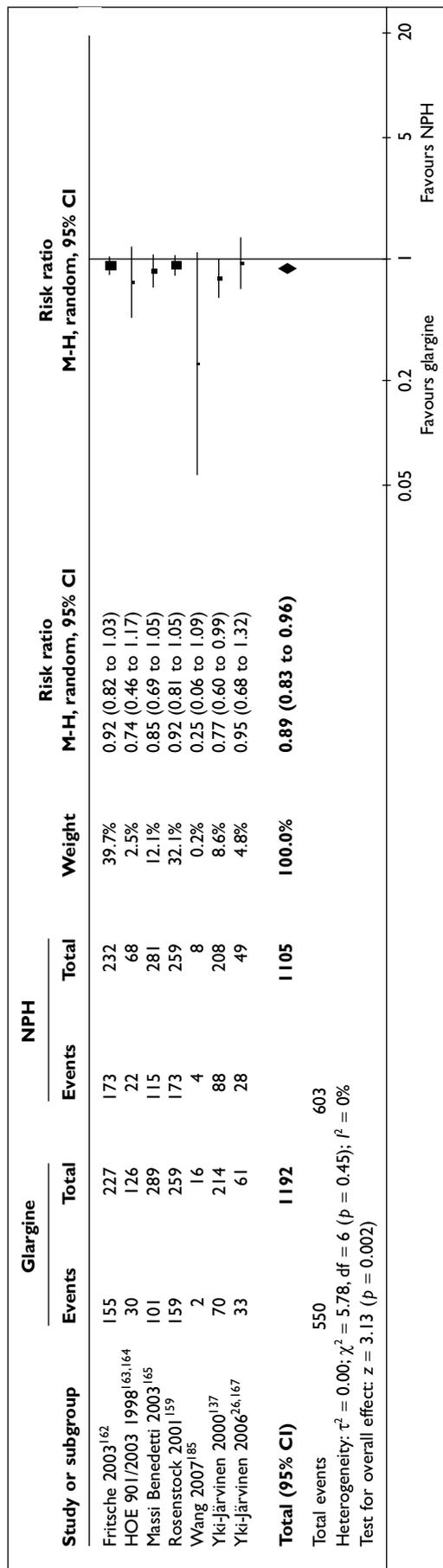


FIGURE 6 Overall hypoglycaemia glargine versus Neutral Protamine Hagedorn.

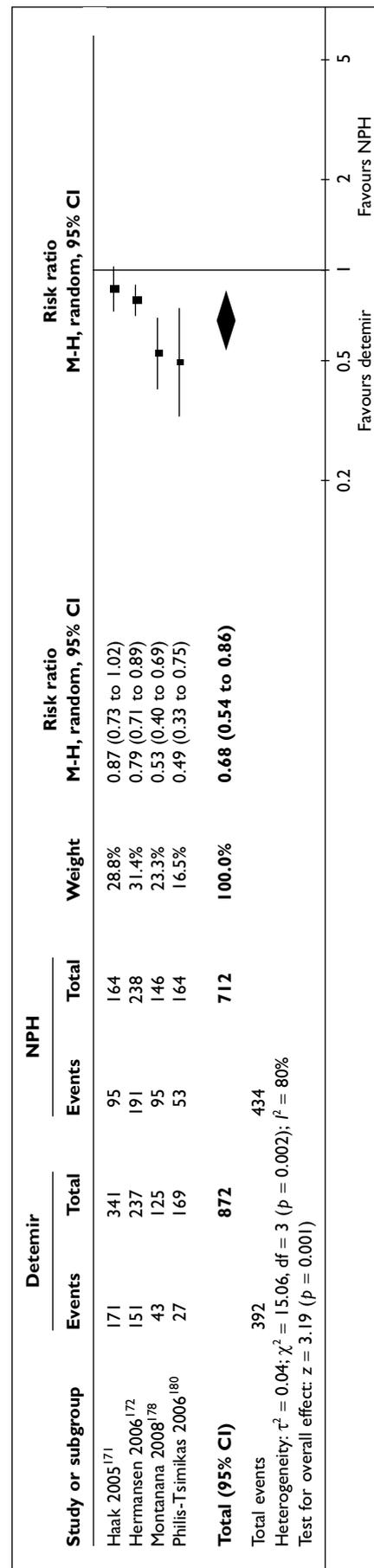


FIGURE 7 Overall hypoglycaemia detemir versus Neutral Protamine Hagedorn.

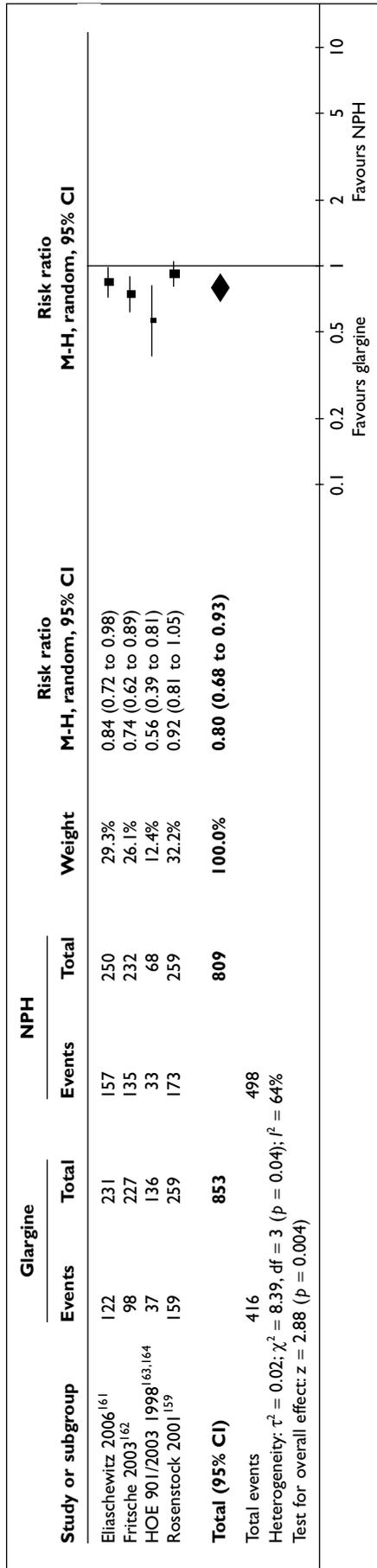


FIGURE 8 Symptomatic hypoglycaemia glargine versus Neutral Protamine Hagedorn.

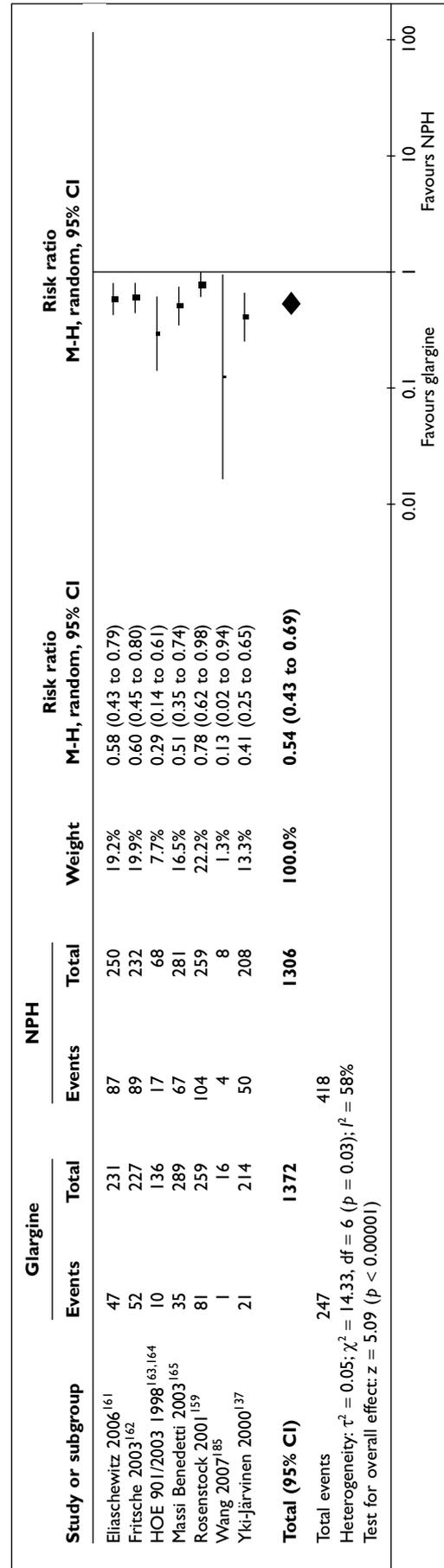


FIGURE 9 Nocturnal hypoglycaemia glargine versus Neutral Protamine Hagedorn.

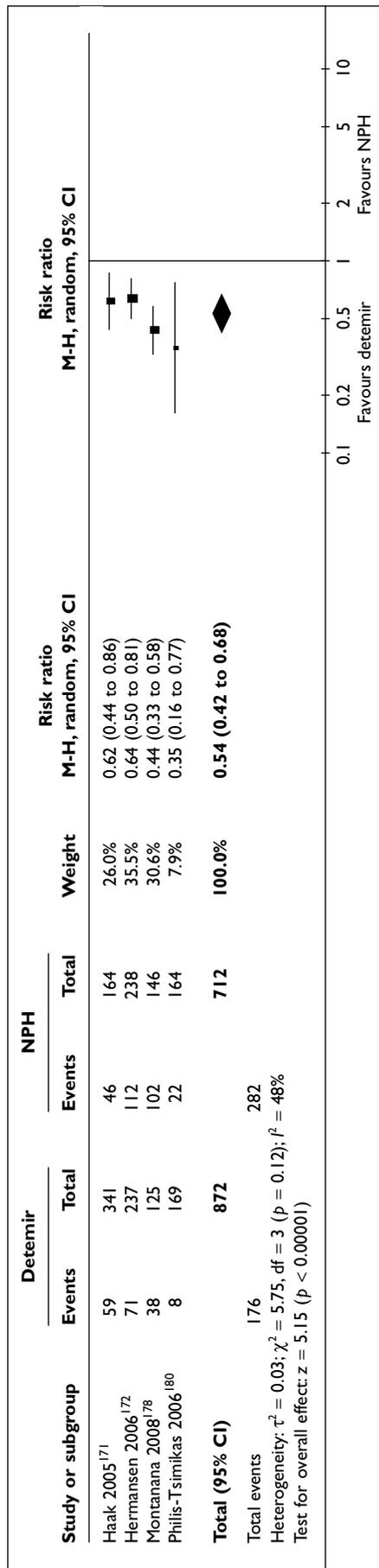


FIGURE 10 Nocturnal hypoglycaemia detemir versus Neutral Protamine Hagedorn.

hypoglycaemia) for insulin glargine versus NPH and four studies for insulin detemir versus NPH. There was a significant difference in the number of patients reporting nocturnal hypoglycaemia in favour of the glargine and detemir groups compared with NPH insulin [RR 0.54 (95% CI 0.43 to 0.69, $p < 0.00001$) for glargine and RR 0.54 (95% CI 0.24 to 0.68, $p < 0.00001$) for detemir]. There was significant heterogeneity for glargine versus NPH ($p = 0.03$) but not for detemir versus NPH. The heterogeneity disappeared when the only study of patients on previous insulin therapy [Rosenstock *et al.* (2001)]¹⁵⁹ was excluded.

Glucose excursions

The LEAD trial (2007)¹⁷⁹ found eight-point blood glucose profiles to be similar between groups at study end, except for postdinner values, where blood glucose concentration in the glargine group was significantly lower than in the NPH group (236 mg/dl versus 249 mg/dl, $p = 0.044$).

In the Wang *et al.* (2007)¹⁸⁵ trial, a continuous glucose monitoring system was used. No differences between glargine and NPH were found in average blood glucose values, pre-breakfast, 2 hours post breakfast, pre-lunch, 2 hours post lunch, and 2 hours post supper blood glucose values, but the SDs of blood glucose, FPG and bedtime PG were significantly smaller with glargine than NPH, pre-supper and bedtime blood glucose values were significantly lower with glargine than NPH, and 3 a.m. blood glucose values were significantly larger with glargine than NPH.

In the trial by Philis-Tsimikas *et al.* (2006),¹⁸⁰ nine-point blood glucose profiles were similar for the two evening insulin groups, whereas the mean profile of the morning insulin detemir group was characterised by lower glycaemic values in the daytime and higher values overnight ($p < 0.001$). Pre-breakfast PG values were between 1.19 and 1.47 mmol/l higher ($p < 0.001$) in the morning detemir group, and pre-dinner PG values between 0.65 and 0.84 mmol/l lower ($p \leq 0.01$) in the morning detemir group than in the evening groups.

Total daily insulin dose

No significant differences in mean daily insulin doses between treatment groups were reported in the LEAD trial (2007),¹⁷⁹ the trial by Wang *et al.*

(2007),¹⁸⁵ the PREDICTIVE-BMI trial (2007),¹⁷⁸ or the trial by Philis-Tsimikas *et al.* (2006).¹⁸⁰

Weight change

In the LEAD trial (2007),¹⁷⁹ BMI increased both in the glargine and in the NPH group to a similar extent during the course of the trial (+1.4 and +1.3 kg/m²). Similarly, in the trial by Wang *et al.* (2007)¹⁸⁵ body weight increased to a similar extent in both groups (+1.47 kg with glargine and +1.20 kg with NPH).

In the PREDICTIVE-BMI trial (2007),¹⁷⁸ significantly less weight gain was seen with insulin detemir than with NPH insulin over the course of the trial (+0.4 kg versus +1.9 kg, $p < 0.0001$). Similarly, patients in the detemir group had a significantly smaller increase in BMI (+0.17 kg/m² versus +0.77 kg/m², $p < 0.0001$).

In the trial by Philis-Tsimikas *et al.* (2006),¹⁸⁰ patients in the morning detemir group gained a mean of 1.2 kg, patients in the evening detemir group gained a mean of 0.7 kg, and patients in the evening NPH group gained a mean of 1.6 kg, with weight gain being significantly less in the evening detemir group than in the evening NPH group ($p = 0.005$, no other significant differences).

Overall (eight studies), the glargine groups gained 0.23 kg less weight than the NPH groups (range -1.10 to +0.23 kg). However, a meta-analysis could not be carried out for this outcome because of too many missing SDs. The detemir groups (four studies) gained 1.20 kg less weight than the NPH groups (range -0.8 to -1.6 kg) but, again, a meta-analysis could not be carried out due to too many missing SDs.

Diabetic complications

These were not reported by any of the trials.

Adverse events

The LEAD study (2007)¹⁷⁹ reported 66 adverse events in 45 patients that were possibly treatment related (22 patients in the glargine group and 23 patients in the NPH group). The majority was related to injection-site reactions, and, although p -values were not reported, there does not seem to have been a significant difference between groups. There was no significant difference in

serious adverse events between groups, and none of the events were considered unusual for the demographic group studied (i.e. not related to the treatment).

The trial by Wang *et al.* (2007)¹⁸⁵ did not report adverse events.

In the PREDICTIVE-BMI trial (2007)¹⁷⁸ there were 91 adverse events in the detemir group and 73 in the NPH group, six of these in the detemir group and four in the NPH group were serious (but thought to be unlikely to be related to basal insulin). There were three withdrawals because of adverse events in the detemir group and none in the NPH group.

In the trial by Philis-Tsimikas *et al.* (2006),¹⁸⁰ there was no significant difference in overall adverse events between comparison groups (123–144 events in 67–82 patients in each group). No serious adverse events were considered to be related to the insulins. There was no significant difference in potential allergic reactions (1–5 events in 1–5 patients per group) or injection site reactions (2–7 events in 2–6 patients per group) between the groups.

Health-related QoL

This was not reported by any of the trials.

Glargine vs detemir

The main results of the included glargine versus detemir trial are shown *Table 23*.

The results of the trial by Rosenstock *et al.* (2008)¹⁷⁷ suggest that the effects of glargine and detemir are similar. After 52 weeks of treatment, there were no significant differences in HbA_{1c} level, percentage of patients reaching HbA_{1c} value of $\leq 7.0\%$ (with or without hypoglycaemia), overall hypoglycaemic events or nocturnal hypoglycaemic events. There was statistically significantly less weight gain with detemir overall than with glargine (+2.7 versus 3.5 kg, $p = 0.03$), but the difference of 0.8 kg is of doubtful clinical significance. However, when analysing use of detemir once or twice daily, only the once-daily detemir group was at an advantage for weight gain (+2.3 kg), whereas the weight gain in the twice-daily detemir group was similar to that of the glargine group (+3.7 kg). The mean daily dose was higher for detemir (0.52 U/kg with

once-daily dosing, 1.00 U/kg with twice-daily dosing) than for glargine (0.44 U/kg). Injection site reactions were slightly more common with detemir than with glargine (4.5% versus 1.4%, p -value not reported).

Another short study, available in abstract only¹⁸⁶ compared the effect of once daily glargine and detemir on blood glucose profiles over the course of a week, and found no significant difference.

Discussion

Taking the evidence from the systematic reviews and the RCTs as a whole, both insulin glargine and insulin detemir appear to be equivalent with respect to parameters of glycaemic control in comparison with NPH insulin. This was confirmed by our meta-analysis of trials included in previous meta-analyses and additional trials identified. A significant reduction in nocturnal hypoglycaemia was associated with both glargine and detemir treatment, but the effect size is not clear from the reviews. The reduction in nocturnal hypoglycaemia both for glargine and detemir was confirmed by our meta-analysis. Some reduction in overall or symptomatic hypoglycaemia was also seen with glargine or detemir, but this was not consistent for all trials. Our meta-analysis did however show a significant reduction in overall hypoglycaemia for both glargine and detemir and for symptomatic hypoglycaemia for glargine (not reported for detemir). In many trials, severe hypoglycaemia did not occur frequently enough to allow a meaningful statistical analysis.

Glycaemic excursions were reported infrequently but where reported, no consistent differences between glargine or detemir and NPH insulin were seen.

Total daily doses of insulin and health-related QoL (or patient satisfaction) were reported too infrequently to allow any conclusions.

Similarly, change in weight or BMI was not reported systematically enough to allow any firm conclusion. There was some indication that there may be less weight gain with the long-acting analogues than with NPH insulin (possibly dependent on previous insulin treatment), but the results on this outcome were not consistent. One study of glargine versus detemir suggested

TABLE 23 Main results of included trial – glargine versus detemir

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
Insulin-naive – glargine vs detemir					
<i>HbA_{1c}</i>					
Rosenstock (2008) ¹⁷⁷	HbA _{1c} (%)	Detemir (n = 291): 8.64, SD 0.78% Glargine (n = 291): 8.62, SD 0.77%	Detemir (n = 268): 7.16, SE 0.08% glargine (n = 275): 7.12, SE 0.08%	Difference glargine – detemir 0.05% (95% CI 0.11 to 0.21)	p = NS
	Patients achieving HbA _{1c} ≤ 7.0% (%)		Detemir (n = 248): 52% Glargine (n = 259): 52%		p = NS
	Patients achieving target HbA _{1c} ≤ 7.0% (%) without hypoglycaemia (%)		Detemir (n = 248): 33% Glargine (n = 259): 35%		p = NS
<i>Hypoglycaemia</i>					
Rosenstock (2008) ¹⁷⁷	All hypoglycaemic episodes		<i>Detemir</i> Participants: 182 (63%) Episodes: 1521 Rate: 5.8 per patient-year <i>Glargine</i> Participants: 191 (66%) Episodes: 1670 Rate: 6.2 per patient-year	Relative risk 0.94 (95% CI 0.71 to 1.25)	p = NS
	Nocturnal hypoglycaemic episodes		<i>Detemir</i> Participants: 95 (33%) Episodes: 352 Rate: 1.3 per patient-year <i>Glargine</i> Participants: 93 (32%) Episodes: 350 Rate: 1.3 per patient-year	Relative risk 1.05 (95% CI 0.69 to 1.58)	p = NS
	Major hypoglycaemic episodes		<i>Detemir</i> Participants: 5 (2%) Episodes: 9 Rate: 0.0 per patient-year <i>Glargine</i> Participants: 8 (3%) Episodes: 8 Rate: 0.0 per patient-year		Not reported, number too small
	Major nocturnal hypoglycaemic episodes		<i>Detemir</i> Participants: 3 (1%) Episodes: 5 Rate: 0.0 per patient-year		Not reported, number too small

TABLE 23 Main results of included trial – glargine versus detemir (continued)

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
	Minor hypoglycaemic episodes		<i>Glargine</i> Participants: 4 (1%) Episodes: 4 Rate: 0.0 per patient-year <i>Detemir</i> Participants: 135 (46%) Episodes: 737 Rate: 2.9 per patient-year	Relative risk 1.05 (95% CI 0.75 to 1.46)	p = NS
	Minor nocturnal hypoglycaemic episodes		<i>Glargine</i> Participants: 151 (52%) Episodes: 786 Rate: 2.9 per patient-year <i>Detemir</i> Participants: 73 (25%) Episodes: 212 Rate: 0.8 per patient-year	Relative risk 1.17 (95% CI 0.75 to 1.83)	p = NS
	Symptoms only hypoglycaemic episodes		<i>Glargine</i> Participants: 71 (24%) Episodes: 192 Rate: 0.7 per patient-year <i>Detemir</i> Participants: 137 (47%) Episodes: 760 Rate: 3.0 per patient-year	Relative risk 0.88 (95% CI 0.61 to 1.25)	p = NS
	Symptoms only nocturnal hypoglycaemic episodes		<i>Glargine</i> Participants: 133 (46%) Episodes: 866 Rate: 3.2 per patient-year <i>Detemir</i> Participants: 48 (17%) Episodes: 128 Rate: 0.5 per patient-year	Relative risk 0.88 (95% CI 0.50 to 1.54)	p = NS
	Glycaemic excursions		<i>Detemir</i> (n = 238): SD 1.06 <i>Glargine</i> (n = 257): SD 1.03		p = NS
Rosenstock (2008) ¹⁷⁷	Within-participant variation (mmol/l) – pre-breakfast		<i>Detemir</i> (n = 238): SD 1.60 <i>Glargine</i> (n = 258): SD 1.55		p = NS
	Within-participant variation (mmol/l) – pre-dinner				p = NS

continued

TABLE 23 Main results of included trial – glargine versus detemir (continued)

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
<i>Total daily dose</i>					
Rosenstock (2008) ¹⁷⁷	Daily insulin dose		Detemir (<i>n</i> = 227): 0.78 U/kg/day (0.52 U/kg for once daily and 1.0 U/kg for twice daily, with 55% on twice daily) Glargine (<i>n</i> = 248): 0.44 U/kg/day		p-value not reported
<i>Weight change</i>					
Rosenstock (2008) ¹⁷⁷	Weight gain	Detemir: 87.4, SD 16.6 kg Glargine: 87.4, SD 17.4 kg		Detemir (<i>n</i> = 230): +3.0, SE 0.4 kg Glargine (<i>n</i> = 252): +3.9, SE 0.4 kg Confirmed in ITT analysis, <i>but</i> weight gain with once daily detemir was +2.3, SE 0.5 kg and with twice-daily detemir +3.7, SE 0.4 kg (no difference to glargine)	p = 0.01
<i>Adverse events</i>					
Rosenstock (2008) ¹⁷⁷	Withdrawal because of adverse events		Detemir: 8% Glargine: 4%		
	Serious adverse events		Detemir: 42 patients with 47 events Glargine: 53 patients with 73 events, but only 5 events with detemir and 4 events with glargine considered to be (possibly) related to study medication		
	Deaths		Detemir: <i>n</i> = 1 (possibly MI) Glargine: <i>n</i> = 1 (pulmonary fibrosis)		
	Injection site disorders		Detemir: 4.5% Glargine: 1.4%		
	Allergic reactions		Detemir: <i>n</i> = 3 Glargine: <i>n</i> = 1		
	Skin disorders (including pruritus and rash)		Detemir: <i>n</i> = 6 Glargine: <i>n</i> = 1		
Health-related QoL – not reported. Complication rates – not reported.					

that there may be less weight gain with once daily detemir than with once daily glargine. Most trials included in this review did not provide enough information to enable a meta-analysis, but data extracted also suggest that there may be slightly less weight gain with detemir than with glargine, though the difference is of doubtful clinical significance. Any effects seen appear to have been independent of whether patients have been treated with insulins previously or not, or were on oral antihyperglycaemic therapy or not.

Reported adverse events appear to have been largely similar between the long-acting insulin analogues and NPH insulin, possibly with more injection site reactions for the analogues. However, no data on the longer term safety of the insulin analogues were available.

No information was available on diabetic complications, and the studies were underpowered to assess such outcomes or mortality reliably.

Horvath *et al.* (2007)¹⁴¹ reported limited data on a possible differential effect of glargine on development of clinically significant macular oedema depending on previous treatment with insulin, suggesting that this may be a point of concern.

Conclusions

Glargine and detemir are equivalent to NPH in terms of glycaemic control as reflected in HbA_{1c} level, but have modest advantages in terms of hypoglycaemia, especially nocturnal.

There is little to choose between the two analogues. Detemir, when used once daily, may be associated with marginally less weight gain, but this is unlikely to be clinically significant. It requires a higher daily dose than glargine which will have cost implications.

Chapter 5

The glitazones

History

There are two TZDs, or glitazones for short, used in the UK: pioglitazone and rosiglitazone. They have been the subject of technology appraisals (TAs) by NICE, starting with appraisals of the individual drugs (TAs 9 and 21), later superseded by a review of both – TA 63, issued in August 2003.¹²

The guidance issued after the review in 2003 stated that:

1.1 For people with type 2 diabetes, the use of a glitazone as second-line therapy added to either metformin or a sulphonylurea – as an alternative to treatment with a combination of metformin and a sulphonylurea – is not recommended except for those who are unable to take metformin and a sulphonylurea in combination because of intolerance or a contraindication to one of the drugs.

1.3 The present UK licence does not allow the Institute to recommend the use of glitazones in triple combination therapy, as monotherapy, or in combination with insulin.

Section 1.1 was based on cost-effectiveness rather than clinical efficacy. Regarding section 1.3, the Appraisal Committee noted (paragraph 4.3.6 of the guidance) that:

The off-licence use of glitazones as part of triple combination therapy is widely practised in the UK. This use has been particularly targeted at a subset of people with diabetes for whom the combination of metformin and sulphonylurea has failed to achieve target HbA_{1c} levels despite appropriate doses of these drugs, and for whom the conventional choice of switching to insulin therapy is not acceptable ...

The Committee was aware of recent trial evidence on the clinical effectiveness of triple therapy. However, NICE is restricted to issuing guidance on licensed indications and so could not comment.

The licensed indications have changed, and are now (based on EMEA 2008):¹⁸⁷

- Rosiglitazone is indicated in the treatment of type 2 diabetes as:
 - *Monotherapy*, in patients (particularly overweight patients) who are inadequately controlled by diet and exercise, for whom metformin is inappropriate because of contraindications or intolerance.
 - *Dual oral therapy in combination with metformin*, in patients (particularly overweight ones) with insufficient glycaemic control, despite maximal tolerated dose of monotherapy with metformin.
 - *Dual oral therapy in combination with a sulphonylurea*, only in patients who show intolerance to metformin, or for whom metformin is contraindicated, with insufficient glycaemic control despite sulphonylurea monotherapy.
 - *Triple oral therapy in combination with metformin*, in patients with insufficient glycaemic control despite dual oral therapy.
- The licence for pioglitazone is as above, but with, in addition:¹⁸⁸
 - Pioglitazone is also indicated for combination with insulin in type 2 diabetes patients with insufficient glycaemic control on insulin for whom metformin is inappropriate because of contraindications or intolerance.

There are now more trials than were available at the time of NICE TA 63. The evidence base for rosiglitazone was updated in a Cochrane review published in July 2007 by Richter *et al.* (2007).¹⁸⁹ Their summary included:

Eighteen trials randomised 3888 people to rosiglitazone therapy. The longest duration of rosiglitazone treatment was 4 years. Most trials lasted around half a year. Unfortunately, the published studies of at least 24 weeks

rosiglitazone treatment in people with type 2 diabetes mellitus did not provide relevant evidence that patient-orientated outcomes are positively influenced by this agent. The chance of developing oedema was approximately doubled. The single large randomised controlled trial showed evidence of raised cardiovascular risk after rosiglitazone treatment. Moreover, new safety data show increased numbers of fractures in women.

The review noted an increased risk of MI in those treated with rosiglitazone but that this was not statistically significant.

A Cochrane review of pioglitazone by the same authors¹⁹⁰ (published Cochrane Library, Issue 4, 2006) was summarised thus:

Twenty-two trials which randomised 6200 people to pioglitazone treatment were identified. Longest duration of therapy was 34.5 months. Published studies of at least 24 weeks pioglitazone treatment in people with type 2 diabetes mellitus did not provide convincing evidence that patient oriented outcomes like mortality, morbidity, adverse effects, costs and health-related QoL are positively influenced by this compound. Metabolic control measured by HbA_{1c} as a surrogate end point did not demonstrate clinically relevant differences to other oral antidiabetic drugs. Occurrence of oedema was significantly raised.

Comments like this would apply to most new diabetes drugs, as trials are usually short term and rely on proxy outcomes – usually HbA_{1c} values. There are few trials, such as UKPDS, which are long enough to produce data on complications or mortality. Nor are they usually long enough to produce data on uncommon side effects.

The only exception to the short-term trials found in the Cochrane review was the PROactive study,¹⁹¹ a large study, with over 500 patients, which did set out to examine the effect of pioglitazone on hard outcomes, in a trial against placebo, in patients who had evidence of macrovascular disease. Patients continued their other diabetes medications, mainly metformin, sulfonylureas, insulin, or combinations thereof. The primary end point was a composite of death and non-fatal cardiovascular outcomes. The pioglitazone group had a lower risk but this did not reach statistical significance [hazard ratio (HR)

0.90, 95% CI 0.80 to 1.02, $p = 0.095$] despite the large numbers of recruits and events (at least one end point event in 514 of the pioglitazone group and 572 of the placebo group). A secondary end point measure of death, non-fatal MI and stroke did reach statistical significance (HR 0.84, 95% CI 0.72 to 0.98, $p = 0.027$). The closing statement focused on the secondary outcome, which was another composite outcome: 'Pioglitazone reduces the composite of all-cause mortality, non-fatal MI and stroke'.

However, oedema and heart failure were commoner in the pioglitazone group, with 11% reported as having heart failure compared with 8% in the placebo group; the proportions needing hospital admission were 6% and 4%. The death rates from heart failure showed no difference. Heart failure was not defined centrally, but was 'as judged by the investigator'. Another outcome was 'oedema in the absence of heart failure'. Heart failure can be difficult to diagnose, and the absence of any difference in mortality from heart disease, might suggest that it could have been overdiagnosed. However, an independent group of cardiologists reviewed all of the cases of serious heart failure and concluded that it did occur more frequently in the pioglitazone group (5.5% versus 4.2% for placebo).¹⁹²

The most relevant finding from the PROactive study, in the light of today's concerns about the safety of rosiglitazone, was that even if the reduction in cardiovascular events was small it was certainly not increased by pioglitazone.

The results have been somewhat optimistically interpreted in later publications. The economic analysis reported that:¹⁹³ 'Within trial cost-effectiveness analysis compared with pioglitazone was associated with improved life expectancy (undiscounted 0.0109 years)'.

(Note: 0.0109 years = 4 days.)

Another finding from PROactive¹⁹¹ was that progression to needing insulin was halved in the pioglitazone group. At the start of the study, about one-third of the patients were on insulin. Their mean age was 62 years, mean BMI = 31 and duration of diabetes 8 years. In total, 75% had a history of hypertension. Mean HbA_{1c} level was around 7.8%. The protocol asked investigators to aim for an HbA_{1c} level of < 6.5%. By the end of follow-up, 11% of the pioglitazone group and 21%

of the placebo group were on insulin treatment. The switch to insulin started early in the trial, presumably due to investigators trying to achieve the HbA_{1c} target.

Given that one alleged benefit of some of the new drugs for diabetes is a delay in, or avoidance of, insulin therapy, this finding seems highly relevant. The reduction in insulin use played a significant part in the economic analysis of the PROactive trial,¹⁹³ where the Center for Outcomes Research (CORE) team, with co-authors from the manufacturer, reported that adding pioglitazone was cost-effective.

Rosiglitazone and safety

The glitazones situation changed in May 2007, when a meta-analysis by Nissen and Wolski (2007)¹⁹⁴ was published in the *New England Journal of Medicine*. It concluded that there was an increased risk (by 40%) of cardiovascular disease with rosiglitazone compared with those on metformin or a sulfonylurea, or placebo. An editorial shortly after stated that a patient level analysis by the manufacturer of rosiglitazone had confirmed the findings.¹⁹⁵

Much debate followed. Another meta-analysis involving adding a new trial, the RECORD study (2007)¹⁹⁶ to those in the meta-analysis by Nissen and Wolski, found that the risk still seemed to be increased, this time at an OR of 1.33 (95% CI 1.02 to 1.72).¹⁹⁷ This was because the RECORD study interim analysis reported a HR of only 1.11.

It is worth noting that the absolute risk in the studies was low.

The meta-analysis by Nissen and Wolski was criticised on various grounds, in particular that it excluded six trials which had no relevant events. With no events, it is impossible to assess the relative cardiovascular risks. However, the lack of events can tell us something about absolute risks. Interestingly, of the 42 trials that were included, 26 were unpublished, with data obtained from trials provided by GlaxoSmithKline (North Carolina, USA) to the US FDA. The FDA later (letter dated 25 March 2008)¹⁹⁸ complained to GlaxoSmithKline about failure to pass on data from some trials and postmarketing studies.

A later meta-analysis [Diamond *et al.* (2007)¹⁹⁹] applied different statistical techniques, included

the six studies with no events, but excluded four studies. They then recalculated the ORs in six different ways, and showed that while there was still an increased risk for both MI and cardiovascular death, the CIs now overlapped with unity, and the ORs varied with method. For example, the OR for cardiovascular death ranged from 1.58 (95% CI 0.91 to 2.74) to 1.16 (0.75 to 1.79).

The Nissen and Wolski (2007) review¹⁹⁴ included all trials, irrespective of duration. Most were too short-term to assess cardiovascular outcomes, but used glycaemic control as the main outcome. Singh *et al.* (2007)²⁰⁰ provided another meta-analysis, but restricted to trials with at least 12 months of follow-up, and which reported cardiovascular events. Their inclusion criteria reduced the number of trials to only four. They found that rosiglitazone increased the risk of MI (RR 1.42; 95% CI 1.06 to 1.91). It also doubled the risk of heart failure, as had been known. However, the overall cardiovascular mortality was not increased (RR 0.9, CI 0.63 to 1.26). The finding that heart failure is increased (with both glitazones), but that cardiovascular death was not, was also reported in yet another meta-analysis by Lago *et al.* (2007).²⁰¹

The NICE GDG reviewed the evidence up to the end of 2007, including trials and statements from regulatory bodies, the EMEA, the FDA and the MHRA. It noted that the new glycaemic control studies did not change what was already known. The main issue was safety. The GDG commented in guideline CG 66⁶ that:

The GDG felt that there was certainly a 'signal' of increased risk of non-fatal myocardial infarction for rosiglitazone.

(The term 'signal' had been used by the FDA.)

But that:

On balance, despite reservations over rosiglitazone, it was not felt to be possible to unequivocally recommend a preference for pioglitazone in all circumstance, but rather to allow the choice of agent to rest with the person with diabetes and their advisor, taking account of the then regulatory advice (which may yet change).

The GDG continued:

However, the issues over fracture and fluid retention/cardiac failure and the costs

of these drugs led the GDG to conclude that the TZDs could not generally replace sulphonylureas as second line therapy, except where sulphonylureas were contraindicated by particular risk of hypoglycaemia.

However, the GDG then went on to note that:

The health economic modelling appeared to identify that these drugs, in particular the then more highly priced rosiglitazone, were not cost-effective compared to insulin therapy.

But hypothesised that this might not apply in people of higher body weight, in whom insulin resistance was marked and weight gain common with insulin treatment.

If a patient is going to receive a glitazone, the key issue is whether pioglitazone is safer than rosiglitazone. If so, the next GDG may wish to recommend that rosiglitazone should not be used.

Recent evidence

No new trials of glitazones with hard clinical outcomes, which were not known to the previous guideline group, were found.

We did find a trial that reported proxy outcomes. In the PERISCOPE trial, Nissen *et al.* (2008)²⁰² compared pioglitazone with glimepiride (a sulphonylurea) to see if there were any differences in progression of coronary artery disease. A total of 543 patients had coronary intravascular ultrasonography to measure the extent of coronary atherosclerosis, were randomised to pioglitazone or glimepiride, and had their coronary investigation repeated 18 months later. The investigators were asked to try to achieve an HbA_{1c} level of < 7%. Baseline HbA_{1c} levels were identical in the two groups (7.4%), but, over time the glimepiride group developed slightly higher levels – HbA_{1c} 7.0% versus 6.9% (from the text: ‘figure 2 suggests that by study end the difference was about 0.3%’).

The main outcome measure was the mean atheroma volume. This increased by 0.73% (95% CI 0.33 to 1.12) in the glimepiride group but decreased by 0.16% (–0.57% to +0.25%) in the pioglitazone group. The clinical significance of this small difference is uncertain, and, if the effect was due to the insulin-sensitising pioglitazone having advantages over the insulin secretagogue glimepiride, then, as the accompanying editorial

points out, the more cost-effective approach would have been to compare metformin with a sulphonylurea.²⁰³

A claim has been made recently that similar results have been obtained with rosiglitazone. These come from an unpublished trial, called VICTORY (Vein-Coronary Atherosclerosis and Rosiglitazone after bypass surgery). The results were presented at the American College of Cardiology 2008 conference, and the claim is reported in a newsletter, *Heartwire* (10 April 2008).²⁰⁴ The data reported are of atheroma plaque volume, with a smaller percentage increase in those on rosiglitazone compared with those on placebo. Two comments are necessary. First, atheroma increased in both groups. Second, the difference was not statistically significant (the *p*-value was 0.22). Further assessment must await full publication, but the details available at present do not justify the claim that the effect of rosiglitazone is similar to those seen with pioglitazone in PERISCOPE.

As reported in the recent guideline, a meta-analysis of the risk of cardiovascular events with pioglitazone was carried out by Lincoff *et al.* (2007)²⁰⁵ (who include Nissen and Wolski, who undertook the similar meta-analysis for rosiglitazone). Based on 19 trials with 16,930 participants, they concluded that pioglitazone was associated with a reduced risk of death, MI or stroke. They speculate that the differences in cardiovascular risk between rosiglitazone and pioglitazone are related to different effects on blood lipids (pioglitazone having a greater reduction in triglycerides and an increase in HDL cholesterol).

This meta-analysis included only trials funded by the manufacturer, because the authors used patient level data obtained from Takeda. Because most trials were short term and had relatively small numbers, around 80% of the events came from the PROactive trial.

Fractures

In the PERISCOPE trial, fractures occurred in 3% of the pioglitazone group but in none of the sulphonylurea group (*p* = 0.004).

Fracture risk has been reported in other studies. Kahn *et al.* (2006)²⁰⁹ in the ‘durability’ study (ADOPT) reported that 9.3% of women on rosiglitazone had fractures compared with 5.1%

on metformin and 3.5% on glibenclamide. The increases were in fractures of upper limb and foot, rather than in the classical osteoporosis-associated neck of femur and vertebrae. There was no difference in men.

A case-control study by Meier *et al.* (2008),²⁰⁶ using British general practice data from General Practice Research Database, also found that use of glitazones was associated with increased fracture rates. No such increase was seen with other oral diabetes drugs.

A letter to physicians issued by Takeda Pharmaceuticals, and posted on the US FDA website²⁰⁷ reported an analysis of its clinical trials database on pioglitazone. They compared the incidence of fractures in over 8100 patients treated with pioglitazone compared to over 7400 patients treated with a comparator.

The fracture incidence calculated was 1.9 fractures per 100 patient-years in women treated with pioglitazone and 1.1 fractures per 100 patient-years in women treated with a comparator. The observed excess risk of fractures for women in this data set on pioglitazone is therefore 0.8 fractures per 100 patient-years of use. There was no increased risk of fracture identified in men.

The letter stated 'the risk of fracture should be considered in the care of female patients with type 2 diabetes mellitus who are currently being treated with pioglitazone, or when initiation of pioglitazone treatment is being considered'.

What have other organisations said about rosiglitazone?

The FDA convened an advisory committee which concluded that:²⁰⁸ 'The use of rosiglitazone for the treatment of type 2 diabetes was associated with a greater risk of myocardial ischemic events than placebo, metformin or sulphonylurea'.

However, the advisory committee did not recommend that rosiglitazone be removed from the market. It asked for label warnings, educational efforts and further trials.

The FDA issued a statement on 14 November 2007, with the key message being as follows:²⁰⁹

- A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared Avandia to placebo, showed Avandia to be associated with an increased risk of myocardial ischemic events such as angina or MI. Three other studies (mean duration 41 months; 14,067 patients) comparing Avandia to some other approved OAD agents, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

Health Canada issued a warning letter announcing new restrictions on the use of rosiglitazone on 6 November 2007, the key messages being:²¹⁰

- Rosiglitazone is no longer approved for use alone to treat type 2 diabetes, except when metformin use is contraindicated or not tolerated.
- Rosiglitazone is no longer approved for use with a sulphonylurea drug (such as glyburide), except when metformin is contraindicated or not tolerated.
- Rosiglitazone should not be used if you have heart failure, or have experienced heart failure in the past.
- Patients who are taking rosiglitazone, especially those with underlying heart disease, or those who are at high risk of heart attack or heart failure, should talk to their doctor about the benefits and risks of continuing rosiglitazone therapy.
- Rosiglitazone should not be taken if you are using insulin.
- Rosiglitazone should not be used in 'triple therapy'.

These restrictions were based on advice from the Scientific Advisory Committee on metabolic and endocrine therapies (SAC-MET). The minutes of the meeting on 16 November 2007 give little detail for confidentiality reasons, but one comment was:²¹¹ 'The Committee expressed concern that the risk data on rosiglitazone were inconclusive'.

The recommendations are curious, in that they say that rosiglitazone can be used when metformin cannot, but do not mention pioglitazone. Given that the evidence suggests cardiovascular harm with rosiglitazone but benefit with pioglitazone, they might have suggested that if metformin was not tolerated, pioglitazone should be the glitazone of choice.

The *Drug and Therapeutics Bulletin* reassessed the glitazones in April 2008.²¹² As regards glycaemic control, the conclusions were that:

- the glitazones were useful in dual combination with metformin or a sulfonylurea in patients who could not tolerate one or other of those
- there was no convincing evidence of any benefits over metformin or a sulfonylurea as monotherapy
- evidence for their use in triple therapy was weak, and that they should be reserved for patients in whom insulin was contraindicated or poorly tolerated
- if a glitazone was thought to be necessary, pioglitazone was probably safer.

Two other UK bodies have issued advice:

The *Midlands Therapeutics Reviews and Advisory Committee (MTRAC)* reviewed both rosiglitazone and pioglitazone in March 2008.^{213,214} They concluded that rosiglitazone should not be used: 'Rosiglitazone cannot be recommended for prescribing, based on the current concerns about potential cardiovascular adverse effects and the lack of evidence for improved patient-oriented outcomes'.

Pioglitazone glitazone was classed as suitable for restricted prescribing, but with a low place in therapy.

The *diabetes managed clinical network for Greater Glasgow and Clyde*, as reported in *The Scotsman* of 8 May 2008,²¹⁵ has recommended that no new patients should be started on rosiglitazone, and that GPs should look carefully at those already taking it. Some consultants favoured withdrawing rosiglitazone completely.

The *consensus group from ADA and EASD*²¹⁶ issued an update about the glitazones to its algorithm on treatment for type 2 diabetes. The update reserved judgement:

At this time, we do not view as definitive the clinical trial data regarding increased or decreased risk of myocardial infarctions with rosiglitazone or pioglitazone, respectively.

On the other hand, we do believe that the weight of the new information ...should prompt clinicians to consider more carefully whether to use this class of drugs versus insulin or sulfonylureas ...

and

The current decision not to remove either or both of the glitazones from the algorithm represents a balance between the preservations of options to treat a challenging and progressive disease, and the recent unfavourable evidence.

The *Australian National Prescribing Service* issued notes on rosiglitazone in December 2007²¹⁷ and on pioglitazone in March 2008.²¹⁸ They also issued a media release in December 2007 saying that:²¹⁹ 'Prescribers should also be aware of a possible increased risk of myocardial ischaemia in patients taking rosiglitazone. The same risk has not been shown with pioglitazone but the possibility cannot be dismissed'.

The December note on rosiglitazone suggested that in patients failing on dual therapy, clinicians should consider using insulin rather than rosiglitazone because:

- Insulin reduces the risk of diabetic complications, whereas the effect of rosiglitazone on diabetes-related morbidity and mortality is still unclear.
- The long-term safety profile of insulin is better defined. The only completed long-term trial of rosiglitazone reported significantly higher rates of heart failure, oedema and fracture among the rosiglitazone group than among those using metformin or glibenclamide.
- Greater reductions in HbA_{1c} levels have been reported among patients with poor glycaemic control who were treated with insulin rather than rosiglitazone.

The pioglitazone note in March 2008 was quite similar. Neither note suggested that pioglitazone should be preferred to rosiglitazone. A practice review for GPs dated February 2008 suggested that:²²⁰ 'If metformin and a sulphonylurea no longer control blood glucose, start insulin promptly. Trialling a glitazone as part of triple oral therapy may be an option but insulin should be started if hyperglycaemia is still uncontrolled after 3 months'.

More on the safety of glitazones

As new trials are reported, they are being added to new meta-analyses. Dahabreh (2008)²²¹ updated the Nissen and Wolski (2007)¹⁹⁴ meta-analysis with the results from the DREAM (Diabetes REduction

Assessment with ramipril and rosiglitazone Medication)²²² and ADOPT²⁹ trials, and the interim report from the RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes) trial.¹⁹⁶ [Note: DREAM included patients with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), not diabetes.] He noted the debate about the methods for doing meta-analysis when some trials had no events, and carried out the analyses using methods that allowed inclusion of such trials, as well as the Peto method, which was used in the original Nissen and Wolski meta-analysis.

The results were consistent with the previous finding of an increase in MI with rosiglitazone but ORs were slightly less, and in two of the five meta-analyses their CIs sometimes just overlapped with no increase (95% CIs of 0.97 to 1.59 and 0.96 to 1.57).

It is curious that rosiglitazone appears to increase non-fatal MI but not cardiovascular death. It may simply be a function of numbers, because the CV death ORs have much wider CIs.

Another meta-analysis by Mannucci *et al.* (2008)¹⁷⁴ included 84 published and 10 unpublished trials of pioglitazone compared with placebo or active comparators, but excluded the PROactive trial. They reported a reduction of all-cause mortality with pioglitazone (OR 0.30; 95% CI 0.14 to 0.63, $p < 0.05$), but no significant effect on non-fatal coronary events.

Several new studies have asked why rosiglitazone should increase cardiovascular events but pioglitazone does not. Most have concluded that the likely reason is that while the two glitazones have the same effects on glycaemic control, and the same side effects of fluid retention and heart failure, they have different effects on blood lipids. Berneis *et al.* (2008)²²³ (based on data from the abstract only) carried out a very small crossover trial in 9 patients, giving them all 12 weeks on pioglitazone and 12 weeks on rosiglitazone. Total cholesterol increased more on rosiglitazone (need absolute levels) than on pioglitazone ($p = 0.04$), and triglycerides increased on rosiglitazone but decreased on pioglitazone ($p = 0.004$).

Chappuis *et al.* (2007)²²⁴ also studied patients on both glitazones, this time with 17 patients having 12 weeks on each. The effects of HbA_{1c} level were similar, but triglyceride and cholesterol levels were lower with pioglitazone.

Deeg *et al.* (2007)²²⁵ carried out a much larger comparison, with 369 randomised to pioglitazone and 366 to rosiglitazone. The two drugs had differing effects on lipids, with rosiglitazone having the more atherogenic pattern, including higher low-density lipoprotein (LDL) cholesterol levels.

Norris *et al.* (2007)²²⁶ carried out a systematic review of the comparative effectiveness and safety of pioglitazone and rosiglitazone. They concluded that effects of glycaemic control, weight and most adverse events were similar, but that rosiglitazone may increase total cholesterol compared with pioglitazone. However, they concluded they had insufficient evidence with which to compare cardiovascular event rates.

Data from the VADT (Veterans Affairs Diabetes Trial) have been used to assert that rosiglitazone does not cause cardiovascular harm [Duckworth (2009)²²⁷]. However, this evidence seems dubious, given that most patients in both arms were taking rosiglitazone.

The effect of all this has been that sales of rosiglitazone have fallen. A report in the newsletter *Endocrine Today*²²⁸ states that sales fell from US\$617M worldwide in the first quarter of 2007 to US\$327M in the fourth quarter (although it does not say whether the price was reduced). A Canadian report notes that there was a sudden decline in the use of rosiglitazone after the publication of the Nissen and Wolski meta-analysis,¹⁹⁴ accompanied by an increase in the use of pioglitazone.²²⁹

Points raised in the consultation process

In their responses to the draft guideline, GlaxoSmithKline referred to new studies that provided safety data. The studies cited were the ACCORD (Action to Control Cardiovascular Risk in Diabetes Study)²³⁰ and the VADT.²²⁷

The ACCORD study was a trial of intensive versus standard therapy, aiming at a separation in HbA_{1c} level. The intensive group did worse with higher mortality and no reduction in cardiovascular events. In the intensive group, 2.6% of patients died from cardiovascular causes, versus 1.8% in the standard group ($p = 0.02$); 91% of the intensive group were treated with rosiglitazone versus 58% of the standard group. So the ACCORD study did not provide new data on the safety of rosiglitazone.

Summary

Little new has emerged since the last guideline was produced. Pioglitazone and rosiglitazone appear to have similar effectiveness in controlling hyperglycaemia, and similar toxicity in terms of oedema, heart failure and (in women only)

fractures. However, the current evidence suggests that rosiglitazone slightly increases cardiovascular mortality but that pioglitazone reduces it. Most of the regulatory and prescribing advisory bodies have asked for warnings on rosiglitazone but have allowed its continued use. Some have suggested that, in future, pioglitazone be used in preference.

Chapter 6

Clinical effectiveness of pioglitazone in combination with insulin

Objectives

In this chapter, we assess the effects of the combination of insulin treatment with pioglitazone compared with:

- insulin treatment alone, and
- pioglitazone treatment alone.

Methods

Inclusion criteria

Types of studies

We considered RCTs with a minimum duration of 12 weeks, although trials of at least 24 weeks' duration were preferred.

Types of participants

Patients with type 2 diabetes, of any age and gender.

Types of interventions

Pioglitazone in combination with any insulin regimen (including insulin plus metformin).

Comparisons could include:

A:

- long-acting insulin plus pioglitazone versus long-acting insulin alone
- long-acting insulin plus metformin plus pioglitazone versus long-acting insulin plus metformin
- twice-daily mixture plus pioglitazone versus twice-daily mixture
- twice-daily mixture plus metformin plus pioglitazone versus twice-daily mixture plus metformin.

B:

- long-acting insulin plus pioglitazone versus pioglitazone alone
- long-acting insulin plus metformin plus pioglitazone versus pioglitazone plus metformin

- twice-daily mixture plus pioglitazone versus pioglitazone alone
- twice-daily mixture plus metformin plus pioglitazone versus pioglitazone plus metformin.

There may be trials of the above with sulfonylurea as well as metformin.

Types of outcomes

We planned to consider the following outcome measures:

- HbA_{1c}
- frequency of hypoglycaemia, especially if severe
- glycaemic excursions, including postprandial hyperglycaemia
- total daily dose of insulin
- weight gain or loss
- complication rates – retinopathy, nephropathy, MI, angina, heart failure, stroke, amputation, death
- adverse events
- health-related QoL.

Search strategy

Relevant literature was identified, and comprehensiveness checked, by:

- searches of bibliographic databases, MEDLINE, Cochrane Library, and EMBASE
- checking reference lists of retrieved studies
- obtaining lists of published studies from manufacturers
- our peer review process.

Searches were also undertaken to identify emerging evidence, from conference abstracts and trial registers. Studies available only in abstract were included in the assessment of clinical effectiveness if there is a paucity of studies published in full in peer reviewed journals, but they were reported with appropriate caution. Our default position is for studies available only in abstract not to be used.

Authors of previous studies were not contacted.

Quality assessment of studies

Randomised controlled trials were assessed on the following criteria based on the NICE guidelines manual:

- method of randomisation
- allocation concealed
- participants and blinded
- outcome assessors blinded
- ITT analysis performed
- proportion of participants excluded/lost to follow-up
- power calculation
- groups comparable at baseline.

Again, overall quality of the trials was classified as good, moderate, or poor.

Data extraction

Data extraction was carried out by one researcher and a sample checked by another. Any disagreements were resolved through discussion, involving a third person if necessary.

Data analysis

The clinical effectiveness, relative to the key comparators, was assessed, in terms of difference in effect size.

Data were summarised in a meta-analysis and using tables and text. For dichotomous outcomes, ORs were calculated and a Mantel-Haenszel random effects model was used. For continuous outcomes, standardised mean differences were calculated and an inverse variance random effects model was used. Heterogeneity was assessed using the chi-squared test.

Systematic reviews

Search results

Eleven papers were identified as potentially relevant RCTs. Of these, eight fulfilled the inclusion criteria and compared pioglitazone plus insulin with insulin.^{231–238} One compared pioglitazone plus insulin with pioglitazone. The remaining trials were excluded because they did

not examine the comparison of interest, and one was the uncontrolled extension of a trial that seemed relevant but could not be identified (shown in *Table 24*).

Description of studies – insulin + pioglitazone vs insulin

Characteristics of the included trials are shown in Appendix 6.

Design

Seven trials were randomised double-blind placebo-controlled trials,^{231–233,235–238} while one trial was a randomised open-label trial.²³⁴ The studies had different emphases: Asnani *et al.* (2006)²³⁸ and Fernandez *et al.* (2008)²³² focused on vascular reactivity; Berhanu *et al.* (2007)²³¹ focused on reduction of insulin dosage; Mattoo *et al.* (2005)²³³ focused on glycaemic control, lipids and cardiovascular risk factors; Raz *et al.* (2005)²³⁴ and Rosenstock (2002)²³⁵ focused on glycaemic control; Scheen and Charbonnel (2006)²³⁶ focused on secondary prevention of macrovascular events; and Shah *et al.* (2007)²³⁷ focused on body fat distribution. Trial duration ranged between 12 and 36 weeks. Where stated, trials were sponsored by industry. Five trials were from the USA,^{231,232,235,237,238} one included centres from a range of European countries,²³⁶ and two included centres worldwide.^{233,234}

Participants

The trials included between 20 and 1760 participants, with between 10 and 896 participants in each comparison group. The total number of patients assessed was 3092. All studies included participants with previous inadequate glucose control [with different definitions, not reported for Shah *et al.* (2007)²³⁷]. Inclusion criteria with respect to previous treatment varied substantially. Only five trials^{232,233,235,237,238} required previous insulin treatment. Three trials^{233,235,238} required previous insulin therapy with or without OAD agents (where reported, previous insulin monotherapy ranged between 48% and 88%). The trial by Fernandez *et al.* (2008)²³² required previous insulin combination therapy,²³² and the trials by Shah *et al.* (2007)²³⁷

TABLE 24 Excluded RCTs – insulin plus pioglitazone versus insulin

Study	Reason for exclusion
Davidson (2006) ²³⁹	No insulin-only group
Rosenblatt (2001) ²⁴⁰	Open-label extension without single treatment of a trial that could not be identified

included only insulin-treated obese patients.²³⁷ Of the remaining trials, the trial by Berhanu *et al.* (2007)²³¹ required previous combination therapy with or without insulin, and in this trial, between 90% and 93% of patients had been on sulfonylurea plus metformin therapy without insulin. The study by Raz *et al.* (2005)²³⁴ required previous therapy with sulfonylurea (alone or as oral combination therapy) and over 80% of patients in that trial had been on sulfonylurea plus metformin previously. The study by Scheen and Charbonnel (2006)²³⁶ included patients previously on diet alone, oral agents, or insulin plus an oral agent and in that trial, over half of the patients (53%) had been on sulfonylurea plus insulin, and the second largest group had been on sulfonylurea monotherapy (24%). Where reported, mean age of participants was between 46 and 59 years, the comparison groups included between 35% and 60% of women, mean BMI was between 29 and 37 kg/m², and diabetes duration was between 6 and 14 years. The trial by Berhanu *et al.* (2007)²³¹ included between 50% and 59% of Hispanic participants, and the study by Fernandez *et al.* (2008)²³² included only Mexican–American participants.²³²

Interventions

The trials used pioglitazone doses up to 45 mg/day. Four trials used titration schemes for pioglitazone (up to 45 mg/day, usually starting at 15 mg/day).^{231,232,236,237} Three trials used fixed doses of 30 mg/day.^{233,234,238} Rosenstock (2002)²³⁵ compared two pioglitazone doses: 15 and 30 mg/day.

As concerns the insulin therapy, Asnani *et al.* (2006),²³⁸ Rosenstock (2002)²³⁵ and Scheen and Charbonnel (2006)²³⁶ only specified that insulin therapy was continued as before. Rosenstock (2002)²³⁵ used a single-blind insulin monotherapy lead-in period. Berhanu *et al.* (2007)²³¹ used a 4-week titration period for insulin (Humalog, Humulin 70/30 or Humulin N) and defined a target FPG of less than 140 mg/dl while avoiding hypoglycaemia. In the study by Fernandez *et al.* (2008)²³² patients could choose between multiple daily injections (basal bolus therapy using combination of insulin glargine at bedtime plus premeal insulin aspart) or continuous subcutaneous infusions (basal infusion and pre-meal boluses of insulin aspart) and defined targets for blood glucose values (fasting and pre-meal capillary blood glucose 80–120 mg/dl, 2 hours post-meal glucose < 160 mg/dl, bedtime glucose < 140 mg/dl). Mattoo *et al.* (2005)²³³ used a 3-month insulin intensification period before randomisation; the

insulin dose was reduced by 10% at randomisation to avoid hypoglycaemia and adjusted thereafter, based on self-monitored blood glucose levels. Raz *et al.* (2005)²³⁴ used biphasic insulin aspart 30/70. In the study by Scheen and Charbonnel (2006),²³⁶ concomitant therapy with metformin was used by 47–52%, sulfonylurea alone by 16%, and metformin plus sulfonylurea by 10–11%. Shah *et al.* (2007)²³⁷ did not give details of the insulin therapy.

Various studies specified cointerventions. Asnani *et al.* (2006)²³⁸ allowed stable lipid lowering therapy with statins and antihypertensive therapy (including ACE inhibitors in all patients). In the study by Berhanu *et al.* (2007)²³¹ statins and metformin were continued as before. Fernandez *et al.* (2008)²³² changed all patients previously on angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers for blood pressure control to alpha-methyl dopa. Fernandez *et al.* (2008)²³² and Rosenstock (2002)²³⁵ allowed lipid-lowering therapy as used before the study.

Outcomes

The trials used a variety of primary end points. HbA_{1c} level was the primary end point in the studies by Mattoo *et al.* (2005),²³³ Raz *et al.* (2005)²³⁴ and Rosenstock (2002).²³⁵ The primary end point in the study by Asnani *et al.* (2006)²³⁸ was flow-mediated dilatation, in the study by Berhanu *et al.* (2007)²³¹ it was change in insulin dosage, Fernandez *et al.* (2008)²³² used vascular analyses as primary end point, in the study by Scheen and Charbonnel (2006)²³⁶ it was a composite macrovascular end point, and in the study by Shah *et al.* (2007)²³⁷ it was body fat distribution. All studies reported on end-of-study HbA_{1c} values; six studies reported on hypoglycaemia;^{231–236} one study reported on glycaemic excursions;²³⁴ six studies reported on total daily dose;^{231–236} six studies reported on weight change;^{231–235,237} five studies reported on adverse events; and six studies reported on lipid parameters,^{231–235,238} while none of the studies reported on rates of diabetic secondary complications or health-related QoL.

Quality of studies – insulin + pioglitazone vs insulin

Details of the quality of included trials are shown in Table 25.

For four^{231,233,234,238} of the eight trials, randomisation was adequate, whereas for the remaining four trials the randomisation procedure was not reported or unclear. Three trials^{231,233,238} had adequate

TABLE 25 Quality of included trials – insulin plus pioglitazone versus insulin

Study	Method of randomisation	Allocation concealment	Blinding	ITT data analysis	Percentage who completed trial	Power calculation	Similarity of groups at baseline	Sponsorship/author affiliation
Asnani (2006) ²³⁸	Carried out by research pharmacist using predetermined randomisation code	Yes	Double blind	Not reported	PIO + Ins: 80% P + Ins: 80%	Yes (on flow-mediated dilatation)	HbA _{1c} higher at baseline for PIO + Ins group (10% vs 8.7%) but not statistically significant	Takeda, National Institutes of Health
Berhanu (2007) ²³¹	Computer-generated schedule	Yes	Double blind	Yes	PIO + Ins: 87.3% P + Ins: 91.1%	Yes (on mean change in insulin dose)	Insulin group had significantly higher BMI (31.8 vs 30.7 kg/m ²) and longer diabetes duration (8.5 vs 7.7 years)	Takeda Global R&D Centre
Fernandez (2008) ²³²	Not reported	Not reported	Double blind	Not reported	Unclear – all?	Yes (on vascular parameters)	Yes	American Diabetes Association, Takeda Pharmaceuticals
Mattoo (2005) ²³³	Central randomisation table administered by an automated interactive voice system	Yes	Double blind	Yes	PIO + Ins: 90% P + Ins: 92%	Yes (on change in HbA _{1c})	Yes	Eli Lilly, Takeda Europe
Raz (2005) ²³⁴	Unclear ('assignment of lowest available patient number')	Not reported	No	Yes	PIO + Ins: 78% Ins mono: 77%	Yes (on change in HbA _{1c})	Yes	Novo Nordisk
Rosenstock (2002) ²³⁵	Not reported	Not reported	Double blind	Yes	PIO 15 + Ins: 84% PIO30 + Ins: 91% P + Ins: 88%	Not reported	Yes	Takeda Pharmaceuticals
Scheen (2006) ²³⁶	Central interactive voice-response system	Not reported	Double blind	Yes	Not reported	Yes	Not reported	Takeda Europe, Eli Lilly
Shah (2007) ²³⁷	Not reported	Not reported	Double blind	Not reported	Not reported	Not reported – small numbers, probably underpowered	Not reported	Not reported

Ins, insulin; P, placebo; PIO, pioglitazone.

allocation concealment, whereas the rest of the trials did not report on allocation concealment. All but one trial²³⁴ were described as double blind. Five trials used ITT analysis.^{231,233–236} Five trials reported on follow-up rates^{231,233–235,238} and in those trials, between 77% and 92% of participants completed the trial, without any significant differences between comparison groups. Six of the eight trials reported that they had carried out a power calculation.^{231–233,235,236,238} Two trials (reported as abstracts)^{236,237} did not report relevant baseline characteristics, five trials reported that there comparison groups were similar at baseline,^{232,233–235,238} while Berhanu *et al.* (2007)²³¹ stated that participants in the placebo group had a slightly higher BMI at baseline and longer diabetes duration, but it was unclear whether these differences were significant. All but one trial²³⁷ reported on sources of funding, and all funding included industry funding.

Results – insulin + pioglitazone vs insulin

Details of the results for included trials for insulin plus pioglitazone versus insulin are shown in Table 26.

HbA_{1c}

All studies reported HbA_{1c} values and could be included in the meta-analysis (Figure 11). Baseline HbA_{1c} values were between 7.6% and 10% in the pioglitazone-plus-insulin groups, and between 7.8% and 9.8% in the insulin-without-pioglitazone groups. End-of-study HbA_{1c} values were significantly lower in the groups taking pioglitazone plus insulin than in the groups taking insulin without pioglitazone (WMD –0.58%, 95% CI –0.70 to –0.46, $p < 0.00001$). There was no significant heterogeneity. In the study by Mattoo *et al.* (2005),²³³ 18% of patients on pioglitazone plus insulin and 6.9% of patients on insulin without pioglitazone attained HbA_{1c} values of below 7.0%. There was no significant difference between patients using two or fewer daily injections and patients using three or more. Similarly, there was no significant difference between patients who had previously been on OAD agents and those who had not. In the study by Rosenstock (2002),²³⁵ no significant difference in HbA_{1c} level was reported for the group using 15 mg/day of pioglitazone and the group using 30 mg/day.

Hypoglycaemia

Six studies reported on hypoglycaemia outcomes and could be summarised in a meta-analysis (Figure 12). There were marginally more

patients with hypoglycaemic episodes in the pioglitazone-plus-insulin groups than with insulin without pioglitazone (RR 1.27, 95% CI 0.99 to 1.63, $p = 0.06$). The results showed significant heterogeneity ($p = 0.001$). The study by Raz *et al.* (2005),²³⁴ which used biphasic insulin aspart 30 (BIAsp 30) rather than other insulin regimens contributed most to the heterogeneity. There is evidence to suggest that BIAsp 30 is associated with a reduced rate of nocturnal and major episodes of hypoglycaemia compared with other types of insulin.²⁴¹ After eliminating this study from the analysis, there remained moderate heterogeneity ($I^2 = 57%$, $p = 0.05$) and there was significantly more hypoglycaemia in the pioglitazone-plus-insulin groups (RR 1.40, 95% CI 1.14 to 1.73, $p = 0.002$).

Dose

Six studies^{231–236} reported insulin doses (as units per kg per day or as units per day). Only two studies reported SDs, so a meta-analysis could not be carried out reliably. Of the six studies, four found that the insulin-plus-pioglitazone groups used significantly less insulin than the insulin without pioglitazone groups (WMD –0.19 U/kg/day or –12.03 U/day). The remaining two studies did not report any p -values. Insulin dose ranged between 42 and 64 U/day, or 0.5–1 U/kg/day in the pioglitazone groups, and between 55 and 70 U/day or 0.7–1.2 U/kg/day in the groups taking no pioglitazone.

Weight change

Six studies reported weight change.^{231–235,237} However, only one of the studies reported a measure of variability, so a meta-analysis could not be carried out reliably. In most studies, patients in the insulin-without-pioglitazone groups gained less weight than patients in the insulin-plus-pioglitazone groups (mean difference 2.91 kg, range 3.85 to –3.50 kg), but no p -values were reported. Weight change ranged between +1.4 and +4.4 kg in the pioglitazone-plus-insulin groups, and between –0.04 and +4.9 kg in the insulin-only groups.

Lipid parameters

Four studies reported results for serum triglycerides.^{231,232,234,235}

Of the four studies, only two^{231,235} found significantly reduced triglyceride values in the pioglitazone groups (reductions of between 0.44 and 0.70 mmol/l in the pioglitazone groups compared with the insulin-only groups).

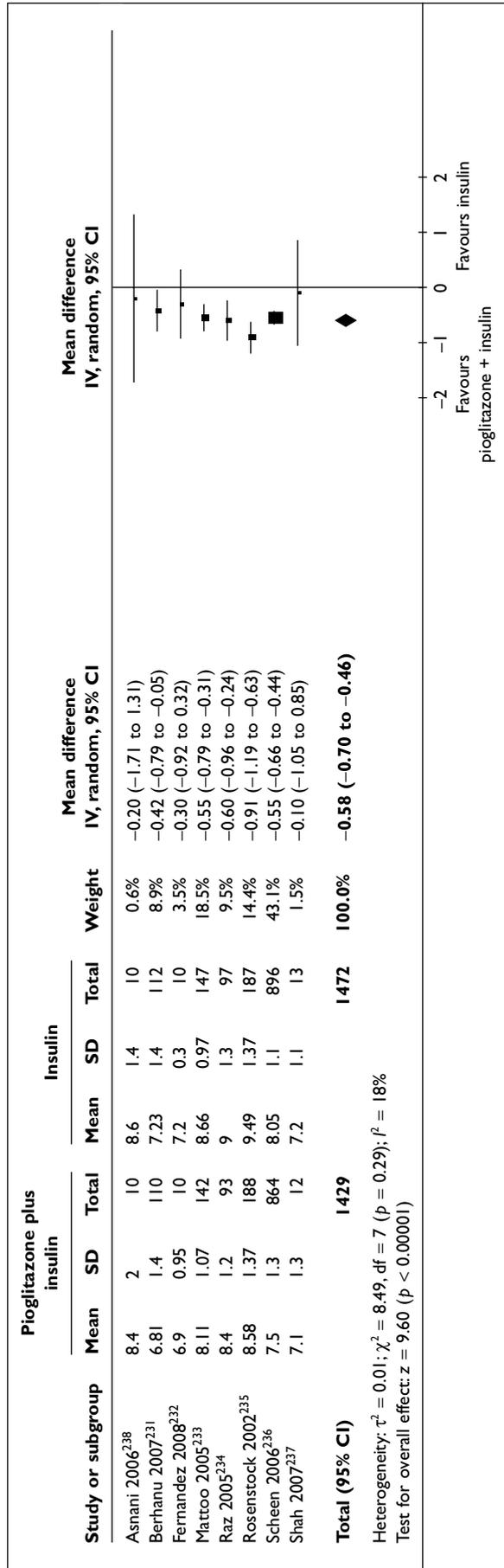


FIGURE 11 Forest plot of HbA_{1c} results – pioglitazone and insulin.

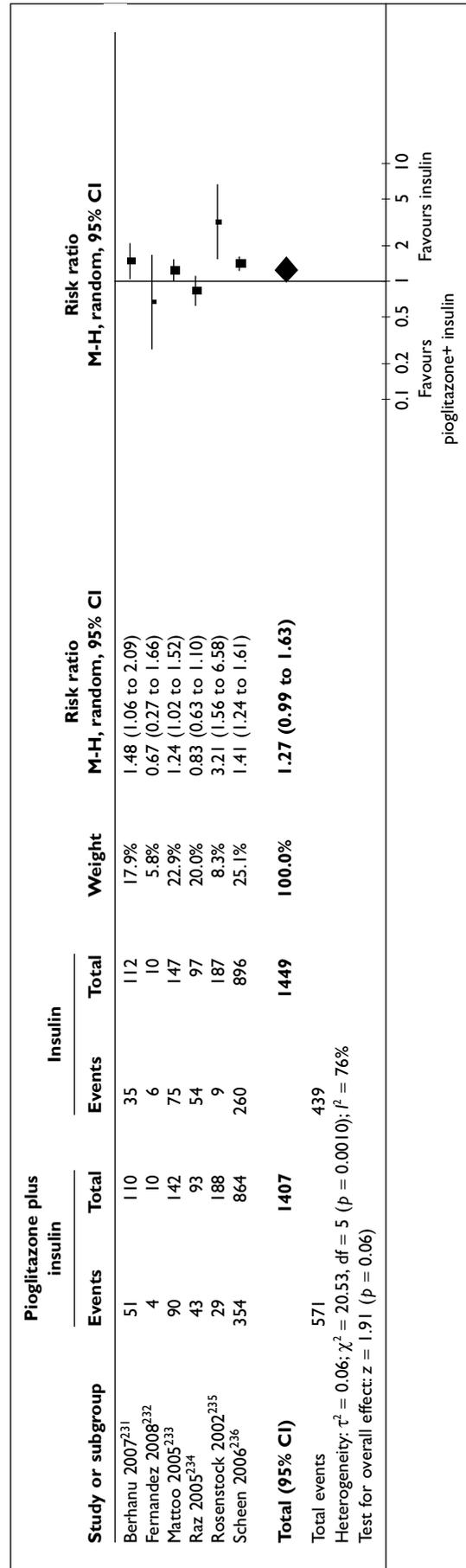


FIGURE 12 Forest plot of frequency of hypoglycaemia – pioglitazone and insulin.

Four studies reported on total serum cholesterol.^{231,232,234,235}

None of the studies found any significant difference in total cholesterol between the pioglitazone-plus-insulin groups and the insulin-without-pioglitazone groups.

Four studies reported on HDL cholesterol.^{231–233,235} Overall, HDL cholesterol was increased by between 0.10 and 0.18 mmol/l in the pioglitazone groups compared with the insulin-only groups.

Four studies reported on LDL cholesterol,^{231–233,235} with none finding any significant difference between the pioglitazone-plus-insulin groups and the insulin-without-pioglitazone groups.

Adverse events

Where reported, there did not appear to be any significant difference in withdrawals due to adverse events between the pioglitazone-plus-insulin groups and the insulin-without-pioglitazone groups. The only adverse event (apart from weight gain) reported as occurring more frequently with pioglitazone was (peripheral) oedema, which was generally classified as mild to moderate, and which would be manageable with a diuretic. However, *p*-values were generally not reported.

Description of studies – insulin + pioglitazone vs pioglitazone

There was only one trial, published as an abstract, comparing pioglitazone with pioglitazone plus insulin. Characteristics of the included trial are shown in Appendix 7.

The focus of the study by Raskin (2006)^{242,243} was on the safety and efficacy of BIAsp 30 (30% soluble and 70% protaminated insulin aspart) in insulin-naive patients with type 2 diabetes, who are taking any two OAD agents. The study was a randomised parallel-group trial with a duration of 34 weeks and was carried out in the USA.

Participants

The trial included 181 participants (93 and 88 in each comparison group). The trial included insulin-naive patients with type 2 diabetes, with a HbA_{1c} value of between 7.5% and 12%, and who were taking any two OAD agents. No demographic characteristics were reported.

Interventions

The trial compared optimised treatment with a combination of pioglitazone and metformin with BIAsp 30 added to an optimised treatment with combination of pioglitazone and metformin. BIAsp 30 was initialised at 6 U twice per day (pre-breakfast and pre-supper) and titrated to target blood glucose values of 4.4–6.1 mmol/l by an algorithm-directed forced titration. There was an 8-week run-in phase during which treatment was changed to metformin (2500 mg/day) and pioglitazone (30 or 45 mg/day).

Outcomes

The primary end point was not reported (but was presumably HbA_{1c} level). Apart from HbA_{1c} level, minor hypoglycaemia (blood glucose < 3.1 mmol/l) and weight were reported.

Quality

The abstract gave no information on the method of randomisation, allocation concealment, blinding, ITT analysis, the percentage of participants who completed the trial, whether a power calculation was carried out, or whether the comparison groups were comparable at baseline. Funding was by Novo Nordisk.

Results – insulin + pioglitazone vs pioglitazone

The trial by Raskin *et al.* (2006)^{241,242} found a significantly greater reduction of HbA_{1c} level at study end in the BIAsp 30-plus-metformin-plus-pioglitazone group than in the metformin-plus-pioglitazone group (–1.5% versus –0.2%, *p* < 0.0001)(Table 27). There were also larger proportions of patients reaching HbA_{1c} values of less than 7% in the BIAsp 30-plus-metformin-plus-pioglitazone group (76.3% versus 24.1% in the metformin-plus-pioglitazone group), as well as values less than or equal to 6.5% (59.1 versus 11.5%), values less than or equal to 6% (33.3 versus 2.3%) and values less than or equal to 5.5% (14.0 versus 0%). However, the BIAsp 30-plus-metformin-plus-pioglitazone group had significantly more minor hypoglycaemic events than the metformin-plus-pioglitazone group (8.3 versus 0.1 events/year, *p* < 0.001). The patients in the BIAsp 30-plus-metformin-plus-pioglitazone group also gained significantly more weight than the patients in the metformin-plus-pioglitazone group (4.6 versus 0.8 kg, *p* < 0.05). Peripheral oedema occurred in 10% of patients in the BIAsp

TABLE 26 Results of included trials – insulin plus pioglitazone versus insulin

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
HbA_{1c}					
Asnani (2006) ²³⁸	HbA _{1c} (%)	PIO + Ins: 10.0, SD 2.3% P + Ins: 8.7, SD 2.3%	PIO + Ins: 8.4, SD 2.0% P + Ins: 8.6, SD 1.4%		p not reported (p < 0.05 for PIO before and after)
Berhanu (2007) ²³¹	HbA _{1c} (%)	PIO + Ins: 8.4, SD 0.13% P + Ins: 8.6, SD 0.13%	PIO + Ins: 6.81% P + Ins: 7.23%	PIO + Ins: -1.6, SE 0.11% P + Ins: -1.4, SE 0.11%	p = NS
Fernandez (2008) ²³²	HbA _{1c} (%)	PIO + Ins: 9.0, SD 0.7% P + Ins: 9.2, SD 0.4%	PIO + Ins: 6.9, SD 0.3% P + Ins: 7.2, SD 0.1%		
Mattoo (2005) ²³³	HbA _{1c} (%)	PIO + Ins: 8.85 SE 0.11% P + Ins: 8.79 SE 0.1%	PIO + Ins: 8.11, SE 0.09% P + Ins: 8.66, SE 0.08%	PIO + Ins difference between groups: 0.69, SE 0.09% P + Ins: -0.13%	p < 0.002
	Percentage attaining HbA _{1c} < 7.0%		PIO + Ins: 18% P + Ins: 6.9%		No significant difference
	HbA _{1c} subgroups: patients using ≤ 2 or ≥ 3 insulin injections				No significant difference for subgroups
	HbA _{1c} subgroups: previous use of OAD agents			Previous use of oral agents PIO + Ins: -0.90, SE 0.14% P + Ins: -0.11, SE 0.13% No previous use of oral agents PIO + Ins: -0.65, SE 0.11% P + Ins: -0.2, SE 0.12%	
Raz (2005) ²³⁴	HbA _{1c} (%)	PIO + Ins: 9.6, SD 1.3% Ins mono: 9.5, SD 1.3%	PIO + Ins: 8.4, SD 1.2% Ins mono: 9.0, SD 1.3%		p = 0.008
Rosenstock (2002) ²³⁵	HbA _{1c} (%)	PIO15 + Ins: 9.75, SE 0.1% PIO30 + Ins: 9.84, SE 0.1% P + Ins: 9.75, SE 0.1%		PIO15 + Ins: -0.99, SE 0.08% PIO30 + Ins: -1.26, SE 0.08% P + Ins: -0.26, SE 0.08%	p < 0.01 pioglitazone vs placebo
Shah (2007) ²³⁷	HbA _{1c} (%)	PIO + Ins: 7.6% P + Ins: 7.8%	PIO + Ins: 7.1% P + Ins: 7.2%		p not reported, presumably non-significant
Scheen (2006) ²³⁶	HbA _{1c} (%)	PIO + Ins: 8.4% P + Ins: 8.5%	PIO + Ins: 7.47% P + Ins: 8.05%	PIO + Ins: -0.93% P + Ins: -0.45%	p < 0.0001

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
Hypoglycaemia					
Berhanu (2007) ²³¹	Patients with hypoglycaemic events		PIO + Ins: 46% (91% mild) P + Ins: 31% (66% mild)		$p < 0.005$
	Severe hypoglycaemia (episodes)		PIO + Ins: $n = 0$ P + Ins: $n = 4$		p not reported
Fernandez (2008) ²³²	Patients with hypoglycaemic episodes		PIO + Ins: $n = 4$ P + Ins: $n = 6$		
Mattoo (2005) ²³³	Patients with subjective hypoglycaemic episodes		PIO + Ins: 63.4% P + Ins: 51.0%		$p < 0.05$
	Clinical hypoglycaemic episodes (blood glucose < 2.8 mmol/l)				No significant difference
Raz (2005) ²³⁴	Major hypoglycaemic episodes		None		
	Minor hypoglycaemic episodes (% patients)		PIO + Ins: 12% Ins mono: 15%		p not reported
	Minor hypoglycaemic episodes (episodes)		PIO + Ins: 15 Ins mono: 47		p not reported
	Symptoms only (% patients)		PIO + Ins: 34% Ins mono: 40%		p not reported
	Symptoms only (episodes)		PIO + Ins: 115 Ins mono: 171		p not reported
	Incidence (per patient-week for all episodes)		PIO + Ins: 0.083 Ins mono: 0.132		$p < 0.05$
	Nocturnal hypoglycaemia (episodes)		PIO + Ins: 0 Ins mono: 8		p not reported
Rosenstock (2002) ²³⁵	Hypoglycaemia		PIO 15 + Ins: 8% PIO 30 + Ins: 15% P + Ins: 5% (all considered mild to moderate)		
Scheen (2006) ²³⁶	Hypoglycaemia (not specified further)		PIO + Ins: 41% P + Ins: 29%		$p < 0.0001$

continued

TABLE 26 Results of included trials – insulin plus pioglitazone versus insulin (continued)

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
Glycaemic excursions					
Raz (2005) ²³⁴					Measurements before dinner, 90 minutes after dinner and at bedtime significantly lower in PIO + Ins group than in Ins-mono group
Total daily dose					
Berhanu (2007) ²³¹	Daily insulin dose	PIO + Ins: 55.8, SD 2.95 units P + Ins: 57.7, SD 2.95 units		PIO + Ins: -12.0, SE 1.84 units P + Ins: +0.8, SE 1.84 units Adjusted mean difference between groups: 12.7 units (95% CI -17.5 to -8.0)	p < 0.001
Fernandez (2008) ²³²	Daily insulin dose	All groups: ~1.2 U/kg/day	PIO + Ins: 1.0 U/kg/day P + Ins: ~1.2 U/kg/day		p not reported
Mattoo (2005) ²³³	Daily insulin dose	PIO + Ins: 0.96, SE 0.03 U/kg/day P + Ins: 0.92, SE 0.03 U/kg/day	PIO + Ins: 0.76, SE 0.02 U/kg/day P + Ins: 0.94, SE 0.02 U/kg/day	Difference between groups -0.18, SE 0.02 U/kg/day	p < 0.002
Raz (2005) ²³⁴	Daily insulin dose	PIO + Ins: 0.2 U/kg/day Ins mono: 0.3 U/kg/day	PIO + Ins: 0.5 U/kg/day Ins mono: 0.7 U/kg/day	PIO + Ins: +0.3 U/kg/day Ins mono: +0.4 U/kg/day	p = 0.002
Rosenstock (2002) ²³⁵	Daily insulin dose	PIO15 + Ins: 70.2, SE 34.0 U/day PIO30 + Ins: 72.3, SE 38.5 U/day P + Ins: 70.7, SE 33.5 U/day	PIO15 + Ins: 67.3, SE 33.5 U/day PIO30 + Ins: 64.2, SE 32.7 U/day P + Ins: 70.1, SE 33.9 U/day		p not reported
Scheen (2006) ²³⁶	Daily insulin dose	PIO + Ins: 47 U/day P + Ins: 47 U/day	PIO + Ins: 42 U/day P + Ins: 55 U/day		p < 0.0001; at final visit, insulin discontinued in 9% of PIO group and 2% of placebo group (p < 0.0001)
Weight change					
Berhanu (2007) ²³¹	Weight (kg)			PIO + Ins: +4.39 kg P + Ins: +2.42 kg	p not reported
Fernandez (2008) ²³²	Patients reporting weight gain			PIO + Ins: n = 10 P + Ins: n = 3	p not reported
Mattoo (2005) ²³³	Weight (kg)			PIO + Ins: +4.4 kg P + Ins: +1.7 kg	p not reported
Mattoo (2005) ²³³	Weight (kg)			PIO + Ins: +4.05, SE 4.03 kg P + Ins: +0.20, SE 2.92 kg	p not reported

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
Raz (2005) ²³⁴	Weight (kg)			PIO + Ins: +4.0 kg Ins mono: +2.2 kg	p not reported
	Patients experiencing weight gain (%)			PIO + Ins: 8% Ins mono: 2%	p not reported
Rosenstock (2002) ²³⁵	Weight (kg)	PIO15 + Ins: 95.4, SE 17.6 kg PIO30 + Ins: 98.7, SE 17.7 kg P + Ins: 95.4, SE 17.0 kg		PIO15 + Ins: +2.3 kg PIO30 + Ins: +3.7 kg P + Ins: -0.04 kg	p not reported; weight gain related to decreases in HbA _{1c} ; p = 0.002
Shah (2007) ²³⁷	Weight (kg)	PIO + Ins: 107.1 kg P + Ins: 108.7 kg	PIO + Ins: 112.0 kg P + Ins: 110.1 kg		p not reported, presumably non-significant
Complication rates					
Berhanu (2007) ²³¹	Cardiac events			PIO + Ins: 5.5% P + Ins: 10.7% (mostly ECG abnormalities)	p not reported
	Deaths			No deaths	
Lipid parameters					
Berhanu (2007) ²³¹	Total cholesterol (mg/dl)	PIO + Ins: 178, SE 3.53 mg/dl P + Ins: 183, SE 3.6 mg/dl		PIO + Ins: +5.7, SD 2.75 mg/dl P + Ins: +4.7, SD 2.78 mg/dl	p = NS
	HDL cholesterol (mg/dl)	PIO + Ins: 44.6, SE 1.3 mg/dl P + Ins: 42, SE 1.3 mg/dl		PIO + Ins: +4.3, SD 0.75 mg/dl P + Ins: -0.2, SD 0.77 mg/dl	p < 0.001
	LDL cholesterol (mg/dl)	PIO + Ins: 107, SE 3.1 mg/dl P + Ins: 111, SE 3.2 mg/dl		PIO + Ins: +4.0, SD 2.37 mg/dl P + Ins: +0.9, SD 2.37 mg/dl	p = NS
	Triglycerides (mg/dl)	PIO + Ins: 123, SE 7.5 mg/dl P + Ins: 141, SE 7.6 mg/dl		PIO + Ins: -0.2, SD 9.80 mg/dl P + Ins: +43.7, SD 9.96 mg/dl	p < 0.001
Fernandez (2008) ²³²	Total cholesterol (mg/dl)	PIO + Ins: 176, SD 9 mg/dl P + Ins: 195, SD 9 mg/dl	PIO + Ins: 175, SD 16 mg/dl P + Ins: 180, SD 8 mg/dl		p = NS
	LDL cholesterol (mg/dl)	PIO + Ins: 107, SD 7 mg/dl P + Ins: 121, SD 8 mg/dl	PIO + Ins: 105, SD 12 mg/dl P + Ins: 115, SD 7 mg/dl		p = NS
	HDL cholesterol (mg/dl)	PIO + Ins: 45, SD 3 mg/dl P + Ins: 49, SD 4 mg/dl	PIO + Ins: 51, SD 3 mg/dl P + Ins: 46, SD 3 mg/dl		p < 0.05 pioglitazone vs baseline
	VLDL cholesterol (mg/dl)	PIO + Ins: 109, SD 16 mg/dl P + Ins: 113, SD 24 mg/dl	PIO + Ins: 88, SD 15 mg/dl P + Ins: 93, SD 19 mg/dl		
	Triglycerides (mg/dl)	PIO + Ins: 148, SD 17 mg/dl P + Ins: 146, SD 15 mg/dl	PIO + Ins: 123, SD 11 mg/dl P + Ins: 132, SD 18 mg/dl		p < 0.05 pioglitazone vs baseline

continued

TABLE 26 Results of included trials – insulin plus pioglitazone versus insulin (continued)

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
Mattoo (2005) ²³³	HDL cholesterol (mmol/l)	PIO + Ins: 1.23, SE 0.03 mmol/l	PIO + Ins: 1.35, SE 0.02 mmol/l	Difference between groups: 0.13, SE 0.03 mmol/l	p < 0.002
		P + Ins: 1.24, SE 0.03 mmol/l	P + Ins: 1.21, SE 0.02 mmol/l		
Raz (2005) ²³⁴	LDL cholesterol (mmol/l)	PIO + Ins: 3.20, SE 0.09 mmol/l	PIO + Ins: 3.18, SE 0.06 mmol/l	p = NS	
		P + Ins: 3.18, SE 0.08 mmol/l	P + Ins: 3.10, SE 0.06 mmol/l		
Rosenstock (2002) ²³⁵	Triglycerides (mg/dl)	PIO + Ins: 149, SD 88 mg/dl	PIO + Ins: 149, SD 88 mg/dl	p = NS	
		Ins mono: 158, SD 88 mg/dl	Ins mono: 158, SD 88 mg/dl		
Rosenstock (2002) ²³⁵	Total cholesterol (mg/dl)	PIO + Ins: 212 mg/dl	PIO + Ins: 212 mg/dl	p = NS	
		Ins mono: 204 mg/dl	Ins mono: 204 mg/dl		
Rosenstock (2002) ²³⁵	HDL cholesterol (mg/l)	PIO15 + Ins: 2.61, SE 0.2 mmol/l	PIO15 + Ins: 2.61, SE 0.2 mmol/l	Difference between PIO + Ins vs Ins mono: +4, SD 1 mg/dl	p < 0.01
		PIO30 + Ins: 2.96, SE 0.2 mmol/l	PIO30 + Ins: 2.96, SE 0.2 mmol/l		
Rosenstock (2002) ²³⁵	LDL cholesterol (mg/l)	PIO15 + Ins: 2.61, SE 0.2 mmol/l	PIO15 + Ins: 2.61, SE 0.2 mmol/l	No data shown	p = NS
		PIO30 + Ins: 2.96, SE 0.2 mmol/l	PIO30 + Ins: 2.96, SE 0.2 mmol/l		
Rosenstock (2002) ²³⁵	Triglycerides (mmol/l)	PIO15 + Ins: 2.61, SE 0.2 mmol/l	PIO15 + Ins: 2.61, SE 0.2 mmol/l	LS % mean change from baseline	p < 0.05, PIO30 vs placebo
		PIO30 + Ins: 2.96, SE 0.2 mmol/l	PIO30 + Ins: 2.96, SE 0.2 mmol/l		
Rosenstock (2002) ²³⁵	HDL cholesterol (mg/dl)	PIO15 + Ins: 43.42, SE 0.95 mg/dl	PIO15 + Ins: 43.42, SE 0.95 mg/dl	LS % mean change from baseline	p < 0.05 PIO30 vs placebo
		PIO30 + Ins: 42.71, SE 0.94 mg/dl	PIO30 + Ins: 42.71, SE 0.94 mg/dl		
Rosenstock (2002) ²³⁵	Total cholesterol (mg/dl)	PIO15 + Ins: 42.66, SE 0.96 mg/dl	PIO15 + Ins: 42.66, SE 0.96 mg/dl	LS % mean change from baseline	p = NS
		PIO30 + Ins: 213.08, SE 3.57 mg/dl	PIO30 + Ins: 207.32, SE 3.53 mg/dl		
Rosenstock (2002) ²³⁵	LDL cholesterol (mg/dl)	PIO15 + Ins: 214.03, SE 3.58 mg/dl	PIO15 + Ins: 214.03, SE 3.58 mg/dl	LS % mean change from baseline	p = NS
		PIO30 + Ins: 127.33, SE 3.07 mg/dl	PIO30 + Ins: 121.69, SE 3.06 mg/dl		
Rosenstock (2002) ²³⁵	Total cholesterol (mg/dl)	PIO15 + Ins: 130.95, SE 3.05 mg/dl	PIO15 + Ins: 130.95, SE 3.05 mg/dl	LS % mean change from baseline	p = NS
		PIO30 + Ins: 130.95, SE 3.05 mg/dl	PIO30 + Ins: 121.69, SE 3.06 mg/dl		
Adverse events					
Berhanu (2007) ²³¹	Oedema			PIO + Ins: n = 10 P + Ins: n = 5 (all mild to moderate)	p not reported

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)	
Mattoo (2005) ²³³	Serious adverse events			PIO + Ins: n = 4	p not reported	
				P + Ins: n = 2 (none considered to be related to study medication)		
Raz (2005) ²³⁴	Withdrawal due to adverse events			PIO + Ins: n = 7	p not reported	
				P + Ins: n = 3		
	Oedema				PIO + Ins: n = 20 (10 classified as mild)	p not reported
					P + Ins: n = 5 (three classified as mild)	
					PIO + Ins: n = 1	p not reported
Patients with product-related adverse events				Ins mono: n = 2		
				PIO + Ins: 28%	p not reported	
Peripheral oedema				Ins mono: 20%		
				PIO + Ins: 6%	p not reported	
Serious adverse events				Ins mono: 0		
				PIO + Ins: n = 0		
Rosenstock (2002) ²³⁵	Withdrawal due to adverse events			Ins mono: n = 2 (none considered to be related to study medication)		
				PIO 15 + Ins: 1.6%	p not reported	
Scheen (2006) ²³⁶	Oedema			PIO 30 + Ins: 2.6%		
				P + Ins: 3.2%		
	Cardiovascular adverse events				PIO 15 + Ins: 12.6%	p not reported
					PIO 30 + Ins: 17.6%	
Oedema				P + Ins: 7.0%		
				PIO 15 + Ins and PIO 30 + Ins: 7.9%	p = NS; none considered related to study medication	
Health-related QoL – not reported				PIO + Ins: 3.1%	p < 0.0001	
				P + Ins: 18%		

ECG, electrocardiogram; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares; mono, monotherapy; P, placebo; PIO, pioglitazone; VLDL, very-low-density lipoprotein.

TABLE 27 Results of included trials – pioglitazone plus insulin versus pioglitazone

Study	Outcome	Baseline	End of study	Change from baseline/difference between groups	p-value (between groups)
HbA_{1c} Raskin (2006) ^{241,242}	HbA _{1c} (%)	BIAsp 30+MET+PIO: 8.1, SD 1.0% MET+PIO: 7.9, SD 0.9%	BIAsp 30+MET+PIO: 6.5, SD 1.0% MET+PIO: 7.8, SD 1.2%	BIAsp 30+MET+PIO: -1.5% MET+PIO: -0.2%	p<0.0001
	Percentage with HbA _{1c} <7.0%		BIAsp 30+MET+PIO: 76.3% MET+PIO: 24.1%		p not reported
	Percentage with HbA _{1c} ≤6.5%		BIAsp 30+MET+PIO: 59.1% MET+PIO: 11.5%		p not reported
	Percentage with HbA _{1c} ≤6.0%		BIAsp 30+MET+PIO: 33.3% MET+PIO: 2.3%		p not reported
	Percentage with HbA _{1c} ≤5.5%		BIAsp 30+MET+PIO: 14.0% MET+PIO: 0%		p not reported
Hypoglycaemia Raskin (2006) ^{241,242}	Minor hypoglycaemia (events/year)		BIAsp 30+MET+PIO: 8.3 events/year MET+PIO: 0.1 events/year		p<0.001
	Weight			BIAsp 30+MET+PIO: +4.6, SD 4.3 kg MET+PIO: +0.8, SD 3.2 kg	p<0.05
Adverse events Raskin (2006) ^{241,242}	Peripheral oedema		BIAsp 30+MET+PIO: 10% MET+PIO: 12%		
	BIAsp, biphasic insulin aspart; MET, metformin, PIO, pioglitazone.				

30-plus-metformin-plus-pioglitazone group and in 12% of patients in the metformin-plus-pioglitazone group.

Discussion

Summary

Eight RCTs were identified comparing combinations of insulin and pioglitazone with insulin without pioglitazone regimes (two published only as abstracts). One trial (published only as abstract) was identified comparing a pioglitazone-plus-insulin regime with a pioglitazone-without-insulin regime. Compared with the insulin regimes, the pioglitazone-plus-insulin regimes reduced HbA_{1c} level by a mean of -0.54% (95% CI -0.70 to -0.38, $p < 0.00001$). However, hypoglycaemic

events were marginally increased with the pioglitazone regimes (RR 1.27, 95% CI 0.99 to 1.63, $p = 0.06$). Where reported, studies tended to find reduced insulin doses in the pioglitazone groups, as well as increased HDL cholesterol values. None of the other lipid parameters reported (triglycerides, total cholesterol, LDL cholesterol) showed any systematic differences between the comparison groups. The studies tended to show increased weight (mean difference 2.91 kg) and more peripheral oedema with pioglitazone. The one trial comparing a pioglitazone-plus-insulin (plus metformin) regime with a pioglitazone (plus metformin) regime found significantly lower HbA_{1c} values in the groups taking insulin, but also more minor hypoglycaemic events and more weight gain. The rates of peripheral oedema appeared to have been similar between the groups.

Chapter 7

Literature review of economic studies on new drugs for diabetes

Methods

Search strategy

The databases MEDLINE, EMBASE, Science Citation Index, ISI Proceedings and the NHS Economic Evaluation Database (NHS EED) were searched, as described in Appendix 1 (see Economic searches). Articles for inclusion were retrieved and initially screened by one author and then further screened selected by the health economist for inclusion.

GLP-1: exenatide

QoL studies

Secnik *et al.* (2006)⁶⁷ summarised the QoL effect of exenatide 10 µg twice daily and glargine once daily as observed in a 26-week Phase III trial among 455 per-protocol patients with type 2 diabetes. These were added to patients' existing regimes of metformin and a sulfonylurea. Both the addition of exenatide and the addition of glargine demonstrated statistically significant improvements in the SF-36 vitality subscale score: from 53.18 to 56.30 for exenatide and from 55.18 to 57.62 for glargine. They were also associated with statistically significant improvements in the DSC-R (range 0–5) total score, with exenatide recording an improvement from 1.07 to 0.90, and glargine an improvement from 0.99 to 0.84. Both exenatide and glargine were reported as showing statistically significant improvements in the psychology: fatigue, psychology: cognitive, ophthalmology, hypoglycaemia and hyperglycaemia subscales of the DSC-R. Statistically significant improvements in the Diabetes Treatment Satisfaction Questionnaire were also observed: from 26.41 to 29.48 for exenatide and from 26.31 to 30.04 for glargine, with the perceived frequency of both hypoglycaemia and hyperglycaemia recording improvements for both groups. However, while the change in EQ-5D was of similar size between the two groups, for exenatide the change from 0.82 to 0.85 was not statistically significant, with $p = 0.08$, whereas for glargine the change from 0.84 to 0.87 was with $p = 0.05$.

A study by Yurgin *et al.* (2006),⁶⁸ available only as an abstract, reported the effects of exenatide compared with biphasic insulin when added to existing regimes of metformin and a sulfonylurea from a 52-week non-inferiority trial among 505 patients with type 2 diabetes. The HbA_{1c} effects were similar, -0.98% for exenatide and -0.88% for biphasic insulin. Exenatide led to statistically significant improvements in EQ-5D visual analogue scale (VAS) of 3.39, the SF-36 vitality scale of 3.89 and the DSC-R of -0.13 . No significant effect was observed in the TFS. There were no statistically significant changes in these for biphasic insulin, although it should be noted that there was also no statistically significant difference between exenatide and biphasic insulin with the exception of the DSC-R, which recorded an increase under biphasic insulin of $+0.05$.

Weight, nausea, QoL and cost of treatment

Ratner *et al.* (2006)²⁴⁴ reported a progressive reduction in weight of an average around 2.4 kg by week 30 within a placebo-controlled trial of exenatide among 150 patients with type 2 diabetes. From these, 92 patients also completed a 52-week follow-up study to give a total time horizon of 82 weeks. The average weight loss at 30 weeks was -3.0 kg, this increasing to -5.3 kg by week 82.

Blonde *et al.* (2006)²⁴⁵ report similar results from a somewhat larger placebo-controlled trial in 1446 patients, of whom 1125 (or 78%) completed the initial 30-week trial. In total, 974 of these patients entered the open-label phase, 668 of these having been originally randomised to receive exenatide within the placebo-controlled trial. Only 551 of these patients could be evaluated at the 82-week point due to enrolment dates, 314 of these completing the 52-week follow-up study. The ITT group and the completer cohort had similar weights and BMIs: 98 kg and 34 kg/m² and 99 kg and 34 kg/m², respectively. For this 82-week completer cohort, the average change at 30 weeks was -2.1 kg, which was reportedly similar to the range of -1.6 kg to -2.8 kg reported for the 10-µg

arm of the placebo-controlled trial. Unfortunately the mean change for the 10- μg arm was not stated, and it should also be noted that the placebo control group also experienced weight loss of between -0.3 kg and -0.6 kg at week 30. Among the 82-week completer cohort, at week 82 the average weight loss was 4.4 kg, with 81% of patients having lost weight. The average change in weight among the 82-week completer cohort showed a generally increasing trend with BMI: for patients of less than 25 kg/m^2 the average weight loss was 2.9%, whereas for patients in increasing BMI increments of 5 kg/m^2 the average weight loss was 3.6%, 4.6%, 4.3%, until those with a BMI of more than 40 kg/m^2 , for whom the average weight loss was 5.5%.

As summarised in Table 6, for the direct comparison with glargine, Heine *et al.* (2005)⁵³ reported, among a patient population with an average BMI of 31 kg, an average 2.3-kg weight loss among those starting exenatide treatment by week 26 compared with an average weight gain of 1.8 kg for those starting glargine treatment.

The submission for exenatide to the Scottish Medicines Consortium, citing trial results for exenatide in terms of weight loss, reported an additional utility estimation exercise conducted among 129 patients with diabetes. This used standard gamble to estimate the utility for patients in their current health state, a basic representative health state for patients with type 2 diabetes, and for the representative health state plus a variety of combinations of nausea and weight loss. The average utility for patients' current health state and the notional representative health state were 0.891 and 0.873, respectively: a difference of -0.018 . The absolute utility impacts of nausea and weight change were estimated, as shown in Table 28.

Dennett *et al.* (2008),²⁴⁶ in a study funded by Eli Lilly, conducted a systematic review of the literature to evaluate the impact of weight gain on patients with or without type 2 diabetes. Utility scores for patients without diabetes who were of normal weight were between 0.71 and 0.93, whereas for obese patients without diabetes the scores ranged from 0.60 to 0.91. Utility scores were lower for patients with diabetes, ranging from 0.57 to 0.77 for those of normal weight compared with 0.33–0.70 for those who were obese. The authors concluded that older studies tended to examine changes in weight or BMI without controlling for whether weight was being

TABLE 28 Utility values for nausea and weight change

Change	
Weight (%)	Utility
Nausea not experienced	
+5	-0.065
+3	-0.044
-3	+0.020
-5	+0.032
Nausea experienced	
+5	-0.095
+3	-0.073
Nil	-0.043
-3	-0.028
-5	-0.010

gained or lost. More recent studies suggest that changes may be asymmetrical, with a percentage gain in weight or BMI having a lesser effect than the same percentage loss. However, no particular study, method of elicitation or values were arrived at or recommended for use. Within the summary of results presented by Dennett *et al.* it is also not clear to what extent other comorbidities have been controlled for within the estimates. Bagust and Beale (2005),²⁴⁷ as referenced within the Dennett *et al.* review, did control for other comorbidities and found, through time trade-off estimates, that for every BMI point above 25 kg/m^2 utility declined by 0.0061. Coffey *et al.* (2002),²⁴⁸ also having controlled for comorbidities, found that being obese with a BMI of more than 30 kg/m^2 reduced utility by 0.021.

Yu *et al.* (2007),²⁴⁹ in a study funded by Eli Lilly and Amylin Pharmaceuticals, analysed data from US Health Maintenance Organizations to assess the impact upon overall treatment costs of weight changes among 458 patients with type 2 diabetes. Over the 6 months of weight measurement, around half of patients gained weight, whereas half were described as non-weight-gainers, both groups having a similar average BMI at baseline of around 34 kg/m^2 . In the year subsequent to the change in weight, emergency room visits were similar between the groups at 11.6% for the weight gainers compared with 11.1% for the non-weight-gainers. Hospitalisations were higher among weight gainers, at 8.0%, compared with 4.7% for the non-weight-gainers, although this was not statistically significant, with $p = 0.143$. Total health-care costs

were statistically significantly different, being US\$3167 for the weight gainers compared with US\$1852 with $p = 0.003$.

Regression analyses appeared to suggest about a 3–4% change in costs for every 1% change in weight. Within an additional regression analysis that controlled for patient obesity, percentage point weight losses among the non-obese were not associated with cost savings but reduced costs among the obese by 6%. Within this analysis for both the non-obese and the obese, percentage point increases in weight increase costs by between 2% and 3%, but these estimates for the subgroups were not statistically significant. These results illustrate the impact of obesity upon the overall treatment costs of diabetes, but cannot be directly appended to the modelling of exenatide given that the effects of obesity on complications and costs will be being indirectly modelled through the effect upon systolic blood pressure (SBP) and high-density lipids as a ratio of total lipids.

Cost-effectiveness studies

Edwards (2006)²⁵⁰ undertook a systematic literature review of the clinical effects of exenatide compared with glargine and NPH insulin, all these being additional to a regime of metformin and sulfonylurea therapy. Only one paper met their inclusion criteria: the 24 week Riddle (2003) *et al.* study.¹⁶⁹ Based upon this, they performed a simple cost-effectiveness analysis, anticipating that for every US\$100 spent the reduction in HbA_{1c} would be 0.091, 0.655 and 0.201 for exenatide, glargine and NPH, respectively. Similarly, they anticipated that for every US\$100 spent there would be a 0.19 kg weight loss for exenatide. Both forms of insulin were associated with weight gain. But given the outcome measures of the analysis and that exenatide was more expensive than either of the insulin treatments, few conclusions as to the treatments' relative cost-effectiveness can be drawn.

Shaya (2007)²⁵¹ analysed manufacturer data for 5 µg and 10 µg of exenatide to evaluate the cost-effectiveness of exenatide relative to placebo using the CORE cost-effectiveness model. Unfortunately, no details of the inputs and assumptions used for the modelling were provided within the paper, but the manufacturer summary referenced suggested the following clinical inputs at 30 weeks, as shown in *Table 29*.

This modelling yielded cost-effectiveness estimates of US\$43,814 per additional life-year and US\$48,921 per QALY. Curtailing the time horizon to 20 years has limited impact upon modelled outputs, but curtailing the time horizon to only 5 years increases the cost per life-year to US\$359,757 and the cost per QALY to US\$104,697. As would be anticipated, the effect upon the cost per life-year is somewhat larger as relatively few in either arm will have died at the 5-year point, but the increase in the cost per QALY underlines the importance of extrapolation and longer-term complications within the lifetime estimate of cost-effectiveness. The assumptions made in terms of longer-term effects upon HbA_{1c} level and weight were not stated, and the likelihood of transferring to an insulin regime at some point for both the placebo arm and the exenatide arm was, similarly, not made clear.

Minshall *et al.* (2008),²⁵² in assessing the cost-effectiveness of exenatide relative to placebo, appear to have used similar 30-week clinical effectiveness data from placebo-controlled trials to Shaya (2007),²⁵¹ although in a more disaggregate form, as outlined in *Table 30*.

These 30-week data were augmented with 82-week clinical effectiveness estimates from an optional open-label extension study, within which exenatide patients had a reported sustained HbA_{1c} level reduction of –1.1% and a progressive mean body

TABLE 29 HbA_{1c} and weight changes as used by Shaya (2007)²⁵¹

	Placebo			Exenatide 5 g			Exenatide 10 µg		
	<i>n</i>	HbA _{1c} (%)	Weight (kg)	<i>n</i>	HbA _{1c} (%)	Weight (kg)	<i>n</i>	HbA _{1c} (%)	Weight (kg)
All patients									
With sulfonylurea	123	+0.1	–0.6	125	–0.5	–0.9	129	–0.9	–1.6
With metformin	113	+0.1	–0.3	110	–0.4	–1.6	113	–0.8	–2.8
With metformin + sulfonylurea	247	+0.2	–0.9	245	–0.6	–1.6	241	–0.8	–1.6

TABLE 30 HbA_{1c} and weight changes as used by Minshall et al. (2008)²⁵²

	n	Exenatide					
		Placebo		5 µg		10 µg	
		HbA _{1c} (%)	Weight (kg)	HbA _{1c} (%)	Weight (kg)	HbA _{1c} (%)	Weight (kg)
All patients							
With sulfonylurea	377	+0.1	-0.6	-0.5	-0.9	-0.9	-1.6
With metformin	336	+0.1	-0.3	-0.4	-1.6	-0.8	-2.8
With metformin + sulfonylurea	733	+0.2	-0.9	-0.6	-1.6	-0.8	-1.6
For patients with HbA_{1c} < 9%							
With sulfonylurea	239	+0.1	-	-0.4	-	-0.7	-
With metformin + sulfonylurea	513	+0.3	-	-0.4	-	-0.5	-
For patients with HbA_{1c} ≥ 9%							
With sulfonylurea	138	+0.1	-	-0.6	-	-1.2	-
With metformin + sulfonylurea	220	+0.0	-	-0.9	-	-1.4	-
For patients with BMI < 30							
With metformin	89	-	+0.4	-	-0.5	-	-2.4
For patients with BMI ≥ 30							
With metformin	247	-	-0.5	-	-2.1	-	-3.0

weight reduction of 4.4 kg. The 82-week data were also used to estimate a reduction in SBP of -1.3 mmHg, a reduction in LDL cholesterol of -1.6 mg/dl, an increase in HDL cholesterol of +4.6 mg/dl and a reduction in triglycerides of 39 mg/dl. After the 82-week point the trend in these variables was assumed to follow the identified UKPDS trend, as seems likely to have been assumed for the placebo arm subsequent to the 30-week point. Medicare costs were applied to adverse events, with utilities being drawn from the European CODE-2 study EQ-5D values as reported in Bagust and Beale (2005).²⁴⁷ As with the study by Shaya (2007),²⁵¹ the paper used the CORE model to assess the cost-effectiveness of adding exenatide to metformin and sulfonylurea compared with patients remaining on just metformin and sulfonylurea. Despite a presumably worsening HbA_{1c} level over time in both arms, there does not appear to have been any consideration of patients transferring to insulin therapy.

Results for exenatide among patients of average age 56, 7 years' duration of diabetes and a baseline HbA_{1c} level of 8.3%, SBP of 123 mmHg, a BMI of 34, HDL level of 38 mg/dl, LDL level of 115 mg/dl and triglyceride level of 239 mg/dl over a 30-year

time horizon, were a discounted life expectancy of 9.63 years and a quality-adjusted life expectancy of 6.33, coupled with a lifetime cost of US\$86,281. For the placebo arm the parallel estimates were 9.10 life-years, 5.81 QALYs and a cost of US\$67,531, yielding a net impact from exenatide of 0.53 life-year, 0.52 QALYs and US\$18,750 to yield a cost-effectiveness estimate of US\$36,133 per QALY. Shortening the time horizon to 20 years had limited impact upon cost-effectiveness, although a time horizon of only 10 years worsened the anticipated cost-effectiveness to US\$64,538 per QALY.

A 20% lessening of the impact of exenatide on HbA_{1c} level from -1.1% to -0.88% had roughly proportionate impact upon cost-effectiveness, worsening it by 16% to US\$41,917 per QALY. Removing the impact upon weight and SBP had reportedly little impact upon cost-effectiveness, although values were not given. Removing the lipid effects also worsened the cost-effectiveness by around 16% to US\$41,738 per QALY. Subgroup analyses among those with HbA_{1c} level < 9% at baseline and those with HbA_{1c} level ≥ 9% suggested marked differences in cost-effectiveness: US\$45,971 and US\$20,548 per QALY, respectively.

The relevance of the studies of both Shaya (2007)²⁵¹ and Minshall *et al.* (2008)²⁵² are limited in that there appears to be no consideration of patients transferring to insulin therapy as HbA_{1c} level worsens. Ray *et al.* (2007)²⁵³ in part addressed this, also having used the CORE model but to model the cost-effectiveness of exenatide relative to glargine. Exenatide was anticipated to result in a slightly lower improvement in HbA_{1c} level than glargine, but greater improvements in a number of other outcomes with the central values as shown in *Table 31*, where nausea was the proportion of patients experiencing nausea, and hypoglycaemia was the average number of hypoglycaemic events per year.

The base case cost of exenatide was drawn from the US cost converted at the prevailing exchange rate, as the UK wholesale cost for exenatide had not been formalised. The insulin dose was assumed to be 25 IU in the first year, and thereafter 40 IU. Annual blood glucose monitoring costs were assumed to be £290 in the exenatide arm and £414 in the glargine arm, based upon predictions from a UK survey of health-care professionals and patients. Prices of complications were drawn from UK sources and indexed to 2004 prices, while utility values were mainly drawn from UKPDS data as reported in Clarke *et al.* (2002).²⁵⁴ Utility gains from weight loss were also applied to the first 2 years of the simulations, the values for this being taken from CODE-2 data that jointly analysed the effect of nausea and BMI. Subsequent to the 2-year point, the CODE-2 time trade-off data of a utility loss of 0.0061 per unit of BMI above 25 kg/m² was applied.

Results for exenatide among patients of average age 59, 10 years' duration of diabetes and a baseline HbA_{1c} level of 8.2%, SBP of 137 mmHg, a BMI of 32, HDL level of 47 mg/dl, LDL of 106 mg/dl and triglycerides of 199 mg/dl over a 35-year time horizon were a discounted life expectancy of 10.66 years and a quality-adjusted life expectancy of 7.39, coupled with a lifetime cost of £29,401. The parallel figures for glargine were 10.61 years, 6.95 QALYs and £19,489, yielding a net impact from exenatide of 0.06 life-years, 0.44

QALYs and an average cost increase of £9912 to yield a cost-effectiveness estimate of £22,420 per QALY.

Results were sensitive to the assumed utility gain from weight loss: the adoption of CODE-2 time trade-off utilities²⁴⁷ for the weight gain worsened the cost-effectiveness of exenatide to £39,763 per QALY. It was also reported in the text that results were sensitive to the utility assumed for nausea. While the impact of nausea upon cost-effectiveness was not separately quantified, it seems likely that the effect of this was encompassed within the £39,763 per QALY figure.

Note that while the Minshall *et al.* (2008)²⁵² study applied long-term trends to the progression of HbA_{1c} after a period of initial treatment success, it appears that there was no explicit allowance for progression to insulin therapy within the modelling. Fewer details were provided within the Shaya (2007)²⁵¹ study, but it appears likely that it made similar assumptions.

Watkins *et al.* (2006)²⁵⁵ used the CORE model to compare the anticipated costs and outcomes among the standard UKPDS population and a modified obese population, these being identical in terms of most characteristics and an HbA_{1c} level of 8.5% at baseline, differing only in weight and the consequences of this for the various risk factors as outlined in *Table 32*.

Both patient groups were assumed to be treated with exenatide. For the UKPDS population this intensification of treatment was assumed to have the CORE default value impacts upon risk factors, with there being no change in weight, a rise of 1.3 mmHg in SBP, a rise of 1.6 mg in LDL levels and a rise of 39 mg in triglycerides. When treated with exenatide the obese population was assumed to experience a weight loss of 8.5% or 3 BMI points, a 10-mm fall in SBP, a 20-mg fall in LDL and a 59-mg fall in triglycerides. Immediately apparent from this is that it appears to have been assumed that the obese population would have a lower SBP, lower levels of LDL and lower levels

TABLE 31 Outcomes changes used by Ray *et al.* (2007)²⁵³

	HbA _{1c} (%)	SBP	Cholesterol	LDL	HDL	Triglyceride	BMI	Nausea (%)	Hypoglycaemia
Exenatide	-0.99	-4.15	-3.47	-1.54	+1.54	-15.04	-0.80	57.1	6.94
Glargine	-1.07	-0.57	-0.39	+5.80	+1.54	-30.08	+0.55	8.6	5.84

TABLE 32 Obese group compared with UKPDS

	BMI	SBP	Cholesterol	HDL	LDL	Triglycerides
UKPDS population	27.5	135	207	41	134	207
Obese population	35.0	145	217	41	144	230

of triglycerides than the UKPDS population. This raises questions as to the reliability of the modelling, or at a minimum the reporting of the conduct of it within the paper. Unfortunately, the paper was also not explicit as to whether any reduction in HbA_{1c} was anticipated for exenatide, although in the introductory sections the authors noted an average reduction of 0.5–0.9%.

Treatment with exenatide was compared with the treatments of once-daily glargine, pioglitazone, glyburide and no additional treatment. The impact of these treatments was reductions in baseline HbA_{1c} levels of 2.0%, 0.6%, 0.9% and 0%, respectively, which appears to be likely to have been coupled with the standard CORE reductions in other variables as reported for exenatide use among the UKPDS population. Treatments were assumed to continue for the time horizon of the model.

Among obese patients, exenatide was anticipated to result in cost savings of around US\$3000 from reduced cardiovascular disease. Exenatide resulted in higher costs of renal disease by around US\$1000 compared with glyburide and glargine, but savings of US\$2600 and US\$3800 compared with pioglitazone and no additional treatment, respectively. A similar cost pattern was observed for neurological and ophthalmic costs with exenatide being of around US\$1700 higher in cost compared with glyburide and glargine, but around US\$1000 lower in cost compared with pioglitazone and placebo. Cost-effectiveness estimates of US\$32,000, US\$13,000 and US\$16,000 per QALY were reported for exenatide against glyburide, glargine and placebo, respectively; while pioglitazone was dominated, although it is not clear whether these estimates were for obese patients or for the patient group as a whole.

As is apparent from the summary above, interpreting the results of Watkins *et al.* (2006)²⁵⁵ is problematic, and it is unclear quite what the cost-effectiveness estimates relate to and their reliability is also questionable. It also does not appear that any subsequent intensification of therapy has been considered in patients as time progresses.

The Scottish Medicines Consortium (SMC) issued guidance on exenatide in June 2007, recommending it for restricted use in combination with metformin and/or sulfonylureas. The SMC appraisal was based on an industry submission that used only one trial – that of exenatide versus biphasic insulin.²⁵⁶ The SMC commented that the comparator of biphasic insulin aspart was more expensive than cheaper forms of insulin, but concluded that additional sensitivity analysis suggested that the incremental cost-effectiveness ratio (ICER) against biphasic human insulin would probably be cost-effective.

DPP-4 inhibitors

Cost-effectiveness studies

Schwarz *et al.* (2008)²⁵⁷ explored the cost-effectiveness of adding second-line sitagliptin to first-line metformin for uncontrolled patients on a regime of metformin in terms of their HbA_{1c} level rising above 6.5%. This was compared on a pair-wise basis with two main comparators: (1) adding second-line rosiglitazone to first-line metformin and (2) adding second-line sulfonylurea to first-line metformin. Those failing on these treatments would progress to metformin plus third-line basal insulin, with possible further progression to fourth-line multidose insulin. For the comparison with adding second-line sulfonylurea to first-line metformin, an additional scenario was modelled with those failing on sitagliptin or sulfonylurea progressing to a third-line combination of rosiglitazone and metformin prior to possible progression to insulin therapy as fourth line. For these later therapies, it appears that the same switching threshold in terms of HbA_{1c} level was used, although the value for this was varied in sensitivity analyses.

Modelling was undertaken for six European countries – Austria, Finland, Portugal, Scotland, Spain and Sweden – and used the Januvia Diabetes Economic (JADE) model. While the JADE model relied extensively upon the UKPDS Outcomes Model risk equations, it will not necessarily have resulted in the same anticipated patient outcomes

as had the UKPDS Outcomes Model been used. The costs of medicines, side effects, direct costs of diabetes related complications and discount rates for both costs and health-related QoL impacts were based upon country-specific data, rather than being drawn from the UKPDS Outcomes Model.

The average treatment effects upon HbA_{1c} level when added to metformin were differentiated by baseline HbA_{1c} level and by comparator treatment as shown in *Table 33*.

For the comparison with rosiglitazone it was anticipated that sitagliptin would provide an incremental discounted QALY gain of between 0.016 and 0.063, with the cost impact being between a cost saving of €687 to a net cost of €208. For the UK modelling based upon Scottish data, the patient gain was anticipated to be 0.016 and the incremental cost £25.08 to yield an estimated cost-effectiveness of £1567 per QALY.

For the comparison with sulfonylurea in which failures progressed to insulin, it was anticipated that sitagliptin would provide an incremental discounted QALY gain of between 0.037 and 0.095, with the cost impact being a net cost of between €331 and €1097. For the UK modelling, the patient gain was anticipated to be 0.095 and the incremental cost £764 to yield an estimated cost-effectiveness of £8045 per QALY.

For the comparison with sulfonylurea in which failures progressed to rosiglitazone plus metformin prior to insulin it was anticipated that sitagliptin would provide an incremental discounted QALY gain of between 0.045 and 0.103, with the cost impact being a net cost of between €339 and €1130. For the UK modelling, the patient gain was anticipated to be 0.103 and the incremental cost £772 to yield an estimated cost-effectiveness of £7502 per QALY.

The average cost-effectiveness of across the modelling was estimated to be €4766 per QALY. Results relative to rosiglitazone were sensitive to the assumed effects of rosiglitazone on cholesterol, SBP and the risk of heart failure. Removing the effect upon cholesterol and SBP, and halving the increase risk of heart failure saw the cost-effectiveness estimate rise to €5012 per QALY, fall to €2630 per QALY and rise to €6677 per QALY, respectively. Varying the utility decrements associated with the long-term complications of diabetes had relatively little impact upon results, a 20% change changing the cost-effectiveness estimate by less than €100 per QALY. Varying the costs of these complications had a somewhat larger impact, a 20% change altering the cost-effectiveness estimate by less than €700 per QALY. However, for all the sensitivity analyses performed, the cost-effectiveness estimate remained below €8000 per QALY. Reducing the effectiveness of sitagliptin by 10% had the largest impact, increasing the cost-effectiveness estimate to €7548 per QALY.

While the analysis of Schwarz *et al.* (2008)²⁵⁷ did explicitly model the progression to insulin, a limitation of the study may be in considering sitagliptin as a second-line treatment rather than as a third-line addition to metformin and sulfonylurea prior to patients progressing to fourth-line insulin therapy compared with patients progressing directly to insulin therapy as a third-line treatment.

Three other papers modelling the cost-effectiveness of DPP-4 inhibitors were available only as abstracts: Minshall *et al.* (2007),²⁵⁸ Celaya *et al.* (2007)²⁵⁹ and Fon *et al.* (2007).²⁶⁰ Minshall *et al.* considered the cost-effectiveness of sitagliptin relative to pioglitazone, whereas both Celaya *et al.* and Fon *et al.* considered the relative cost-effectiveness of sitagliptin, vildagliptin, rosiglitazone and pioglitazone. Minshall adopted a US perspective, while both Fon and Celaya adopted

TABLE 33 Effects on HbA_{1c} according to baseline level

Baseline HbA _{1c} (%)	Comparison			
	Rosiglitazone		Sulfonylurea	
	Sitagliptin (%)	Rosiglitazone (%)	Sitagliptin (%)	Sulfonylurea (%)
<7	-0.46	-0.10	-0.47	-0.44
7-8	-0.63	-0.77	-0.74	-0.90
8-9	-1.04	-0.86	-1.35	-1.41
>9	-1.64	-1.98	-1.89	-2.07

a Mexican health-care perspective, with it seeming likely that treatments under consideration were second-line treatments being added to first-line metformin for patients failing on metformin alone.

Minshall *et al.* (2007),²⁵⁸ estimated the effectiveness of sitagliptin from a separate study of the effectiveness of pioglitazone, although noted that the baseline HbA_{1c} values were similar between the two studies, at 8.04% for sitagliptin and 7.60% for pioglitazone. Daily drug acquisition costs were also similar – US\$4.86 and US\$4.91, respectively. Given this, pioglitazone was associated with an incremental cost over 35 years of US\$359, but also an incremental 0.075 QALYs to yield a cost-effectiveness estimate of US\$4804 per QALY.

The Fon *et al.* and Celaya *et al.* studies^{259,260} both relied upon a meta-analysis for their estimates of the effectiveness of sitagliptin, vildagliptin, rosiglitazone and pioglitazone. It appears likely that the Celaya paper was a development of the Fon paper, given their similarities and that both lead authors are named authors of the other paper. While it is not explicit within the abstracts, it appears likely that the same meta-analysis was used by both, Celaya *et al.* noting that it standardised the baseline HbA_{1c} level at 9% across treatments. Both studies adopted a 1-year perspective, estimating the direct treatment costs, outpatient visits, inpatient admissions, emergency room admissions, etc. to estimate the incremental cost-effectiveness and incremental net benefits. Few details were provided within the abstracts, to the extent that the outcome measures were not clear, although it may have been as simple as per unit of HbA_{1c} reduction. Vildagliptin was estimated to have the lowest overall annual treatment cost – US\$1434 within the Fon paper compared with US\$9176 within the Celaya paper. Vildagliptin was also estimated to have the lowest cost per successful unit US\$1304 in the Fon paper compared with US\$8342 within the Celaya one, these figures both implying an additional 1.10 units of outcome arising from vildagliptin use. The authors concluded that vildagliptin dominated the other treatments. The reasons for the differences in cost estimates between Fon and Celaya were not clear.

The SMC issued guidance on vildagliptin in March 2008²⁶¹ and on sitagliptin in September 2008.²⁶² The guidance on vildagliptin was based on the Novartis submission, which provided a cost-minimisation analysis comparing vildagliptin with the glitazones. The assumption was that they

were equally clinically effective. Costs were over a 1-year period. The comparison used the maximum daily dose of rosiglitazone, which is not used in the majority of patients in Scotland. However, the SMC guidance concluded that using a lower dose would not change the conclusions. The SMC noted that there were limited data, at that time, on some of the assumptions. However, vildagliptin was accepted for restricted use. The guidance does not specify any costs per QALY.

The guidance on sitagliptin was based on the Merck Sharp and Dohme submission, which provided two cost-utility analyses, both with a glitazone as the comparator. One was sitagliptin added to metformin and a sulfonylurea versus a glitazone added to metformin and sulfonylurea; the other assumed that metformin was not tolerated, and compared sulfonylurea plus sitagliptin with sulfonylurea plus a glitazone. The UKPDS model was used. The SMC guidance notes that the main drivers were the congestive heart failure associated with the glitazones, and the cardiovascular risk associated with weight gain – also a feature of the glitazones. The modelling produced very low ICERs, at £5007 and £1902 for the two cost-utility analyses, respectively. The SMC identified some limitations and problems with the modelling, but accepted that the economics case had been demonstrated. The SMC guidances are quite short, and little detail is given.

Economic literature review: glargine and detemir

The previous TAR investigating the cost-effectiveness of the long-acting insulin analogues – TA53 – undertook a systematic review of the literature to January 2002 and concluded that ‘There are no published studies investigating the cost-effectiveness of insulin glargine, or indeed any other insulin analogue. In addition, there are no published studies investigating the cost-effectiveness of NPH insulin, the most likely comparator for insulin glargine’.¹²

What follows reviews the cost-effectiveness studies, arising subsequent to this, of glargine, detemir and NPH among patients with type 2 diabetes, although a number of these were available in only abstract or summaries of International Society For Pharmacoeconomics and Outcomes Research (ISPOR) poster presentations. It will become obvious that most of these studies have been funded by the manufacturers, often with co-authors from the companies, and a consistent finding is

that the studies funded by manufacturers find their own products cost-effective. The modelling is often well done and thorough, but will not be convincing if based on assumptions that seem unduly favourable to the product under review.

Full papers

Cost-effectiveness

The report from the Canadian Agency for Drugs and Technologies in Health (CADTH) by Tran *et al.* (2007)¹⁴² includes a cost-effectiveness analysis. However, it included no cost-effectiveness studies for type 2 diabetes.

Brandle *et al.* (2007)²⁶³ estimated the cost-effectiveness of glargine compared with NPH among patients failing on OAD agents over a 10-year time horizon, from the perspective of the Swiss health-care system. Patient characteristics were an average age of 66 years, 9 years' duration of diabetes, a BMI of 29.4 kg/m² and an SBP of 155 mm. Modelling was implemented through the Diabetes Mellitus Model, the main inputs being two possible effects upon HbA_{1c} level for glargine of -0.96%, which was labelled as pessimistic, and -1.24%, which was labelled as optimistic, compared with an assumed effect for NPH of -0.84%. These values were drawn from a single study within the literature. This was the study by Fritsche *et al.* (2003),¹⁶² details of which are in the clinical effectiveness section of this review. As shown in *Figure 2*, it reported one of the bigger differences in HbA_{1c} level. As a consequence, glargine was seen as having a superior effect on HbA_{1c} level – of between 0.12% and 0.40%. These relative benefits appear to have been assumed to persist indefinitely, as a common annual increase of 0.1% was applied after the first 2 years to both glargine and NPH. The HbA_{1c} effects were applied to three patient groups with differing baseline HbA_{1c} levels: 10%, 9% and 8%. Effects upon severe hypoglycaemic events and weight were not modelled.

Within the pessimistic scenario, glargine was seen as costing Swiss francs (CHF)1532, CHF1685 and CHF1887 more per patient with net patient benefits of 0.038, 0.037 and 0.038 QALYs, respectively, resulting in cost-effectiveness estimates of CHF49,441, CHF45,701 and CHF49,468 per QALY. Within the optimistic scenario, glargine was seen as saving CHF95, costing CHF350 and costing CHF734 more per patient with net patient benefits of 0.123, 0.123 and 0.128 QALYs, respectively, resulting in cost-effectiveness estimates of dominance, CHF2853 and CHF5711 per QALY.

While these appear relatively favourable cost-effectiveness estimates for glargine, the relevance of the study is undermined through the reliance upon a single study for the estimate of glargine having a 0.12–0.40% superior HbA_{1c} impact compared with NPH, and the assumption that this absolute benefit will be maintained through time through the application of a common 0.1% annual increase.

This analysis by Brandle *et al.* (2007)²⁶³ was funded by Sanofi-aventis, the manufacturer of glargine, and one of the authors was from that company.

A similar study by Maxion-Bergemann *et al.* (2005)²⁶⁴ from the German branch of Aventis Pharma and the consultancy firm, Analytica International (Lörrach, Germany), funded by Aventis, also used the Diabetes Mellitus Model, also with similarly favourable assumptions, and also concluded that glargine would give better glycaemic control, and hence reductions in complications, mortality and costs. However, they did test the effect of three different levels of improved glycaemia control with differences between NPH and glargine of 0.13%, 0.44% and 0.85%. (Note: Our meta-analysis showed no difference.) It is a careful and thorough analysis but all underpinned by what we think are unduly favourable assumptions about differences in HbA_{1c} level.

Grima *et al.* (2007),²⁶⁵ from Sanofi-aventis and an economics consultancy, funded by the manufacturer, developed their own Markov model from data within the literature, mainly the UKPDS papers and the Diabetes Control and Complications Trial (DCCT) trial, to assess the cost-effectiveness of glargine relative to NPH for both patients with type 1 diabetes and patients with type 2 diabetes. While the paper noted that meta-analysis suggested similar effects from both glargine and NPH upon HbA_{1c} level, it was assumed [based on analysis by Yki-Järvinen *et al.* (2003)²⁶⁶] that the lower rate of hypoglycaemia with glargine compared with NPH could be translated into an additional effect upon HbA_{1c} level of -0.87% for glargine, over and above that observed for NPH. This relative effect was assumed to persist over a patient's lifetime, with a common annual drift on HbA_{1c} level of 0.135% being applied to both arms. Patients with type 2 diabetes, averaging the age of 53 years were simulated across cohorts of differing baseline HbA_{1c} level: 7%, 8%, 9% and 10%+.

The average net cost of glargine compared with NPH among patients with type 2 diabetes was estimated as Can\$1992. This varied considerably across the cohorts simulated: additional costs of C\$3310, C\$2160 and C\$896 for those of 7%, 8% and 9% at baseline, respectively. Within the cohort of more than 10% HbA_{1c} level at baseline, glargine was found to be cost saving at – C\$320. In terms of patient impact, the net benefit from glargine was estimated to be 0.22, 0.23, 0.24 and 0.25 QALYs for the four cohorts of HbA_{1c} levels 7%, 8%, 9% and 10%+, respectively.

Overall, glargine was estimated as conferring an additional 0.25 years' survival and a gain of 0.23 QALYs, resulting in a cost-effectiveness estimate of C\$8618 per QALY relative to NPH. While the study is interesting in terms of the de novo model structure, the applicability of the conjectured 0.87% relative absolute benefit on HbA_{1c} from glargine over NPH may be questionable. The assumption that this absolute benefit persists over the patient lifetime is also questionable.

McEwan *et al.* (2006)²⁶⁷ in two abstracts and a full paper (funded by Sanofi-aventis and with an author from the company) evaluated the use of glargine from an NHS perspective. The first abstract by McEwan *et al.*²⁶⁷ assumed that the main impact was on rates of severe, symptomatic and nocturnal hypoglycaemic events, with there being no difference in HbA_{1c} level between glargine and NPH. Currie²⁶⁸ was listed as an author, and it seems likely that the QoL impacts of hypoglycaemic events were as previously estimated within the paper listing him as first author, and as reviewed within the cost-effectiveness modelling chapter below. Given these impacts, the authors estimated cost-effectiveness for glargine of £15,197 per QALY.

In the second abstract, of an ISPOR presentation by McEwan *et al.* (2007),²⁶⁹ glargine was anticipated to lead to a 0.21% superior HbA_{1c} level in comparison with NPH, and also to confer benefits in terms of reduced hypoglycaemia events. Overall, the cost-effectiveness of glargine was estimated to be £5806 per QALY for insulin-naïve patients, and £3415 per QALY for non-insulin-naïve patients. Excluding the effects upon hypoglycaemic events raised these to £18,179 per QALY and £7973 per QALY, respectively.

In the full paper by McEwan *et al.* (2007),²⁷⁰ it is noted that the key assumption on HbA_{1c} level comes from the same meta-analysis by Yki-Järvinen

et al. (2003)²⁶⁶ used in the Grima *et al.* (2007) analysis,²⁶⁵ which probably overestimates the difference. However, McEwan *et al.* also carried out their analysis assuming no difference in HbA_{1c} level, but only in the frequency of hypoglycaemia. But the assumptions there were derived partly from a recent meta-analysis carried out for the manufacturer, and not in the public domain. This gave a relative reduction in hypoglycaemia of 40%. But the background rates of hypoglycaemia appear to come partly from studies in type 1, such as the DCCT, which may not be relevant to patients in the situation of just starting insulin.

So, again, the underlying assumptions may favour glargine.

Only one full paper evaluating the cost-effectiveness of detemir was identified among those with type 2 diabetes: Valentine *et al.* (2007),²⁷¹ from the IMS consultancy, and Novo Nordisk, the manufacturers of detemir. Modelling was over a 35-year time horizon for an average age at baseline of 62 years, duration of diabetes of 7 years and BMI of 30 kg/m². It appears to have used the CORE diabetes model. The costing perspective was that of the US health-care system. Clinical effectiveness estimates were drawn from the German part of the PREDICTIVE study (2007),¹⁷⁸ an observational study of 2000 patients who were uncontrolled on either oral hypoglycaemic agents, NPH plus oral hypoglycaemic agents or glargine plus oral hypoglycaemic agents, and who were switched to detemir.²⁷² This anticipated beneficial effects from switching to detemir upon both HbA_{1c} level and BMI, and typically also upon hypoglycaemic events, as shown in *Table 34*.

Given those assumptions, modelling anticipated that switching to detemir would yield an additional 0.71, 0.35 and 0.34 undiscounted life years compared with remaining on OHAs, NPH and glargine, respectively. The impact on discounted QALYs was 0.31, 0.45 and 0.46, which, when coupled with net costs of US\$2290, US\$2824 and US\$1834, resulted in cost-effectiveness estimates of US\$7412 per QALY, US\$6269 per QALY and US\$3951 per QALY compared with OHA, NPH and glargine, respectively.

However, some of the improvements could be due a 'trial effect', even although the study was not a trial. Patients who were not well controlled on glargine might have improved their control, given more attention, even if left on glargine. The clinical effectiveness estimates for the effect of detemir

TABLE 34 Benefits of detemir as reported by PREDICTIVE study

	Switching to detemir from:		
	Oral hypoglycaemic agents	NPH	Glargine
HbA _{1c}	-1.29%	-0.60%	-0.59%
BMI	-0.138	-0.382	-0.520
Hypoglycaemic events per annum	+1.17	-6.76	-7.28

on HbA_{1c} level being superior to those of both NPH and glargine are very favourable to detemir, making the cost-effectiveness results questionable.

Comparative costs

Two studies compared the costs of care with detemir and glargine. Poole *et al.* (2007),²⁷³ in a study funded by Sanofi-aventis, and published in a journal supplement sponsored by Sanofi-aventis, concluded that: 'Diabetes management with glargine results in markedly reduced costs of diabetes-related treatment compared with detemir in people with type 1 or type 2 diabetes'.

Valentine *et al.* (2006),²⁷⁴ in a study sponsored by Novo Nordisk, concluded that: 'In comparison with glargine, detemir ... reduced direct medical costs and decreased indirect costs ...'.

Premixed regimens

While not the focus of the review, two full papers were identified comparing the cost-effectiveness of once-daily glargine with twice-daily premixed insulin (70 : 30) [Ray *et al.* (2007)²⁷⁵ and Goodall *et al.* (2008)²⁷⁶].

Ray *et al.* (2007)²⁷⁵ assessed the cost-effectiveness of once-daily glargine with twice-daily premixed insulin among those failing on OAD drugs from the perspective of the US health-care system, using the CORE diabetes model. Baseline patient characteristics were an average age of 52 years, 9 years' duration of diabetes, BMI of 31 kg/m² and a baseline HbA_{1c} level of 9.77%. Clinical effectiveness estimates were drawn from the INITIATE trial: a 28-week randomised open-label US study. The mean reduction in HbA_{1c} level within this was statistically significantly greater for premixed insulin than for glargine, the average changes being -2.79% and -2.36%, respectively, although premixed insulin was associated with a slightly greater increase in BMI: 1.88 kg/m², as against 1.22 kg/m² for glargine. Premixed insulin was associated with a greater insulin dose increase

by end of study to 0.82 IU/kg compared with 0.55 IU/kg for glargine.

Results of the modelling were that premixed insulin conferred an additional 0.19 discounted years' life expectancy, and by coincidence an identical additional 0.19 discounted QALYs. Total lifetime costs were around 9% higher with premixed insulin at a net cost of US\$8824, resulting in a cost-effectiveness estimate for premixed insulin of US\$46,533 per QALY relative to glargine.

Goodall *et al.* (2008)²⁷⁶ assessed the cost-effectiveness of once-daily glargine with twice-daily premixed insulin among those failing on OAD drugs within the Swedish setting, also using the CORE diabetes model. Baseline patient characteristics and clinical effectiveness estimates were drawn from the INITIATE trial and were the same as reported for Ray *et al.* (2007),²⁷⁵ above.

Results of the modelling were that premixed insulin conferred an additional 0.21 discounted years' life expectancy, and an additional 0.21 discounted QALYs. The source of the slightly larger net patient benefits compared with the estimates of Ray *et al.* (2007)²⁷⁵ reported above is not clear, given apparently identical patient characteristics, clinical effectiveness estimates and discount rates. Total lifetime costs were also around 2.5% less with premixed insulin, a saving of Swedish kronor (SEK)10,367, resulting in the authors concluding that premixed insulin dominated glargine.

The modelling of Ray *et al.* (2007)²⁷⁵ and Goodall *et al.* (2008)²⁷⁶ was much the same, but with net costs differing due to a difference balance between the direct treatment costs and the costs of the downstream complications of diabetes. The extent to which they may overstate the relative cost-effectiveness of premixed insulin may be influenced by patients on once-daily glargine, presumably at some point progressing to mealtime insulin, which will not have been captured within the clinical trial.

Cost

While not the focus of this review, two full papers were identified comparing the costs of once-daily glargine with twice-daily premixed insulin.

Lechleitner *et al.* (2005)²⁷⁷ conducted a prospective observational study among 678 Austrian patients with type 2 diabetes being switched from oral therapy to either once-daily glargine with continued OAD agents or, typically, twice-daily conventional insulin therapy with premixed insulin, although 5% required only once-daily injections and 20% required more than twice-daily injections. The effectiveness on control of HbA_{1c} level was the same for both groups and, as a consequence, the study undertook a cost analysis.

Within the glargine group, 93% of patients continued their oral therapy regimen, mainly of metformin (43%) and sulfonylurea (43%), while within the conventional insulin therapy group only 46% continued with their oral regime. Probably as a result of this, the median daily dose of insulin was considerably lower in the glargine group, at only 16 IU, compared with 40 IU for the conventional insulin therapy group, thereby introducing a bias. A fairer comparison of the insulins would have kept the oral agents the same, but the trialists were presumably more interested in the total regime. Not surprisingly, the median monthly use of blood monitoring strips was lower in the glargine group, at 60, than at 80 for the conventional insulin therapy group. In the light of this, the higher cost of glargine was largely offset by lower insulin test strip usage, leading to similar average costs per day: €1.90 for glargine compared with €1.99 for the conventional insulin therapy group. HbA_{1c} results were 7.8% in both groups.

Janka and Hogy (2008)²⁷⁸ undertook a similar study to Lechleitner *et al.* (2005),²⁷⁷ above, estimating the cost differences between once daily glargine plus oral agents, against twice-daily premixed insulin. Glargine was estimated to have half of the annual needle costs, testing strip costs and lancet costs, at only €375, compared with €750 for premixed insulin. This helped offset the additional cost of metformin and gliclazide of €346 within the glargine arm. Insulin usage was considerably lower within the glargine arm, being less than half of that of the premixed insulin arm, resulting in an insulin cost, including pens, of around €510 for glargine compared with €735 for premixed insulin. This resulted in an average annual cost of €1259 for once-daily glargine compared with €1495

for twice-daily premixed insulin. The study was sponsored by, and the author for correspondence was from, Sanofi-aventis.

Meeting abstracts

Thompson *et al.* (2005)²⁷⁹ in an ISPOR poster (co-authors from Sanofi-aventis) present the results of cost-effectiveness modelling of glargine compared with NPH. This appears to be a precursor to the full Grima *et al.* (2007)²⁶⁵ paper reported above, as the author list is the same, with the same 0.25 QALY gain being estimated from the use of glargine. The estimated cost-effectiveness differed slightly at Can\$9804 for reasons that are not clear.

Smith *et al.* (2004),²⁸⁰ in an ISPOR poster presentation from CORE and Novo Nordisk authors, estimated the cost-effectiveness of detemir compared with NPH basal bolus among UK patients with type 2 diabetes from the perspective of the NHS. Clinical effectiveness estimates were not explicitly stated, but it appears to have been assumed that the only significant difference would be in weight, with detemir leading to a 0.4-kg gain compared with 1.3 kg for NPH. It was noted that detemir has been demonstrated to be non-inferior in terms of both HbA_{1c} level and hypoglycaemic events. The modelling predicted a survival gain of 0.13 years from detemir and a gain of 0.08 QALYs, for an additional cost of £1534: yielding a cost-effectiveness estimate of £19,218 per QALY for detemir relative to NPH.

Valentine *et al.* (2006)²⁸¹ in an ISPOR presentation (CORE and Novo Nordisk) appear to have undertaken a similar cost-effectiveness analysis for detemir as that reported above for their full 2007 paper,²⁸² but only for the subset of those transferring from NPH to detemir. An additional 0.30 QALYs was anticipated from the transfer to detemir, although in this analysis it was also anticipated to be cost saving by US\$2416 due mainly to reduced severe hypoglycaemic events, coupled with lower rates of retinopathy and cardiovascular complications. An additional 2006 ISPOR poster presentation by the same authors²⁸³ concluded that over a 5-year time horizon detemir would result in an additional 0.17 QALYs compared with NPH, with a cost-effectiveness of US\$25,368 per QALY.

A third ISPOR poster presentation by Valentine *et al.* (2007)²⁷¹ (Novo Nordisk and the IMS consultancy, which took over CORE) considered the cost-effectiveness of patients transferring from

glargine to detemir. Clinical effectiveness estimates were as for their full 2007 paper, but costs were from the German perspective. Cost savings of €1032 were anticipated from the conversion to detemir among those failing on glargine, alongside a gain of 0.29 QALYs. The reason for the lower QALY gain compared with their full 2007 paper is not apparent.

In a like manner to the poster presentations of Valentine *et al.* summarised above, Palmer *et al.* (2006)²⁸⁴ (CORE and Novo Nordisk) in an ISPOR poster presentation appear to have undertaken a similar cost-effectiveness analysis for detemir as that within the Valentine *et al.* (2007)²⁸² full paper, but for the subset of those transferring from orals to detemir. Transferring to detemir was estimated to result in an additional 0.17 QALYs at minimal

total cost to yield a cost-effectiveness estimate of US\$657 per QALY. Within this, transfer to an insulin other than detemir for those failing on oral agents does not appear to have been considered, which is a major weakness.

Palmer *et al.* (2005)²⁸⁵ [sponsorship not given, but several authors also authors of the Ray *et al.* (2007)²⁷⁵ paper, from Novo Nordisk and CORE] estimated the cost-effectiveness of premixed insulin compared with glargine from the US Medicare perspective, using clinical effectiveness estimates from the INNOVATE trial. As such, it mirrors the results of the full paper of Ray *et al.* (2007)²⁷⁵ reported above, although estimates a slightly lower gain of 0.15 QALYs but also a slightly lower ICER of £39,000 per QALY for premixed insulin compared with glargine.

Chapter 8

Cost-effectiveness modelling of the new drugs

UKPDS Outcomes Model

As summarised by Clarke *et al.* (2004),²⁸⁶ the UKPDS Outcomes Model is a lifetime model that aims to estimate the first occurrence of a number of diabetes complications: MI, which may or may not be fatal, ischaemic heart disease (IHD), stroke, congestive heart failure, amputation, renal failure and blindness in one eye. The likelihoods of complications were estimated from the data of the 3642 patients with type 2 diabetes who took part in the UKPDS. The utilities and costs associated with complications and with routine ongoing care are included within the model, having also been estimated from the UKPDS population. These are discounted at rates specified by the user.

The likelihoods of complications occurring are functions of patient characteristics, some of which are time varying and projected by the model, and past complications' history. The main time-varying factors are HbA_{1c}, SBP and the ratio of total cholesterol to HDL cholesterol, their evolution being estimated using panel data and random effects modelling. Past complications cascade through the model, in that:

- ischaemic heart disease increases the risk of MI
- chronic heart failure (CHF) increases the risk of MI, stroke and death
- blindness increases the risk of renal failure and amputation
- myocardial infarction stroke, renal failure and amputation all increase the risk of death.

Details of the above complications are shown in *Figure 13*.

For example, a one-point increase in a patient's BMI increases the annual risk of heart failure by a factor of 1.07, whereas a 1% point increase in a patient's HbA_{1c} level increases the annual risk of CHF by 1.17. As can be seen from the above, a patient's BMI has limited direct impact, affecting only the likelihood of CHF as already outlined. However, this is because most of the effect of BMI is mediated through changes in SBP and the total 'cholesterol-HDL cholesterol' ratio. But should CHF occur, the effects cascade through the model, increasing the risk of MI, stroke and death.

The implementation of the model is also most easily seen through reference from the figure within Clarke *et al.* (2004),²⁸⁶ shown in *Figure 14*.

Limitations to the model, as noted in Clarke *et al.* (2004),²⁸⁶ are that:

- It estimates only the first event (strictly speaking, the first new event, as patients may have had past events).
- Not all complications are modelled, for example peripheral neuropathy.
- Hypoglycaemic events are not modelled.
- Quality-of-life impacts are derived only from complications.

Note that within the model it is possible to specify the evolution of risk factors such as HbA_{1c} level through time, and, as a consequence, the effect of intensification of treatment can be specified upon these risk factors, from oral agents to basal insulin, and from basal insulin to basal bolus insulin, even if these intensifications occur some time after baseline.

Other parameters, such as weight, can be specified for the baseline as patient characteristics. For these parameters an initial treatment effect can be implemented between treatments; for example (1) for exenatide versus glargine, by specifying the baseline value for exenatide to be equal to the baseline value plus initial treatment effect for exenatide, and (2) for glargine, by specifying the baseline value for glargine to be equal to the baseline value plus initial treatment effect for glargine. But these parameters cannot be altered at any intensifications of treatment after baseline. This is also common to other models of diabetes, such as the Economic Assessment of Glycemic control and Long-Term Effects (EAGLE) model,²⁸⁷ and the CORE model.²⁸⁸ This has implications for comparing treatments with different effects on weight.

The UKPDS Outcomes Model²⁸⁶ is a patient-level simulation model that provides the point estimates in terms of average life expectancy, quality-adjusted life expectancies, and the costs of complications using a set of central parameter values to predict the likelihood of diabetes-related complications

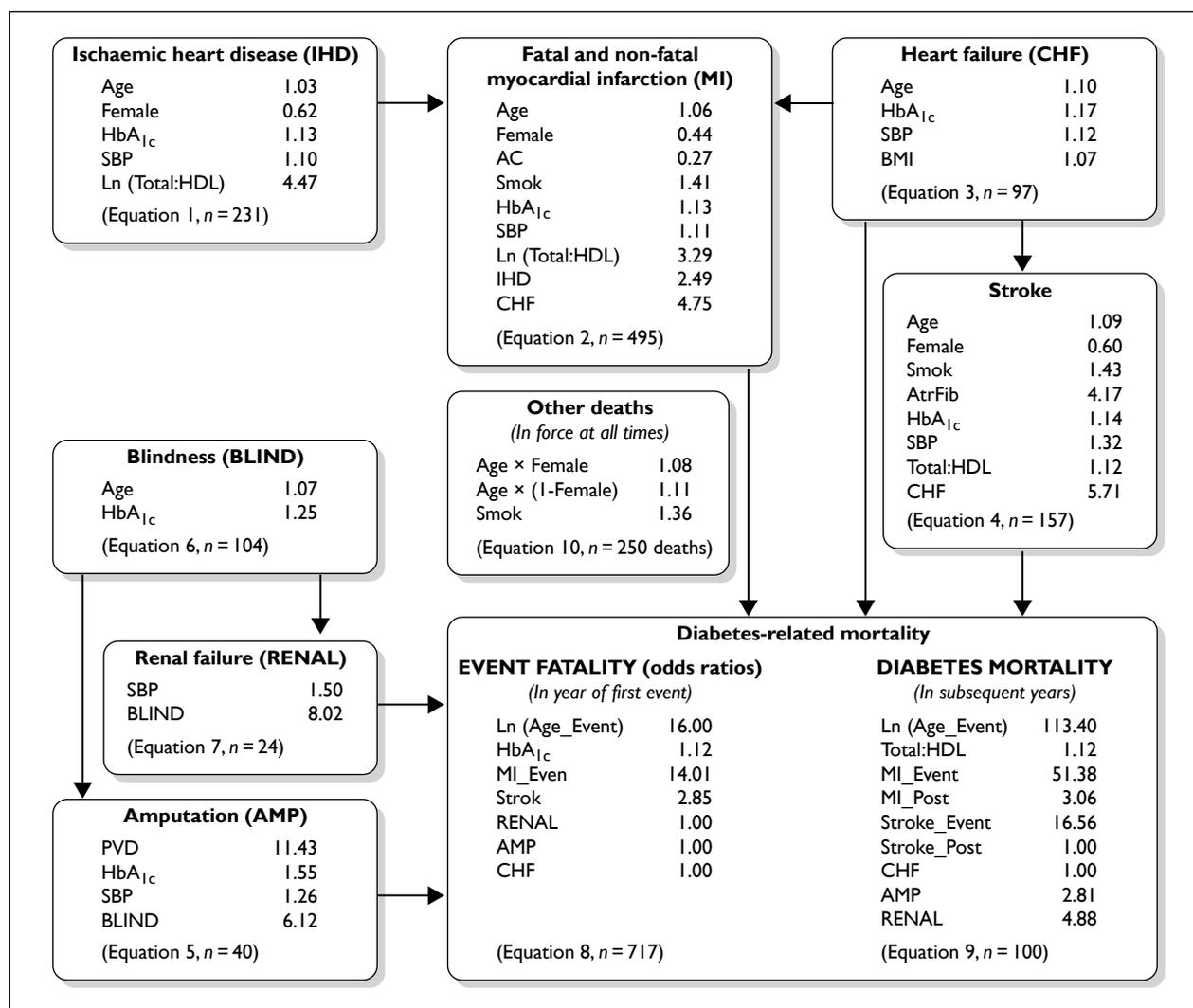


FIGURE 13 The United Kingdom Prospective Diabetes Study model algorithm (taken from Clarke et al. 2004²⁸⁶). With kind permission of Springer Science + Business Media. AC, Afro-Caribbean; AMP, amputation; AtrFib, atrial fibrillation; BLIND, blindness; BMI, body mass index; CHF, congestive heart failure; IHD, ischaemic heart disease; Ln, logarithm; MI, myocardial infarction; PVD, peripheral vascular disease; RENAL, renal failure; SBP, systolic blood pressure; SMOK, smoking.

occurring, given various patient characteristics. The model also outputs the central estimate of the cumulative mortality through time, this again being based upon the results of modelling using the set of central parameter values. Due to the patient-level simulation approach, a number of iterations of the model have to be performed in order to reduce variability within the estimates and achieve convergence for the point estimates, i.e. for each treatment regime simulated for a given patient the model performs a number of iterations to achieve convergence for the point estimates for that one treatment-patient combination.

To illustrate the impact of the number of iterations and their effect upon convergence of model estimates, the impact of increasing the number

of iterations upon the SD as a percentage of the average value of the model outputs across 1000 identical patients can be examined as below. Within this, the patient characteristics for each of 1000 patients was taken to be as outlined for the male patient, with a BMI of 35 kg/m², receiving exenatide followed by glargine upon the intensification to insulin at year 6, as outlined later in this chapter. For current purposes the patient characteristics are secondary to the illustration of the impact of increasing the number of iterations upon the SD of the estimated outputs, as shown in Table 35.

Given the above and computational availability, 250,000 iterations were performed in order to approach convergence. However, there remains

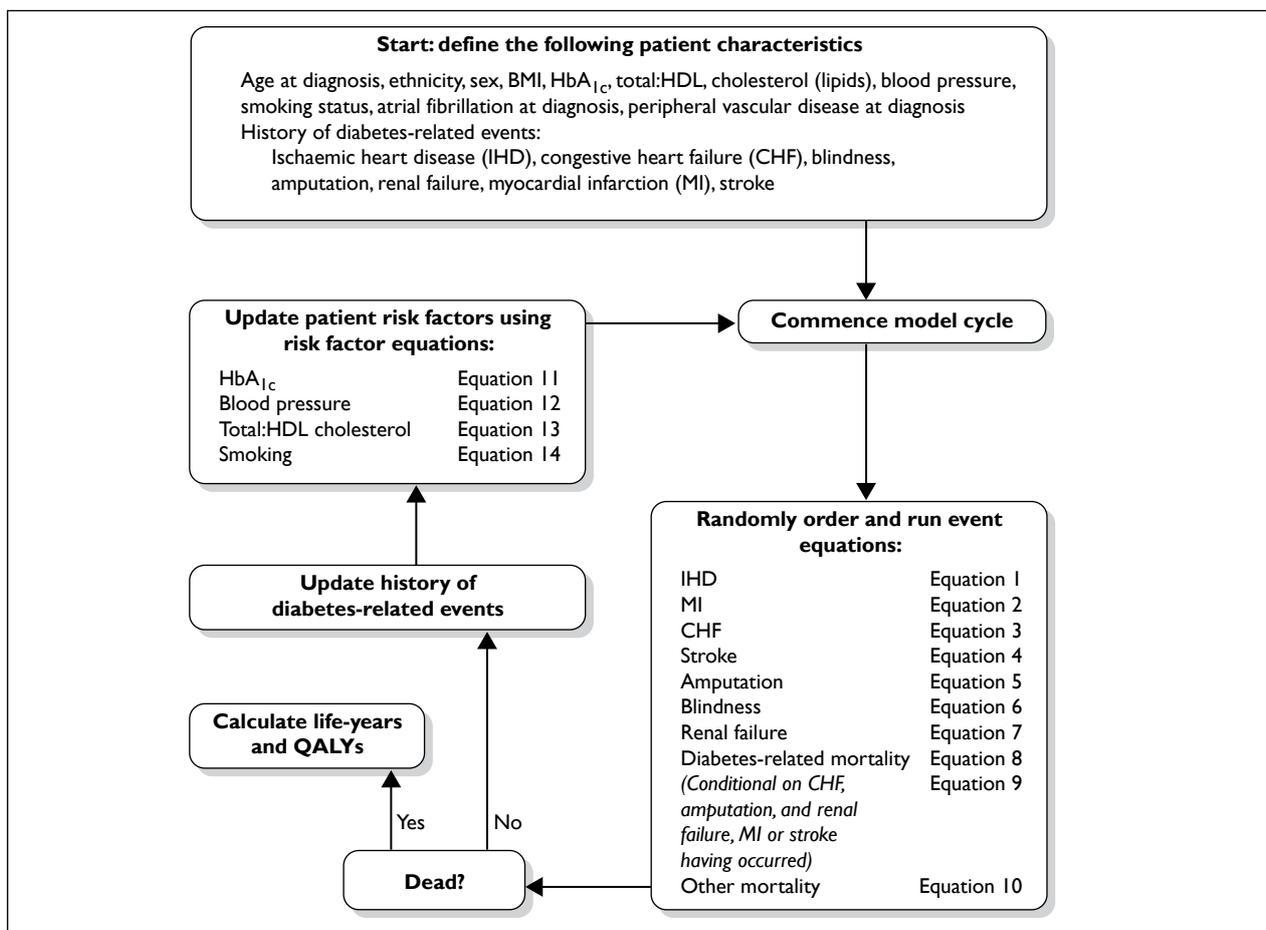


FIGURE 14 The United Kingdom Prospective Diabetes Study model equations (taken from Clarke et al. 2004²⁸⁶). With kind permission of Springer Science + Business Media.

small variability across estimates as shown above. The size of this variability should be borne in mind when examining the results of the modelling and their practical significance, even given that 250,000 iterations have been applied.

The UKPDS Outcomes Model incorporates, and allows the user to modify, the following: the immediate costs of routine care excluding the immediate drug therapy costs, the immediate and long-term costs of complications, and the QoL impact of the complications modelled. It does not provide a ready means of including other costs or effects, but it does output point estimates, through time, of the cumulative mortality for a given treatment simulation. As outlined below, there is a range of other inputs to the modelling that need to be included: the drug therapy costs and the costs of switching to insulin, and the direct QoL impacts arising from nausea, severe hypoglycaemic events and weight changes. These will be appended to the output of the UKPDS Outcomes Model in a deterministic fashion, annual quantities

being conditioned by the proportion of patients remaining alive within the relevant year, prior to being discounted at the 3.5% as recommended by NICE. For ease of reference, these will be described as the ‘bolt-ons’.

It should be noted that the UKPDS Outcomes Model also has a facility to perform additional runs of the model for a set of up to 999 bootstrapped sets of parameter values. This facility can be used to characterise the second-order uncertainty around the outputs of the model, i.e. to perform a probabilistic sensitivity analysis (PSA), for a given evolution of HbA_{1c}. This facility has not been used and a PSA has not been undertaken for the current review for two reasons:

- First, full characterisation of second-order uncertainty as required for a PSA would also require characterisation of the second-order uncertainty around treatment effectiveness parameters. Indeed, it could be argued that the second-order uncertainty around the

TABLE 35 Effect of number of iterations on convergence

Estimated outputs	Model iterations			
	1000	10,000	100,000	250,000
SD (QALYs)/E (QALYs) (%)	1.27	0.44	0.24	0.18
SD (costs)/E (costs) (%)	6.65	2.14	0.67	0.44
E, expected.				

treatment effectiveness parameters is the most important second-order uncertainty that needs to be introduced for a PSA to be meaningfully undertaken, or at a minimum is necessary if not sufficient for a PSA. Unfortunately, this is not easily implementable within the UKPDS Outcomes Model, within which it is not possible to specify a distribution around relative treatment effects. Any attempt to introduce this might also conflict with the reliable elimination of first-order uncertainty.

- Second, given the centrality of the point estimates of cumulative mortality and resultant survival function to the estimated effect of the ‘bolt-ons’, aligning the three aspects of the modelling: the model point estimates, the bootstraps and the ‘bolt-ons’ would be complicated. The ‘bolt-ons’ rely upon the estimated survival function, and as a consequence require that the point estimates be used.

But the main difficulty in terms of implementing a PSA within the UKPDS Outcomes Model is that there are no ready means to characterise the second-order uncertainty around the treatment effectiveness parameters for a head-to-head comparison of two treatments.

Methods

Patient population modelled

The previous clinical guideline (CG 66) drew patient baseline characteristics from expert opinion rather than the UKPDS, as this was felt to be more likely to reflect those moving on to third-line therapy.⁶ These were broadly in line with the inputs to the modelling reported in the economic literature above, and will be adopted for the current modelling. Note that within this, the representative patient is assumed to have progressed from metformin, to combined metformin and sulfonylurea, but now to having poor control as defined by HbA_{1c} level rising above 7.5%. Given this worsening of control, there is a choice as to how to intensify therapy with the newer agents – such as exenatide, vildagliptin and sitagliptin, older ones – such as rosiglitazone and pioglitazone, and the insulins – glargine, NPH and detemir – all being possible options.

Table 36 shows baseline characteristics of patient populations.

Note that male and female patients will be modelled separately. Being typically slightly shorter, for a given BMI the average female patient weight will be slightly less. Since the BMI modelled

TABLE 36 Baseline characteristics of patient population – male and female

Characteristic	Gender	
	Male	Female
Age (years)	58 years	58 years
Duration of diabetes (years)	5 years	5 years
HbA _{1c} (%)	7.5	7.5
Height (cm)	170	165
Weight (kg)	87	82
BMI (kg/m ²)	30	30
SBP (mmHg)	140	140
Total cholesterol (mmol/l)	4.4	4.4
HDL cholesterol (mmol/l)	1.0	1.0

is the same for both male and female patients, any differences in the output of the UKPDS Outcomes Model are anticipated to be a pure gender effect.

Similarly, since insulin dosage is weight dependent and BMI has some, though limited, impact upon the outcomes of the UKPDS Outcomes Model, the impact of weight upon cost-effectiveness will also be explored through applying a BMI of 35 kg/m².

For a given BMI and insulin dose per kilogram, women will also require a lower overall insulin requirement.

The previous guideline did not outline the background prevalences of complications associated with diabetes. The study by THIN²⁸⁸ outlines rates of complications for those transferring to insulin therapy, using data from a large UK general practice database. Adopting the rates of complications as reported for the HbA_{1c} values $\geq 7\%$ would imply prevalences, as shown in *Table 37*.

However, it should be noted that a proportion of patients within this group would have had somewhat worse HbA_{1c} levels than is being assumed within the baseline UKPDS patient characteristics. There may also have been some correlation among these, with some patients having more than one complication. This is not easily accounted for within the UKPDS Outcome Model, and as a consequence the base case will first model using an assumption of no complications at entry. Since we know from the UKPDS that many (about 25%) had complications at entry, this will be followed by with an analysis assuming the above complication rates coupled with a further assumption that patients

with one complication did not have another concurrently. This latter analysis may provide an upper estimate since: the rates of complications may be too high for the group modelled; and, the likelihood is that some patients had a range of comorbidities and while these patients would do relatively poorly this would be more than balanced by other patients having no comorbidities and performing rather better.

It is worth noting also that the UKPDS excluded newly diagnosed patients who had experienced recent MI, or who had angina.

Comparator treatments: direct head-to-head comparisons

As previously noted, all patients reaching this stage have failed on dual oral therapy, usually with metformin and a sulfonylurea, and so the issue is which drug to add as third line. Given the clinical effectiveness review, the comparisons chosen for modelling are:

1. exenatide and glargine [as reported above in the summary of Heine *et al.* (2005)⁵³³]
2. sitagliptin and rosiglitazone [as reported above in the summary of Scott *et al.* (2008)¹²¹]
3. vildagliptin and pioglitazone [as reported above in the summary of Bolli *et al.* (2008)¹²³]
4. glargine and NPH insulin (as reported within the meta-analysis in Chapter 4)
5. detemir and NPH insulin (as reported within the meta-analysis in Chapter 4).

This gives rise to the following clinical effectiveness estimates for the modelling for the base-case male patient with a BMI of 30 kg/m² (*Table 38*).

TABLE 37 Baseline morbidity

Morbidity	Prevalence assumed (%)	Source
Congestive heart failure	3.7	UKPDS ²⁸⁶ and THIN ²⁸⁹
Amputations	0	UKPDS
Neuropathy	6.5	THIN
Blindness	0	UKPDS
Retinopathy	17.7	THIN
End-stage renal failure	0	UKPDS
Nephropathy	0.7	THIN
Stroke	4.9	THIN
Myocardial infarction	8.2	THIN

THIN, The Health Improvement Network.

TABLE 38 Inputs to model

	Comparison 1		Comparison 2		Comparison 3		Comparison 4		Comparison 5	
	Exenatide	Glargine	Sitagliptin	Rosiglitazone	Vildagliptin	Pioglitazone	Glargine	NPH	Detemir	NPH
HbA _{1c} (%)	-1.11	-1.11	-0.79	-0.76	-0.88	-0.98	No difference	No difference	0.08% higher with detemir	-
Weight (kg)	-2.3	+1.8	-0.4	+1.5	+0.3	+1.9	-0.28	-	-1.20	-
Nausea (%)	57	9	1	1	-	-	-	-	-	-
Severe hypoglycaemic attacks	0.3 p.a.	0.3 p.a.	-	-	0	0	0.82 RR	-	0.76 RR	-
Nocturnal hypoglycaemic attacks	-	2.67 RR	-	-	-	-	0.56 RR	-	0.61 RR	-
p.a., per annum.										

Note that within these comparisons many of the differences in point estimates did not reach statistical significance. Also note that the comparison of exenatide and glargine is based upon the results of Heine *et al.* (2005).⁵³ The results of Barnett *et al.* (2007)⁵⁰ would imply relatively greater effect from exenatide upon severe hypoglycaemic events but a relatively lesser effect upon patient weight. Given the results of Barnett *et al.*, the effect upon BMI will be taken to apply across the other patients simulated.

Insulin doses

A distinction between the newer drugs, such as exenatide and the insulins, is that the insulin dose is weight dependent. There is also evidence that the insulin dose increase with patients' BMIs, (as shown in *Figure 15*) from data of the Aberdeen Diabetic Clinic (unpublished).

Figure 15 suggests an average requirement for the base case of around 0.55 IU/kg/day. Patients with BMIs in the mid-30s would require a higher dose of around 0.65 IU/kg/day.

Direct drug costs

The annual direct drug costs and monitoring of the various regimes are valued using BNF 56,²⁹⁰ resulting in costs for a male patient of BMI 30 kg/m² as shown below in *Table 39*.

The ingredient cost per unit of detemir is the same as for glargine, but there is evidence of there

being an estimated 18% higher dosing requirement for detemir in type 2 diabetes compared with glargine. With a slightly higher cost per pen, this yields a cost for detemir of £716.09 compared with the £634.63 for glargine shown above. Note that while the non-insulin regimens postpone the need for insulin, they do not prevent the need for insulin eventually. For example, the UKPDS model indicates that given the initial HbA_{1c} effect from exenatide, the patient's HbA_{1c} will progressively worsen until after 5 years, the 7.5% threshold will be reached, triggering an intensification of treatment, with a switch to insulin.

For those intensifying to mealtime insulin it will be assumed that the dose of insulin increases by 0.2 IU/kg/day with the estimated regimen costs as shown in *Table 40*.

Again, it will be assumed that detemir requires an additional 18% dose compared with glargine, leading to a cost of £864.92 compared with the £783.47 as reported above for glargine.

For a female patient of BMI 30 kg/m², the slightly lower average weight due to slightly lesser average height slightly reduces the average costs of the insulin-containing regimes. Similarly, increasing the BMI of male and female patients to 35 kg/m² increases the costs of the insulin-containing regimes, due to both the greater weight of the patient and the higher dose require per kilogram (*Table 41*).

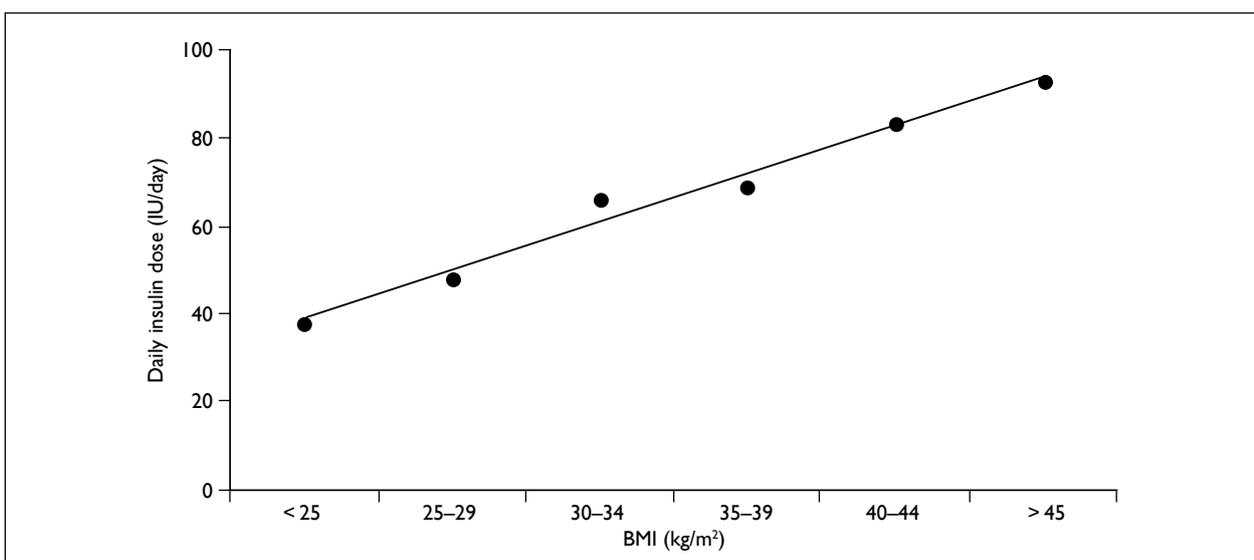


FIGURE 15 Mean insulin dose per day vs body mass index.

TABLE 39 Direct drug costs

	Cost (£)
Met + sulf + exenatide	
Metformin 2 g/day	26.07
Gliclazide 160 mg/day	20.56
Exenatide b.i.d.:	830.25
snap-on needle cost	31.10
<i>Annual total</i>	907.98
Met + sitagliptin	
Metformin 2 g/day	26.07
Sitagliptin 100 mg/day	433.57
<i>Annual total</i>	459.64
Met + vildagliptin	
Metformin 0 g/day	–
Vildagliptin 2 × 50 mg/1 mg Met	386.41
<i>Annual total</i>	386.41
Met + sulf + rosiglitazone	
Metformin 0 g/day	–
Gliclazide 160 mg/day	20.56
Rosiglitazone 8 mg + Met (2 × 4 mg/1 mg)	481.80
<i>Annual total</i>	502.36
Met + sulf + pioglitazone	
Metformin 2 g/day	26.07
Gliclazide 160 mg/day	20.56
Pioglitazone 30 mg/day	437.22
<i>Annual total</i>	483.85
Met + sulf + glargine	
Metformin 2 g/day	26.07
Gliclazide 80 mg/day	10.28
Glargine 0.55 U/kg/day:	452.53
pen	5.15
needles	31.10
Monitoring strips I	109.50
<i>Annual total</i>	634.63
Met + sulf + NPH	
Metformin 2 g/day	26.07
Gliclazide 80 mg/day	10.28
NPH average 0.55 U/kg/day:	284.09
pen	6.89
needles	31.10
Monitoring strips I	109.50
<i>Annual total</i>	467.93
Met, metformin; sulf, sulfonylurea.	

TABLE 40 Cost of insulin regimens

	Cost (£)
Met + glargine + bolus	
Metformin 2 g/day	26.07
Glargine 0.55 U/kg/day:	452.53
pen	5.15
needles	31.10
Short-acting 0.2 U/kg/day:	121.82
pen	6.19
needles	31.10
Monitoring strips I	109.50
<i>Annual total</i>	783.47
Met + NPH + bolus	
Metformin 2 g/day	26.07
NPH 0.55 U/kg/day:	284.09
pen	5.15
needles	31.10
Short-acting 0.2 U/kg/day:	121.82
pen	6.19
needles	31.10
Monitoring strips I	109.50
<i>Annual total</i>	615.02
Met, metformin.	

Other costs of treatment

In addition to the above costs, transferring to insulin requires patient education in the use of pens and titration of dosage over time, which involves specialist nursing time with an associated cost. If it is assumed that this requires an additional 15 minutes of nurse time for training in blood glucose monitoring, 30 minutes in the use of pens plus two follow-up phone calls then this would amount to roughly an additional hour of a senior nurse's time – currently costing by the Personal Social Services Research Unit (PSSRU) at £60 per hour.²⁹¹ More conservatively, the 2006–7 reference costs state the average cost per non-consultant-led outpatient attendance for diabetic medicine as being £84, which, when combined with the additional follow-up phone calls, would suggest an overall cost of £178. This cost of £178 will be used for the base case. Note that this contrast with the fixed doses of exenatide, where the only change is the doubling from half dose to full dose to minimise early side effects.

The costs of the complications of diabetes as estimated within the UKPDS Outcomes Model

TABLE 41 Costs of drug regimens by BMI

	Cost (£)		
	Female, BMI = 30	Male, BMI = 35	Female, BMI = 35
Metformin + sulfonylurea + glargine	608.41	806.05	769.88
Metformin + sulfonylurea + NPH	451.46	575.54	552.83
Metformin + sulfonylurea + detemir	685.14	918.36	875.69
Metformin + glargine + bolus	750.18	975.19	930.79
Metformin + NPH + bolus	593.24	744.68	713.74
Metformin + detemir + bolus	826.91	1087.50	1036.59

are intrinsic to the model, having been estimated from UKPDS data (*Table 42*). These will be updated from 2004 prices to 2007 prices using the PSSRU Hospital & Community Health Services Pay and Prices Index, showing a general inflation of 12% over the period as below.²⁹¹

Similarly, in the absence of complications the annual costs excluding the costs of therapy will be drawn from the UKPDS Outcomes Model and inflated to £419.

QoL impacts of complications within the UKPDS Outcomes Model

For the QoL impacts of the complications modelled, the UKPDS Outcomes Model applies the following decrements to a baseline average QoL of 0.785 (*Table 43*).

Evolution of HbA_{1c} within the modelling

The new drugs such as exenatide and the gliptins may postpone the transfer of patients to insulin. However, the assumption will be one of postponement rather than avoidance. Given this, there will be a sawtooth pattern to the evolution of HbA_{1c} from the new drugs, with their initial reduction in HbA_{1c} being followed by a slow rise as beta-cell function declines.

The evolution of HbA_{1c} will be that projected by the UKPDS Outcomes Model. But, as advised by the GDG, treatment will be intensified when the HbA_{1c} level rises above 7.5%. If this implies a switch to insulin therapy, a treatment effect, as outlined in the summary of model inputs, will be assumed, depending on the insulin regimen adopted. If treatment intensification is to add mealtime insulin to basal insulin, an initial effect of a 0.5%

improvement in HbA_{1c} level will be assumed. Note that within the implementation of the UKPDS Outcomes Model, it will be assumed that patients will rise above the 7.5% intensification threshold. The HbA_{1c} effect of treatment intensification will be assumed to apply for the year subsequent to this, with the evolution of HbA_{1c} level being that projected by the UKPDS Outcomes Model thereafter. This gives rise to a sawtooth evolution.

The evolution of HbA_{1c} under different treatments requires consideration, and, for some drugs, long-term data are not available.

The UKPDS showed progression of disease, irrespective of which drug was used. That study used two sulfonylureas: metformin and insulin. It has been suggested in the 'durability' study²⁹ that progression might be slower on a glitazone than a sulfonylurea, but, if true, that would not be relevant here because the glitazone would be used after the sulfonylurea, and the relevant comparison would be with a gliptin or exenatide.

Despite assertions that exenatide or the gliptins might preserve beta-cell function, the evidence from studies in which these drugs have been used, and then withdrawn, show no lasting effect. We will assume, therefore, that there are no differences in progression rates amongst the glitazones, the gliptins, exenatide or the insulins. (Note: The UKPDS did not report on progression according to weight loss – those with dramatic weight loss might have been expected to show slower, or no, progression. However, dramatic weight loss is not common enough to be relevant here.)

However, the evolution of HbA_{1c} may be different with insulins. Take, for example, the comparison of exenatide and glargine as third-line therapy (i.e. in addition to metformin and a sulfonylurea). After exenatide is started, there is a fall in HbA_{1c} level

TABLE 42 Costs of complications

	Cost		
	At time of event		
	Fatal (£)	Non-fatal (£)	Annual thereafter (£)
Ischaemic heart disease	–	3020	998
Myocardial infarction	1530	5823	959
Heart failure	3368	3368	1180
Stroke	4492	3562	673
Amputation	11,596	11,596	670
Blindness	–	1521	644
Renal failure	33,600	33,600	33,600

of about 1.1%, after which the HbA_{1c} level slowly rises because of progression of disease, and because the dose is fixed. After about 5 years, the HbA_{1c} level reaches 7.5%, triggering intensification with a switch to long-acting insulin, with a drop in HbA_{1c} of about 1%.

If glargine is started rather than exenatide then there is the same 1.1% fall, but with some differences. The dose needs to be titrated, so that the fall may occur more slowly. However, the dose of glargine can be increased further (unlike fixed-dose exenatide). So when the HbA_{1c} level starts rising, the dose of glargine can be increased further, so that the rise in HbA_{1c} level should be slower with glargine than exenatide (although possibly at the cost of further weight gain).

Hence over the first period the rising curve for HbA_{1c} level for exenatide might be expected to stay above that for glargine. The 7.5% threshold for intensification will be reached sooner with exenatide than glargine, and the exenatide group may switch to glargine sooner than the glargine group require to intensify to a basal bolus insulin regimen. This may not apply if those on exenatide

lose a lot of weight and those on glargine gain a lot.

Many of those on glargine, whether as third line, or as fourth line after a period on exenatide, will still progress to requiring intensification, because with disease progression and loss of beta-cell capacity they will be unable to control postprandial glucose with only a basal insulin (or will do so only at the cost of troublesome hypoglycaemia). When they do progress to a basal bolus insulin regimen, they will experience another ‘sawtooth’ drop in HbA_{1c} level, after which they will be controlled by titration of the mealtime insulin.

As both of the exenatide and glargine groups are assumed to progress at the same rate, their HbA_{1c} curves will in time come to converge. Any differences in areas under the curves will be temporary. We lack data on the difference – there may be a slightly higher curve with exenatide – and it may not be clinically significant over a lifetime.

Note that where the figure for HbA_{1c} level during any year is only marginally less than 7.5%, but where the UKPDS Outcomes Model would project it to increase somewhat above this during the following year, the intensification of therapy will be assumed to occur during this following year. This avoids introducing what seems likely to be spurious gains from one treatment postponing the intensification of therapy by an additional year compared with another treatment when the modelled evolution of HbA_{1c} level is only very marginally different between the two treatments.

The reductions in HbA_{1c} level observed in the four trials in *Table 11* should not be used to conclude that, for example, vildagliptin was more potent

TABLE 43 Utility decrements from complications

Complication	Utility decrement
Ischaemic heart disease	–0.090
Myocardial infarction	–0.055
Heart failure	–0.108
Stroke	–0.164
Amputation	–0.280
Blindness	–0.074
Renal failure	–0.263

than sitagliptin, or pioglitazone than rosiglitazone, because there were no head-to-head comparisons, and the baseline HbA_{1c} levels in the trials were different. For our base case, we have to assume that in terms of glucose-lowering effects, there are no significant differences amongst any of sitagliptin, vildagliptin, pioglitazone or rosiglitazone.

Evolution of weight within the modelling

As noted within the section describing the UKPDS Outcomes Model (Chapter 8), the weight of a patient at baseline, and as modified by the initial treatment intensification, can be specified by the user (with the necessary mechanism of assuming that weight change is immediate), but, unlike other input parameters, its evolution through time cannot. As a consequence, although HbA_{1c} level can be specified to change as patients intensify treatment and move from, say, exenatide to glargine, to glargine plus mealtime insulin, the patient weight cannot be specified to change and remains principally determined by the value set at baseline. So, while the initial fall in weight on exenatide can be entered explicitly within the UKPDS Outcomes Model, the subsequent gain after the switch to insulin cannot.

This may tend to bias the analysis in favour of those treatments that tend to reduce patient weight from the baseline value. For example, exenatide is anticipated to give a weight loss of 2.3 kg. This will affect both the likelihood of developing CHF, as estimated through the UKPDS Outcomes Model, and the direct QoL effect of weight changes. But when the patient intensifies treatment and moves from exenatide to insulin, it is not possible to dial this weight loss effect out of the UKPDS Model. It can only be reversed for the direct QoL effect of weight change. As a consequence, a sensitivity analysis will explore the effect of equalising patient weights at baseline within the UKPDS Outcomes Model and only exploring the effects of weight differentials associated with concurrent treatments through their direct impact upon QoL as outlined below.

Impact of weight changes and nausea

Applying the estimates of the impact of weight upon QoL as reported in Bagust and Beale (2005)²⁴⁷ to the results of Heine *et al.* (2005)⁵³ suggest that the weight loss associated with exenatide would result in a direct QoL increment

of 0.005. This compares with a QoL loss of around 0.004 for the weight gain associated with glargine a net treatment effect of a gain of in QoL from the use of exenatide over glargine of a little under 0.01 arising from the weight dimension alone. At mean weight loss values, the parameter estimate of Coffey *et al.* (2002)²⁴⁸ would not anticipate any QoL impact, although this is due to the dichotomous nature of the variable, which is of only limited applicability to the scenario described.

Among the 82-week completer cohort as reported in Blonde *et al.* (2006),²⁴⁵ the changes in BMI can be inferred if a common height of 1.68 m is assumed across categories. This would imply a QoL increment of around 0.004, 0.006, 0.009, 0.010 and 0.014 for the baseline categories of BMI < 25 kg/m², 25 kg/m² < BMI < 30 kg/m², 30 kg/m² < BMI < 35 kg/m², 35 kg/m² < BMI < 40 kg/m² and BMI > 40 kg/m² respectively.

The above does not take into account the effects of nausea as reported within Heine *et al.* (2005)⁵³. At the 26-week point, 57% of patients receiving exenatide had experienced nausea compared with 9% of patients receiving glargine. Given the weight loss of 2.63%, on average (ratio of mean weight loss and baseline weight), from exenatide, and QoL increment estimates as reported within the exenatide SMC submission, this suggests that those on exenatide had a QoL increment of a little less than 0.020 for the 43% not experiencing nausea compared with a QoL decrement of a little less than 0.028 for the 57% who did have nausea, giving a net effect of an average slight utility decrement among those trialling exenatide of a little less than 0.007. The parallel utility decrements for the 91% of glargine patients not experiencing nausea but seeing an average weight gain of 2.05% would be perhaps around two-thirds of the -0.044 associated with a 3% weight loss. The remaining 9% experiencing both a 2.05% weight gain and nausea might experience a similar fraction of the -0.073 QoL decrement estimated for those gaining 3% weight and experiencing nausea, as within the SMC submission. (Note: We have accepted the frequency of nausea as reported by the study. The 9% may seem high for those on insulin use, but 'nausea' is probably used to cover a range of feelings, and the opinion of the GDG indicated that though the precise rate might differ according to definition, the absolute difference between exenatide and insulin appeared correct. Note that this is incident not prevalent nausea, so one episode in the 6 months is enough for patients to be included in the 9%.)

However, the QoL increments due to weight change as reported in Lilly's SMC submission, based on the study by Matza *et al.* (2007),²⁹² are considerably higher than those of Bagust and Beale (2005).²⁴⁷ For instance, given a patient height of 1.68 cm and a BMI of 31 kg/m², for patients not experiencing nausea the Bagust and Beale estimates would imply a QoL increment of around 0.006 for a 3% weight loss and of around 0.010 for a 5% weight loss, these estimates being roughly symmetric for weight gains. The QoL increments from weight loss as reported by Matza *et al.* (2007)²⁹² are around three to four times those of Bagust and Beale, while weight gains are around seven to eight times those of Bagust and Beale.

It can also be noted that the economic appendix of the NICE guideline on obesity²⁹³ applied the following utility modifiers within the economic modelling, as shown in *Table 44*.

These would suggest that a move from the mid-point of the 26–30 kg/m² to the mid point of 31–39 kg/m², an increase of 7 points on the BMI scale, would be associated with a 0.04 loss, or around –0.0057 per BMI point. This is very similar to the –0.0061 per BMI point as estimated for those with type 2 diabetes by Bagust and Beale (2005).²⁴⁷

For the base case it will be assumed that nausea is mainly experienced during the first 3 months of treatment with exenatide, which from a QoL decrement of 0.048 implies a QALY loss of 0.012. Given the results of Heine *et al.* (2005),⁵³ it will be further assumed that a net 50% of patients treated with exenatide will experience nausea, implying an average QALY loss of 0.006 from treatment with exenatide.

The direct utility effect of weight changes associated with the different therapies will be assessed in the base case using the parameter estimates of Bagust and Beale (2005).²⁴⁷ As noted above, the new non-insulin therapies will be assumed to postpone treatment with insulin but

not prevent it. In assessing the direct utility effect of weight changes, upon transferring to insulin it will be assumed that any weight loss associated with the non-insulin will be reversed and will also be coupled with the weight gain associated with the transfer to insulin.

Note that to apply these QoL impacts from weight changes, the treatment sequences modelled and associated weight changes need to be conditioned by the survival curves as modelled by the UKPDS Outcomes Model, i.e. the QoL effect of any weight change associated with treatment is applied only to the surviving cohort. From this, it is possible to vary the QoL increments and decrements arising from weight changes to reflect the treatment sequence; for example, a patient initially using exenatide would experience the QoL impact of a 2.3-kg fall in weight while on exenatide, but, when switching to glargine, would experience the QoL impact of returning to the baseline weight and putting on an additional 1.8 kg. (Note: These trial-based data may underestimate differences in routine care and longer follow-up, which may be larger.)

Furthermore, within this calculation, in the absence of other information, the switch to mealtime insulin is assumed to cause the same weight gain as with glargine. This latter assumption may cause a slight bias against detemir within the indirect comparison with glargine, given that the weight gain from glargine as drawn from the indirect comparison appears slightly greater, although it seems unlikely to have a significant impact upon the comparisons between non-insulin regimes, being a common factor to all. But in general the possible differences between the permutations of weight gain upon the switch from basal to basal bolus insulin seems likely to be slight.

Impact of severe hypoglycaemia events

The UKPDS Outcomes Model does not permit the direct evaluation of changes to rates of severe hypoglycaemic event rates. But in the technology appraisal (TA 53) of long-acting insulin analogues (at that time only glargine), the NICE Appraisal Committee accepted that both hypoglycaemic episodes, and the fear of such episodes recurring, caused significant disutility. The relevant paragraph states:¹²

The Committee accepted that episodes of hypoglycaemia are potentially detrimental to an individual's quality of life. This is partly

TABLE 44 Utilities used in NICE obesity guideline

BMI (kg/m ²)	Male	Female
<21	0.86	0.85
21–25	0.87	0.87
26–30	0.86	0.82
31–39	0.82	0.78

the result of an individual's objective fear of symptomatic hypoglycaemic attacks as indicated in the economic models reviewed in the Assessment Report. In addition, as reported by the experts who attended the appraisal meeting, individuals' quality of life is affected by increased awareness and uncertainty of their daily blood glucose status and their recognition of the need to achieve a balance between the risk of hypoglycaemia and the benefits of longer-term glycaemic control. The Committee understood that improvement in this area of concern regarding the balance between hypoglycaemia and hyperglycaemia could have a significant effect on an individual's quality of life.

However, the guidance did not specify the amount of utility lost because of fear of hypoglycaemic episodes, and nor did the TAR,¹⁴⁴ because it was based on the industry submission from Aventis, which was classed as confidential. But, clearly, the utility gain from reducing the fear of hypoglycaemia was enough to change a very large cost per QALY to an affordable one. There is the probability that a reduction in the rate of severe hypoglycaemia events may reduce the fear of severe hypoglycaemia events, though the impact of this seems likely to be variable across patients. The QoL impact arising from this would be over and above the direct QoL impact of severe hypoglycaemia events in themselves.

This fear effect may only apply to a subgroup of patients, but as an illustration of the possible impact of this, the social tariffs derived by Dolan *et al.* (1995)²⁹⁴ suggest that a move from level 2 within the anxiety subscale of EQ-5D to level 1 would be associated with a 0.07 QoL gain. In a similar vein, the coefficients derived by Brazier *et al.* (1998)²⁹⁵ for the SF-6D questionnaire for the consistent model using standard gamble valuations suggest that a movement within the social dimension from health problems interfering moderately to not interfering would be associated with a 0.022 QoL improvement. Similarly, an improvement in the mental health subscale from feeling downhearted some of the time to little or none of the time would be associated with a 0.021 QoL improvement. However, the proportion of patients in whom a reduction in severe hypoglycaemic events would result in these changes to the social dimension or mental dimension is not known.

Currie *et al.* (2006)²⁶⁸ surveyed 1305 UK patients with type 1 diabetes and type 2 diabetes, using

both the HFS and the EQ-5D. Each severe hypoglycaemic event avoided was associated with a change of 5.9 on the HFS. Given a further estimate that each unit change on the HFS was associated with an EQ-5D QoL change of 0.008 this led to an estimated benefit from reduced fear of severe hypoglycaemic events of 0.047 per annual event avoided. This was coupled with a direct utility loss associated with a severe hypoglycaemic event of 0.0016 to yield an overall patient benefit of 0.05 per unit reduction in annual severe hypoglycaemic events.

The 0.05 QoL increment was adopted by the previous guideline (CG 66) in its evaluation of the effects of exenatide. However, at face value this estimate may be quite high. It suggests that a patient with diabetes in less than perfect health and currently experiencing one severe hypoglycaemia event every 2 years would in effect be willing to sacrifice an annual 11 days' survival to avoid this risk. A patient experiencing one severe hypoglycaemic event would be willing to sacrifice an annual three weeks' survival to avoid this risk.

The findings of the study by Currie *et al.* (2006)²⁶⁸ have been given considerable weight by industry and NICE. There are weaknesses in it that need to be considered. It involved a first questionnaire survey of 1500 subjects who had received diabetes care in primary care and hospital, and, later, another 3200 who had been admitted to hospital or attended outpatient appointments. The response rate was 31%. The hypoglycaemic events were reported for the 3 months before the survey, and this could mean that the results only apply to those with recent events, fresh in the memory; 45% were treated with insulin, and about 63% of these had type 2 diabetes.

Bias might arise through the response bias, and through the effect of recent hypoglycaemic episodes. The economists amongst the authors were from industry, and the study was funded by Sanofi-aventis and Novo Nordisk.

The independent technology assessment team from Sheffield that did the assessment report for NICE considered that the disutility was overestimated.

In terms of the cost per *severe* hypoglycaemic event that requires medical attention, Leese *et al.* (2003)²⁹⁶ coupled TA 53¹² and NHS reference costs, and suggested costs per hypoglycaemia as shown in *Table 45*.

TABLE 45 Cost of severe hypoglycaemic events

	Unit cost (£)	Percentage receiving	Weighted (£)	Source
Glucagon	20	90	18	Glargine TAR
Ambulance	144	34	49	Leese
A&E	29	7	2	Leese & NHS reference costs TA&E
Ambulance and A&E	173	52	90	Leese & NHS reference costs TA&E
Hospital	631	28	176	Leese & NHS reference costs TNELIP
<i>Weighted total</i>			335	

A&E, accident and emergency department; TA&E, Tayside Accident and Emergency; TAR, Technology Assessment Report; TNELIP, Tayside Non-Elective In-Patients.

Note that using the unit costs of Leese *et al.* (2003)²⁹⁶ and indexing to the current year (2008) gives an average of £424. However, only a minority of severe hypoglycaemia events will require medical attention, and the average cost per severe hypoglycaemia event will fall proportionately with the percentage of severe hypoglycaemia events that are attended to by relatives or friends and do not require outside medical assistance. For the base case it will be assumed that 20% of severe hypoglycaemia events require outside medical assistance.

Given these uncertainties, where a difference in severe hypoglycaemic event rates has been demonstrated between two treatments, an exploratory analysis will be performed. This will append QoL increments within the ranges suggested above to the avoidance of a severe hypoglycaemic event, coupled with a range of possible cost savings per hypoglycaemic event avoided.

In terms of the baseline rate of severe hypoglycaemia events that will be assumed to model any observed differences, within the ScHARR modelling of the cost-effectiveness of glargine (TA 53)¹² the cost per severe hypoglycaemic event was reported as £62 (although note that this was subsequently revised) and the 9-year cost of severe hypoglycaemic events of around £175 for both glargine and NPH. This, in turn, implied an annual incidence of severe hypoglycaemic events of 0.35 per patient-year, as drawn from the Diabetes Audit and Research in Tayside Scotland (DARTS) data.²⁹⁷ This is roughly in line with the rate of severe hypoglycaemic events over 26 weeks as reported in Heine *et al.* (2005)⁵³ – eight events among 549 patients, which converts to an annual rate of 0.3 per patient.

The base case will assume a 0.01 utility gain from the reduced fear associated with an annual severe hypoglycaemic event, while the baseline annual rate will be assumed to be 0.35.

Impact of nocturnal hypoglycaemic events

The Heine *et al.* (2005)⁵³ and Barnett *et al.* (2007)⁵⁰ studies reported that exenatide caused fewer nocturnal hypoglycaemic events than glargine. While these are unlikely to significantly affect costs, the GDG was of the opinion that the reduction in nocturnal hypoglycaemia would yield a significant benefit to at least a subset of patients for similar reasons as the reduced fear associated with an annual severe hypoglycaemic event outlined above. In order to address this, an additional literature search was undertaken to identify whether any concrete values for this effect could be identified. Two papers were identified that addressed QoL and nocturnal hypoglycaemic events – Davis *et al.* (2005)²⁹⁸ and Levy *et al.* (2007),²⁹⁹ though the latter was available only as an abstract.

Davis *et al.* (2005)²⁹⁸ administered a postal survey among 3200 patients with diabetes – both type 1 and type 2 – and 897 questionnaires were returned to give a response rate of only 28%: 590 patients with type 2 diabetes and 271 with type 1 diabetes. The average EQ-5D score among those with type 2 diabetes experiencing only nocturnal hypoglycaemia events, was marginally better than those experiencing daytime hypoglycaemia events that were defined as either mild or moderate. However, patient numbers falling into the only nocturnal category were small. While this was not reported for the EQ-5D results, within the 361 patients with type 2 diabetes who completed SF-36 only two patients were reported as having only

nocturnal hypoglycaemia events. Within patients with type 1 diabetes a similar pattern was observed.

Across all respondents the average EQ-5D value was reported as being 0.77 for those experiencing only nocturnal hypoglycaemic events compared with 0.65 among those whose worst hypoglycaemic event was classified as mild or moderate. Again sample size may have been small with only seven respondents of the 605 respondents within the SF-36 data having only nocturnal hypoglycaemic events.

Note that the results of Davis *et al.* (2005)²⁹⁸ would not be anticipated to uncover any additional QoL impacts from the fear of nocturnal hypoglycaemia.

The abstract of Levy *et al.* (2007)²⁹⁹ summarises the paper as having undertaken a time trade off exercise among both patients with diabetes ($n = 50$) and patients without diabetes ($n = 75$) to estimate the utility loss associated with hypoglycaemic episodes. The health state descriptors were based upon the HFS. The patients with diabetes apparently reported a disutility from rare hypoglycaemic events of -0.01 , from intermittent hypoglycaemic events of -0.05 , from frequent hypoglycaemic events of -0.17 and from nocturnal hypoglycaemic events of -0.12 . Unfortunately, the abstract was not sufficiently detailed to outline either the severity of the hypoglycaemic events or their frequency and as a consequence is of limited use. In comparison with the other estimates for hypoglycaemic events as outlined above the estimates appear to be quite large.

Given the above, the possible effects of treatments' effects upon nocturnal hypoglycaemic events have not been formally quantified within the economic modelling, though the limited results of Davis *et al.* (2005)²⁹⁸ suggest that on average the impact of nocturnal hypoglycaemia events may be limited. Some of the impact of nocturnal hypoglycaemia on QoL will in any case be captured via the fear-of-hypoglycaemic-events aspect.

Results

Within the pair-wise comparisons that follow, the default will be to present the numerical results for the male patient with a BMI of 30 kg/m^2 , augmenting this with a description of results of the other modelling undertaken. The full set of results for the pair-wise comparisons for the five patients modelled – male with BMI 30 kg/m^2 ,

female with BMI 30 kg/m^2 , male with BMI 30 kg/m^2 but excluding the weight changes from the UKPDS Outcomes Model while retaining their effect within the 'bolt-ons', male with BMI 35 kg/m^2 and female with BMI 35 kg/m^2 – can be found in Appendix 8.

Comparison I: exenatide vs glargine

The comparison here is in people failing to achieve satisfactory control on dual therapy with metformin and sulfonylurea, and the options are to start exenatide, with the expectation of needing insulin at a later stage, or to start insulin right away. Because glargine is the market leader in basal insulins in England, we use that as the comparator here. This, in effect, assumes that glargine is cost-effective compared with NPH. The cost-effectiveness of glargine and detemir versus NPH is examined later.

No allowance is made for pancreatitis in the modelling, on the grounds that the link is as yet unproven – although, even if it is confirmed, the occurrence is probably too rare to have any effect on the modelling.

Because the trials were quite short, we lack data on the longer-term relative evolutions of HbA_{1c} on exenatide followed by glargine, and on immediate glargine. There is probably little difference (results were similar in the trials) but differences may emerge over time for reasons given above. One could plausibly speculate that either treatment might have a slight advantage in HbA_{1c} level, which, however, would not be the sole factor in the cost-effectiveness equations, because, as will be seen, weight changes also have effects. We give results, therefore, for both scenarios to see what happens if evolution of HbA_{1c} is slightly better on immediate glargine (comparison 1a), and then what happens if it is slightly better on exenatide (comparison 1b).

Comparison 1a: evolution of HbA_{1c} assumed to be slower with initial glargine

The evolution of HbA_{1c}, and the resultant intensifications of therapy once HbA_{1c} level rises above 7.5%, has been assumed to follow the path as projected by the UKPDS Outcomes Model.

As previously noted, glargine has the benefit of possible titration and, when compared to the fixed-dose exenatide, this may result in a slower

worsening of HbA_{1c} level through time. So when comparing the evolution of HbA_{1c} on glargine and exenatide we might see the curve for exenatide lying above that for glargine, as shown in *Figure 16*. (Note: The peaks are exaggerated due to the truncated vertical scale.)

Within the above, for both first-line exenatide and first-line glargine there is assumed to be a therapy switch to second-line at the start of year 8. Those on first-line exenatide switch to basal glargine, while those on first-line basal glargine switch to a basal bolus combination involving glargine. Thereafter, those starting on first-line exenatide see a further therapy switch to a third-line basal bolus combination involving glargine at year 12.

For the base-case model of the male patient with a BMI of 30 kg/m² the modelling anticipates the following, as shown in *Table 46*.

Within this comparison, as before the underlying assumption is that intensification to insulin therapy uses a long-acting insulin analogue rather than NPH, with glargine used here as the current market leader.

The patient impact of treatment with exenatide compared with treatment with glargine is not large: the UKPDS Outcomes Model suggests an average gain of around 0.01 QALYs. As before, this should be read in conjunction with the section on convergence of the UKPDS Outcomes Model, and represents only a small fraction of the overall lifetime patient QALYs of one-eighth of 1%.

Paralleling this is the relative cost of treatment. The additional lifetime direct drug cost from adopting exenatide prior to glargine of around £1260 is partially offset by a relatively minor saving from a reduction in the longer-term complications of diabetes to result in an overall net total cost of around £1140. In the light of this, adopting exenatide prior to glargine is estimated to have a cost-effectiveness of between £19,000 and £20,000 per QALY.

Similar results applied for the female patient with a BMI of 30 kg/m², (*Table 47*) with a similar absolute gain in QALYs being anticipated, although it should be noted that within the UKPDS Outcomes Model results there is effectively no gain from exenatide, presumably due to the superior weight profile being counterbalanced in effect by the worse HbA_{1c} profile between years 8 and 12. But, again, these should be read in conjunction with the section on convergence of the UKPDS Outcomes Model.

Despite the greater female life expectancy, the lower absolute patient weight results in the overall net cost falling to around £950, resulting in a slightly better cost-effectiveness estimate for the adoption of exenatide prior to glargine of £18,408 per QALY for the no-complications modelling and £18,005 per QALY for the with-complications modelling.

These results rely upon even smaller estimates of QALY gains than before, and are extremely sensitive to small absolute changes in these.

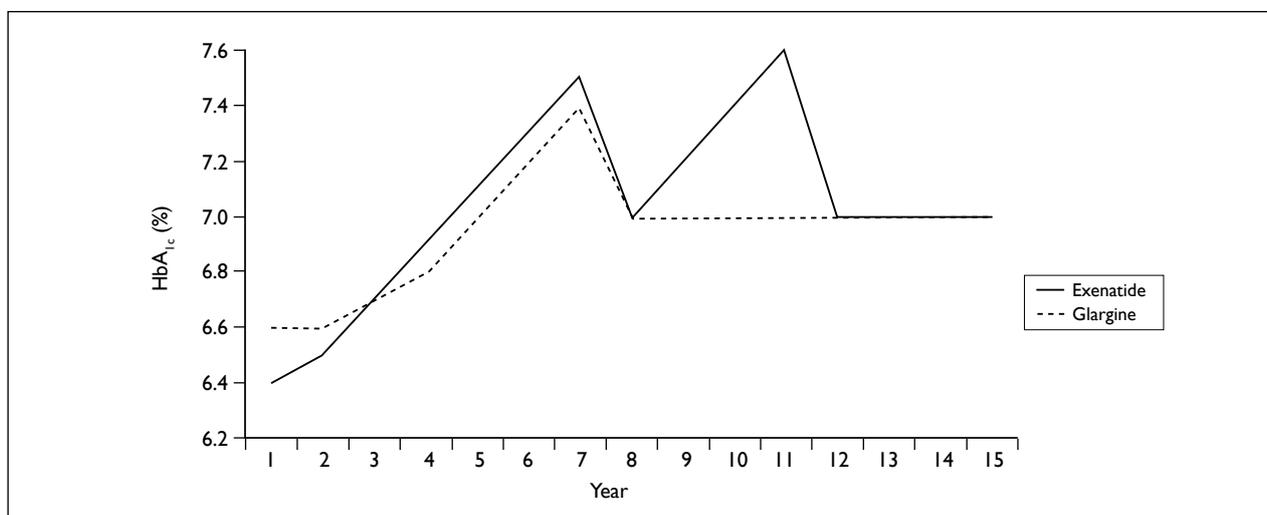


FIGURE 16 HbA_{1c}: exenatide versus glargine with dose titration for glargine.

TABLE 46 Cost per QALY: comparison 1a, exenatide versus glargine – male, BMI 30

	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.648	8.638	0.011	8.432	8.422	0.010
Total QALYs	8.617	8.559	0.058	8.402	8.345	0.057
Direct drug cost (£)	9084	7814	1271	8857	7599	1257
Total cost (£)	19,128	17,977	1151	19,634	18,501	1133
ICER (£)			19,854			19,995

Removing the direct QoL impact from weight changes from the analysis worsens the anticipated cost-effectiveness of exenatide for the male patient with a BMI of 30 kg/m² from £19,854 per QALY to £263,100 per QALY within the no complications modelling, and from £19,995 per QALY to £293,551 per QALY within the with complications modelling.

For the female patient with a BMI of 30 kg/m², removing the direct QoL impact from weight changes from the analysis results in the gain from exenatide disappearing. A very slight loss is anticipated due to the higher rate of nausea, but the overall effect is so small as to be inconsequential. In this circumstance, glargine would be estimated to be the more cost-effective treatment on the basis of its lower direct treatment costs.

As previously noted, the effect of weight changes after intensification from the first-line treatment cannot be cancelled or changed to those of the second-line treatment in the UKPDS Outcomes Model. A sensitivity analysis that assumed no weight changes from treatments within the UKPDS Outcomes Model, but retained the direct QoL impact of these within the 'bolt-ons', resulted in the following for the male patient with a BMI of 30 kg/m² (Table 48).

The above suggests that despite the better initial HbA_{1c} profile from exenatide, the superior profile of glargine during years 8–12 results in a very small anticipated patient loss from the use of exenatide if there are no weight effects entered into the UKPDS Outcomes Model. Despite this, the bolt-on elements to the survival curves are sufficient to still cause exenatide to result in minor patient gains and cost-effectiveness estimates of between around £28,200 and £28,500 per QALY. As would be anticipated, removing the direct QoL impacts from weight gain within this analysis would see exenatide being dominated by glargine.

For the male patient with a BMI of 35 kg/m² the annual net drug cost of treatment with exenatide relative to glargine compared with the male patient with a BMI of 30 kg/m² is much reduced. These results are shown in Table 49.

The higher weight and greater dose per kilogram for glargine for the male patient with a BMI of 35 kg/m², coupled with a slight increase in the net QALY gain from exenatide, results in exenatide having an overall lifetime additional direct drug of around £230, although this is offset from increased downstream cost savings to result in an overall net cost of only around £100. While exenatide does not dominate glargine, given the changing net drug costs and that glargine costs are increasing

TABLE 47 Cost per QALY: comparison 1a, exenatide versus glargine – female, BMI 30

	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	9.512	9.511	0.001	9.252	9.250	0.002
Total QALYs	9.476	9.427	0.049	9.218	9.168	0.050
Direct drug cost (£)	9206	8261	945	8970	8014	957
Total cost (£)	19,083	18,181	902	19,640	18,739	900
ICER (£)			18,408			18,005

TABLE 48 Exenatide versus glargine: comparison 1a – male, BMI 30, no weight changes

	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.641	8.645	-0.005	8.425	8.429	-0.004
Total QALYs	8.609	8.566	0.043	8.394	8.352	0.042
Direct drug cost (£)	9079	7819	1260	8852	7604	1248
Total cost (£)	19,156	17,937	1219	19,661	18,465	1196
ICER (£)			28,509			28,226

with weight, the adoption of exenatide prior to glargine appears to result in only a small overall cost increase. Patient gains do not have to be large to justify this and provided the direct QoL impacts from weight changes are realised, the cost-effectiveness estimates appear reasonable at around £1600 per QALY. However, if the direct QoL impacts from weight changes are not realised, these cost-effectiveness estimates worsen to £9301 per QALY for the no complications modelling and £21,531 per QALY for the with complications modelling.

Given their slightly lesser average weight for a BMI of 35 kg/m², the results are not as dramatic for the female patient but it remains the case that the net drug costs are much reduced given the greater patient weight (as shown in *Table 50*).

The additional direct drug cost falls to around £420, with the total net cost being only around £300. Given the direct QoL gains from weight changes, this results in cost-effectiveness estimates of around £7000 per QALY. However, if these direct QoL gains from weight changes are not realised, the UKPDS Outcomes Model estimates glargine as being very slightly more effective, and, as it is also cheaper than exenatide, it dominates.

Comparison 1b: evolution of HbA_{1c} assumed to be slower with exenatide

The underlying assumption here is that over the period before the HbA_{1c} lines converge, exenatide gives a small advantage to HbA_{1c}. This gives rise to the results in *Table 51*.

The QoL impact of treatment with exenatide compared with treatment with glargine is not large: the UKPDS Outcomes Model suggests an average gain of between 0.06 and 0.07 QALYs or around three-quarters of 1% of the overall lifetime patient QALYs. Due to the superior weight profile from the use of exenatide, the 'bolt-ons' increase this gain to around 0.10 QALYs, which is a little over 1% of the overall lifetime patient QALYs.

Paralleling this is the relative cost of treatment. The additional lifetime direct drug cost from adopting exenatide prior to glargine of around £900 is partially offset by a relatively minor saving from a reduction in the longer-term complications of diabetes to result in an overall net total cost of around £700. In the light of this, adopting exenatide prior to glargine is estimated to have a cost-effectiveness of between £6700 and £7200 per QALY.

TABLE 49 Exenatide versus glargine: comparison 1a – male, BMI 35

	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.577	8.559	0.018	8.363	8.353	0.010
Total QALYs	8.546	8.481	0.065	8.333	8.276	0.057
Direct drug cost (£)	9976	9745	231	9713	9487	226
Total cost (£)	20,180	20,077	104	20,648	20,559	89
ICER (£)			1602			1568

TABLE 50 Exenatide versus glargine: comparison 1a – female, BMI 35

	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	9.452	9.457	-0.005	9.200	9.202	-0.003
Total QALYs	9.417	9.373	0.044	9.165	9.120	0.045
Direct drug cost (£)	10,719	10,297	422	10,421	9995	426
Total cost (£)	20,739	20,434	306	21,243	20,925	318
ICER (£)			7021			7034

Similar results applied for the female patient with a BMI of 30 kg/m², with a similar absolute gain in QALYs being anticipated. However, given the greater female life expectancy, the overall net cost increased to around £1000 resulting in a slightly worse cost-effectiveness estimate for the adoption of exenatide prior to glargine of £7970 per QALY for the no complications modelling and £8653 per QALY for the with complications modelling.

These results rely upon relatively small estimates of QALY gains, and as would be anticipated are sensitive to small absolute changes in these. Removing the direct QoL impact from weight changes from the analysis worsens the anticipated cost-effectiveness of exenatide for the male patient with a BMI of 30 kg/m² from £6755 per QALY to £11,136 per QALY within the no complications modelling, and from £7180 per QALY to £12,303 per QALY within the with complications modelling. Similarly, for the female patient with a BMI of 30 kg/m², removing the direct QoL impact from weight changes from the analysis worsens the anticipated cost-effectiveness of exenatide from £7970 per QALY to £13,103 per QALY within the no-complications modelling, and from £8653 per QALY to £15,041 per QALY within the with-complications modelling.

Within the UKPDS Outcomes Model, it was noted that the effect of the first therapy upon weight could be modelled. But, whereas the effect of the switch to the second therapy upon HbA_{1c} could be modelled through the risk input sheets, the effect of the first therapy upon weight could not be undone. As a consequence, additional modelling was undertaken that assumed no weight changes from treatments within the UKPDS Outcomes Model but retained the direct QoL impact of these within the 'bolt-ons' to the resultant estimates from the UKPDS Outcomes Model.

If we assume a slight advantage in HbA_{1c} with exenatide, removing the differential impact upon weight from exenatide relative to glargine within the UKPDS Outcomes Model reduces, but does not eliminate, the QoL gain as estimated by the UKPDS Outcomes Model. A gain of around 0.05 QALYs remains, which, when coupled with the 'bolt-ons' suggests an overall QALY gain to between 0.08 and 0.09 QALYs. The overall net cost also increased slightly due to a smaller net effect upon the complications of diabetes and their associated costs, resulting in a cost-effectiveness estimate for the adoption of exenatide prior to glargine of £8967 per QALY for the no-complications modelling and £9449 per QALY for the with-complications modelling.

TABLE 51 Exenatide versus glargine: comparison 1b – male, BMI 30

	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.607	8.538	0.069	8.394	8.331	0.063
Total QALYs	8.567	8.464	0.103	8.354	8.258	0.096
Direct drug cost (£)	8813	7939	875	8592	7727	865
Total cost (£)	18,953	18,258	696	19,469	18,778	691
ICER (£)			6755			7180

Whether the estimate of the cost-effectiveness for the male patient of between £6700 and £7200 per QALY from the application of weight effects within the UKPDS Outcomes Model is a more accurate estimate than the £9000–10,000 per QALY when these weight effects are excluded cannot be determined within the modelling, and relates to model structure.

For the male patient with a BMI of 35 kg/m² the annual net drug cost of treatment with exenatide relative to glargine compared with the male patient with a BMI of 30 kg/m² is much reduced. Similarly, though the life expectancy is shorter for the patient with a BMI of 35 kg/m² this has the effect of slightly increasing the impact of the up-front weight loss on the total lifetime QALYs, given the assumption of the same absolute impact upon patients' BMI from the use of exenatide and from the use of glargine. As a consequence, modelling results in the following (as shown in Table 52).

The higher weight and greater dose per kilogram for glargine for the male patient with a BMI of 35 kg/m², coupled with a slight increase in the net QALY gain from exenatide, results in exenatide having a small overall lifetime additional direct drug cost of around £100. When coupled with some additional downstream cost savings the modelling suggests that exenatide is slightly cost saving when adopted prior to glargine for the heavier patient. Given this, adopting exenatide prior to glargine is estimated to dominate moving straight to glargine for the male patient with a BMI of 35 kg/m².

This result does not quite carry over to the female patient with a BMI of 35 kg/m², as the absolute effects upon the cost of the glargine containing regimes is slightly less for the female patient compared with the male patient. When coupled with the slightly better survival curves this leads to an anticipated lifetime total drug cost increase of around £250 for the female patient, although cost

offsets reduce the overall additional cost to a little over £100. This is still a relatively marginal cost increase, and results in cost-effectiveness estimates of only around £1000 per QALY from adopting exenatide prior to glargine compared with moving straight to glargine.

The above comparisons between exenatide and glargine recognise that glargine is the market leader, but in effect assume that glargine is cost effective (relative to NPH). Previous NICE guidance and modelling has typically found glargine to be of poor or borderline cost-effectiveness unless QoL gains are anticipated from the reduced fear of severe hypoglycaemic events. In the light of this, for comparisons 2 and 3 below the default assumption will be that intensification will lead to the use of NPH insulin.

In summary, taking into account effects, side effects, costs and expected time to progression, and assuming sufficient weight is lost, exenatide, when compared with glargine, appears to give ICERs within the range usually regarded as cost-effective for patients with a BMI of 30 kg/m². Provided that the effect of exenatide upon BMI is reasonably consistent across the weight range, the cost-effectiveness of exenatide relative to glargine improves as BMI worsens, due, in large part, to the increasing cost of the required total glargine dose.

Comparison 2: sitagliptin vs rosiglitazone

Table 53 shows the first comparison of sitagliptin versus rosiglitazone.

The point estimates above suggest that the very slightly greater improvement in HbA_{1c} level from the use of sitagliptin coupled with a superior weight profile results in a small net gain for patients from its use relative to rosiglitazone, as estimated by the UKPDS Outcomes Model. But the absolute gains are so small that despite the 250,000

TABLE 52 Exenatide versus glargine: comparison 1b – male, BMI 35

	No complications			With complications		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8.533	8.448	0.085	8.328	8.252	0.076
Total QALYs	8.493	8.375	0.118	8.289	8.180	0.109
Direct drug cost (£)	9958	9863	96	9703	9612	91
Total cost (£)	20,311	20,360	-49	20,787	20,844	-57
ICER (£)	Dominant			Dominant		

TABLE 53 Sitagliptin versus rosiglitazone – male, BMI 30

	No complications			With complications		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
UKPDS QALYs	8.566	8.549	0.017	8.347	8.342	0.005
Total QALYs	8.479	8.447	0.032	8.263	8.242	0.021
Direct drug cost (£)	5793	5938	-145	5628	5779	-151
Total cost (£)	16,083	16,277	-194	16,650	16,853	-203
ICER (£)	Dominant			Dominant		

iterations applied within the modelling, it may be more appropriate to conclude that sitagliptin is clinically equivalent to rosiglitazone, and could even be slightly less effective. However, the patient gain from sitagliptin increases to around 0.02 to 0.03 QALYs with the application of the 'bolt-ons' as would be anticipated given the better weight profile, but this remains a relatively small gain of only between one-quarter and one-third of 1% of the overall lifetime patient QALYs.

The more reliable results, as would be anticipated given the minor differences in treatment effect, are the differences in the direct drug costs. Sitagliptin is somewhat cheaper than rosiglitazone and, as a consequence, results in an anticipated lifetime direct drug cost saving of around £150 per patient, or around 2.7%. Note that this is the lifetime cost and includes the cost of later NPH insulin therapies, which are common to both regimes. While on first-line therapies the differences in direct drug costs are somewhat larger, at 9.4%. This net direct drug cost saving of around £150 applies with reasonable consistency across the patients modelled. But it should be borne in mind that the glitazones will shortly be coming off patent, with the likelihood of significant price reductions as generic formulations become available. Paralleling the difference in the drug costs of the two regimes, a fall of 9% in the price of rosiglitazone would equalise its regimen cost with one containing sitagliptin.

Concerns about the cardiovascular safety of rosiglitazone mean that its use is also declining, which may limit the relevance of this comparison.

Comparison 3: vildagliptin vs pioglitazone

Table 54 shows the first comparison of vildagliptin versus pioglitazone.

The pairwise comparison of vildagliptin against pioglitazone is unusual in having the main clinical outcomes pull in opposite directions, though this recurs in the pair-wise comparison of detemir and NPH. Vildagliptin has a marginally poorer effect upon HbA_{1c}: -0.88% as compared with -0.98% for pioglitazone, but it has a slightly better weight profile: a gain of only 0.3kg compared with a gain of 1.9kg for pioglitazone.

Note that in the above, the move from pioglitazone to vildagliptin is anticipated to result in a slight loss of utility while also being coupled with a reduction on overall cost. In this situation, cost-effectiveness improves as cost saving increases. For instance, both the no-complications and the with-complications modelling anticipate roughly the same cost-saving of -£450, but the patient loss is greater at -0.011 QALYs within the no-complications modelling compared with -0.007 within the with-complications modelling. Both sets of modelling suggest that the cost-saving from vildagliptin is warranted as the patient loss is small in both cases, but the case for this is stronger within the with-complications modelling. However, the situation is reversed within the modelling of the female patient with a BMI of 30 kg/m², as outlined in Table 55.

The UKPDS Outcomes Model now no longer anticipates any real gain from the use of pioglitazone, and the bolt-on effects of the direct QoL impacts result in a small gain from the use of vildagliptin. Within the UKPDS Outcomes Model it appears that the greater longevity of the female patient in general may lead to the impact of BMI upon CHF having more time to lead to the resultant knock-on effects upon the other complications modelled, so causing the superior weight profile of vildagliptin to balance its marginally worse impact upon HbA_{1c} level.

TABLE 54 Vildagliptin versus pioglitazone – male, BMI 30

	No complications			With complications		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	8.561	8.590	-0.029	8.353	8.378	-0.025
Total QALYs	8.468	8.479	-0.011	8.262	8.269	-0.007
Direct drug cost (£)	5371	5824	-453	5220	5665	-445
Total cost (£)	15,731	16,180	-449	16,309	16,756	-446
ICER (£)			39,846			66,799

This pattern broadly repeats itself for the modelling of patients with a BMI of 35 kg/m², the only notable change within this being that for the male patient while the UKPDS Outcomes Model still projects a vanishingly small loss from the use of vildagliptin, -0.014 QALYs per patient, the 'bolt-ons' are sufficient to turn the overall patient impact into an even smaller gain of 0.04 QALYs per patient.

The reliability of QALY differences of this magnitude is questionable, particularly in the light of the previous discussion as to convergence within the modelling. It may be better to conclude that there remains uncertainty as to the patient impact of vildagliptin compared with pioglitazone, with any net effect arising from the impact of changes in weight and HbA_{1c} level being likely to be minor. The more reliable result is a fairly consistent reduction in the average direct drug cost of around £450.

As with the comparison of sitagliptin with rosiglitazone, the above will change when pioglitazone comes off patent. A fall of around 22% in the price of pioglitazone would equalise its regime cost with one containing vildagliptin.

In summary, the gliptins and the glitazones appear roughly equivalent in glycaemic effect, but the former

have an advantage in avoidance of weight gain, which, together with their lower (at present) costs may give them an edge. However, given the size of the QALY estimates and uncertainties around them, it would be inappropriate to say that the glitazones were definitely less cost-effective than the gliptins. This does not take into account the side effects of the glitazones. These apply more with rosiglitazone, but pioglitazone also has problems with fractures and heart failure. However, until we have longer follow-up we will not know whether the gliptins have as yet unreported long-term side effects.

Comparison 4: glargine vs NPH

Table 56 shows a comparison of glargine versus NPH.

In the base UKPDS Outcomes Model, for the male patient with a BMI of 30 kg/m², there was no difference in QALYs between glargine and NPH. (Indeed one run indicated a very small loss of between -0.002 and -0.003 QALYs when compared with NPH, which, given the same effect upon HbA_{1c} level and a slightly superior weight profile for glargine, appears to have arisen from the convergence issues alluded to previously.)

The bolt-on direct QoL impacts of the slightly superior weight profile of glargine, coupled with its 0.82 RR of severe hypoglycaemic events compared

TABLE 55 Vildagliptin versus pioglitazone – female, BMI 30

	No complications			With complications		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	9.428	9.427	0.000	9.175	9.176	-0.001
Total QALYs	9.328	9.310	0.019	9.078	9.061	0.017
Direct drug cost (£)	5824	6265	-441	5646	6082	-437
Total cost (£)	15,959	16,502	-543	16,581	17,112	-531
ICER (£)			Dominant			Dominant

TABLE 56 Glargine versus NPH – male, BMI 30

	No complications			With complications		
	Glargine	NPH	Net	Glargine	NPH	Net
UKPDS QALYs	8.538	8.540	-0.002	8.331	8.333	-0.003
Total QALYs	8.464	8.457	0.007	8.258	8.253	0.006
Direct drug cost (£)	7939	6111	1828	7727	5946	1780
Total cost (£)	18,258	16,402	1855	18,778	16,980	1798
ICER (£)			281,349			320,029

with NPH yield, a gain of 0.009 QALYs, to lead to an overall net impact gain of 0.006–0.007 QALYs from the use of glargine. This is inconsequential.

The female modelling, again for a BMI of 30 kg/m², shows similar results, although for this the UKPDS Outcome Model results in a gain from glargine of 0.002 QALYs, which is again likely to be well within the bounds of modelling variability due to convergence, despite 250,000 iterations. The bolt-on gains are similarly small at 0.008 QALYs to take the overall net gain from the use of glargine to 0.010 QALYs for both the no-complications modelling and the with-complications modelling. While this reduces the estimate cost-effectiveness of glargine to £177,940 per QALY for the no-complications modelling, and to £179,074 per QALY for the with-complications modelling, these estimates are clearly well outside the usual bounds for cost-effectiveness.

Among patients with a BMI of 30 kg/m² the clear result is an average net direct drug cost of between £1800 and £1900 from the use of glargine.

For patients with a BMI of 35 kg/m² the UKPDS Outcomes Model suggests slightly larger gains of between 0.002 and 0.005 QALYs, with the 'bolt-ons' increasing this to between 0.010 and 0.013 QALYs. However, the greater weight and dose per kilogram increase the overall net cost and the estimated cost-effectiveness of glargine remains poor, at between £189,400 per QALY and £233,187 per QALY.

Among patients with a BMI of 35 kg/m² glargine is estimated to result in a net direct drug cost increase from the use of glargine of around £2500.

The above calculations do not take account of any differences in mortality from severe hypoglycaemia, which might be expected to run in parallel with, for example, the frequency of nocturnal

hypoglycaemia. Such mortality is not easily integrated into the UKPDS model, but data are lacking in any case.

Comparison 5: detemir vs NPH

Table 57 shows the comparison of detemir versus NPH.

The results for detemir relative to NPH mirror those of glargine relative to NPH outlined above. There is a slight worsening in the anticipated net patient impact from the UKPDS Outcomes Model for detemir. While this might be anticipated given the slightly worse HbA_{1c} profile, the overall effect is small, may have been impacted by the slightly superior weight profile for detemir and may still be subject to a degree of variability due to convergence given the size of the overall impact.

The 'bolt-ons' have a slightly larger effect than in the modelling of glargine relative to NPH, as would be anticipated given that detemir has a superior weight profile and a slightly better relative risk of severe hypoglycaemic events of 0.72. But the net patient impacts remain slight. The resulting estimates of the cost-effectiveness of detemir relative to NPH are well outside conventional thresholds.

Note that as in the modelling of glargine relative to NPH for the female patient of BMI 30 kg/m², within the comparison of detemir with NPH the UKPDS Outcomes Model again suggests little to no difference in patient impact between the two treatments. The 'bolt-ons' in terms of the direct QoL impacts from weight changes and severe hypoglycaemic events lead to an anticipated gain of between 0.024 and 0.027 QALYs, but this still results in cost-effectiveness estimates of £102,007 per QALY for the no-complications modelling and £113,988 for the with-complications modelling.

TABLE 57 *Detemir versus NPH – male, BMI 30*

	No complications			With complications		
	Detemir	NPH	Net	Detemir	NPH	Net
UKPDS QALYs	8.530	8.540	-0.010	8.316	8.333	-0.018
Total QALYs	8.472	8.457	0.015	8.259	8.253	0.006
Direct drug cost (£)	8826	6111	2715	8585	5946	2638
Total cost (£)	19,128	16,402	2726	19,621	16,980	2641
ICER (£)			187,726			417,625

Net costs are somewhat worse for detemir relative to NPH when compared with glargine relative to NPH. This is mainly due to the difference in dosing requirement, the cost per unit being the same. For patients with a BMI of 30 kg/m² the net direct drug cost is anticipated to be around £2700 to £2800, while for patients with a BMI of 35 kg/m² the net direct drug cost is anticipated to be around £3600–3800.

Caveats

For all the results above the anticipated differences in the QALYs are small given the 40-year time horizon. The differences in overall QALYs as outputted from the UKPDS Outcomes Model are small. Despite 250,000 iterations, small variations may remain between treatments due to the model not having completely converged. This should be borne in mind, as, given modelling uncertainties, even small reductions in the anticipated QALY differences could give rise to large increases in the cost-effectiveness estimates. Also note that although the utility coefficient on patients' BMI is small, with a detriment per point of only 0.0061 QALYs, it is sufficient to drive some of the analysis, given the small differences in overall QALYs as outputted from the UKPDS Outcomes Model.

Given the findings of our review and meta-analyses of the insulins, it is not surprising that the long-acting analogues are not cost-effective compared with NPH. The cost-effectiveness analysis hinges on small differences in weight gain, the poorly quantified fear of hypoglycaemia, and the baseline BMI and hence daily dose. The price difference is larger and the clinical advantages small.

One caveat is that the results of the meta-analyses are based on averages from trials. Some patients will have more trouble with hypoglycaemia than others, either having more episodes, or having

poorer control of glucose levels because of fear of hypoglycaemic events. For them, the utility gain from switching to an analogue may be greater, and hence cost-effectiveness better.

We also heard from members of the GDG that injection devices for the newer insulins were better. This might also have some effect on QoL.

A caveat is necessary when comparing detemir with glargine. In the head-to-head trial by Rosenstock *et al.* (2008),¹⁷⁷ detemir was used twice daily in 55% of patients, whereas glargine was used once daily. The total daily doses were 1.0 U/kg with twice-daily detemir, 0.52 U/kg with once-daily detemir, and 0.44 U/kg with glargine. This would make detemir more expensive. However, in the very large PREDICTIVE study (2007),¹⁷⁸ 82% of over 20,000 patients on detemir took it once daily.²⁷²

The only definite advantage of NPH is cost. (There could be other unknown advantages if the analogues have any as yet undiscovered side effects.) The cost difference may only be £170–230 per year per patient for glargine relative to NPH, although this would increase for very obese patients. However, if about 30% of the roughly 2.2 million people with type 2 diabetes in England are treated with insulin, the difference between using NPH and the analogues could be of the order of £100–150M per annum. This might have to be taken from other forms of diabetes care, such as structured education, or screening for complications.

In summary, as was recommended in the NICE Clinical Guideline CG 66, NPH should be preferred as first-line insulin, rather than a long-acting analogue. The analogues have modest advantages but at present much higher cost. In some patients, the benefits of the analogues relative to NPH may be greater, and cost-effectiveness correspondingly better.

Comparator treatments – exploratory indirect comparisons

In an ideal world, we would have direct comparisons of all the competing drugs. Unfortunately, as reported in the clinical effectiveness chapter, there are comparisons for which there are no trials, and others for which evidence is sparse. The most important example is probably the lack of trials comparing exenatide with the gliptins, since when looking for new third-line agents, these are the truly new ones.

The National Institute for Health and Clinical Excellence (NICE) therefore asked us to carry out some indirect comparisons. These involve comparing one drug with another through two or more trials against other agents, for example using one trial of drug A versus drug B, and another of drug B versus drug C, to compare A and C indirectly. There are various problems in that sort of analysis, such as selection bias. The patients in the trial may have different characteristics, which affect the outcomes. These characteristics might have different implications for the different drugs. For example, increases in BMI increase the cost of glargine but not of exenatide. If drug B was

exenatide and the patients in one trial are much heavier than in the other, comparing drugs A and C could be misleading.

The problems of indirect comparisons have been reported by Glenny *et al.* (2005),³⁰⁰ who examined the results of 44 analyses in which interventions could be compared both directly and indirectly, and found that ‘There were considerable statistical discrepancies between the direct and indirect estimates, but the direction of such discrepancy was unpredictable. The relative efficacy may be overestimated or underestimated by the indirect comparison ...’.

The clinical effectiveness section reports the number of drug options for clinicians to consider. For some choices, there is strong evidence from RCTs with direct head-to-head comparisons. For other choices, there are no direct comparisons at present. In order to examine possible relativities, exploratory indirect comparisons were carried out. These were regarded as hypothesis generating rather than as firm evidence, and may be a useful way of identifying comparators for future head-to-head trials. The results were provided to the GDG for discussion purposes but are not included here.

Chapter 9

Discussion

The new (and some not so new) drugs are useful additions to the therapeutic armamentarium in diabetes, and our review shows that they are clinically effective. Their cost-effectiveness depends on when they are used, and the comparators. NPH should be the insulin of first use in type 2 diabetes but has now been largely superseded. So the cost-effectiveness of exenatide depends on whether it is compared with what is used (mainly glargine) or what should be used (NPH).

The key question for drug use is where the drugs fit into the treatment pathways, but this question is an issue for the NICE GDG, not this review.

Limitations of this review

The main weaknesses are evidence gaps on clinically relevant scenarios and on long-term safety. For example, there are about 15 trials of the DPP-4 inhibitors against placebo, and almost as many against other drugs as monotherapy, but few with them as third-line agents (i.e. added to dual treatment with metformin and a sulfonylurea), and even fewer in head-to-head comparisons with other potential third-line agents.

Most trials are short term, and may not provide any indication of long-term safety issues, such as pancreatitis with exenatide. Only time will tell how often that happens, and whether (if confirmed) it is a problem only with exenatide or with all GLP-1 agonists.

When comparing drugs, one problem is that the primary effects on glycaemic control are often roughly similar, in that the drugs improve blood glucose control by similar amounts. Comparisons then depend mostly on side effects, such as weight gain or hypoglycaemia, or on QoL effects, which may be less well-defined or less well-documented than the primary outcome, which is usually HbA_{1c} level.

Problems arose with the economic modelling, partly because of a few limitations of the UKPDS model, such as inability for weight changes to be

evolved over time. This was particularly relevant to the comparison of exenatide and insulin where weight loss with the former and gain with the latter was a key difference. However, the biggest problem in economic analysis was that differences in QALYs were often very small, leading to instability of the ICERs. For example, the direct utility of weight loss though small, was sufficient to drive some analyses because of the otherwise very small QALY differences.

Compliance

People with type 2 diabetes often have comorbidities such as hypertension or hyperlipidaemia for which they receive medications. Many should be on a statin to reduce the risk of cardiovascular disease; most are overweight. Data from Aberdeen City practices (unpublished) show that 70% to 91% of people with diabetes are overweight, and that 34–53% are obese. Many will have weight-induced osteoarthritis and will be taking medication for that too. So they may be taking several non-diabetic drugs.

The more drugs a patient has to take, the poorer the adherence. Donnan *et al.* (2002),³⁰¹ from Dundee, found that even those on only one glucose-lowering agent have poor compliance, with adequate adherence in only one in three. Compliance is better with a single daily dose.³⁰¹ Those taking other medications had poorer compliance than those on just a hypoglycaemic agent. In another study from Dundee, Donnelly *et al.* (2007)³⁰² found that adherence to prescribed insulin dose was only 71%. Poorer adherence was associated with poorer control.

Farmer *et al.* (2006)³⁰³ carried out a questionnaire survey in Aylesbury. Most of the 121 respondents (all with type 2 diabetes) had positive views about the benefits of taking their medications. In particular, 86% believed that taking them regularly would reduce the chance of them needing insulin treatment. The proportion worried about weight gain was small (13%) and the fear of weight gain did not appear to reduce adherence.

A systematic review of medication adherence by Odegard and Capoccia (2007)³⁰⁴ summarises the barriers to taking medicines, and the interventions that may help. Some of the studies are more relevant to the North American situation, where people have to pay for drugs, but much of it is relevant to the UK. The review concurs with the work of Donnan *et al.* (2002)³⁰¹ (mentioned above), that common barriers to adherence include complexity of regimen and number of doses.

The implication for the treatment of type 2 diabetes may be that we should keep both the number of drugs and the number of tablets or injections per day as low as possible.

Research needs

The key question is that after metformin and sulfonylurea therapy has failed, what is the most effective and cost-effective next step? And for whom? Different drugs might be better for different subgroups (for example, subgroups based on weight).

We also need more data on some subgroups that are under-represented in the trials, such as the elderly, ethnic groups, obese children with type 2 diabetes, and those with renal impairment.

The main weaknesses in the evidence base at present are:

- the lack of long-term data on the efficacy and safety of exenatide and the gliptins
- the need for long-term data on whether the incretin-based drugs will slow the progression of disease, for example compared with progression rates on insulin
- the lack of trials directly comparing exenatide and the gliptins
- the need for more data on combined treatment with insulin and either exenatide or a gliptin
- the need for a UK trial of intensive lifestyle intervention in patients with type 2 diabetes who are failing on maximal oral agents, similar to the trial by Aas *et al.* (2005).²⁷

At the Diabetes UK Annual Professional Conference 2009, there was a large batch of abstracts, mainly posters, reporting the results of case series of patients on exenatide. Most had small numbers, and follow-up was usually for only 3 months. Without control groups, we cannot say how much of the changes were 'trial effects', but

many posters reported reductions in HbA_{1c} level of more than 1% and in weight of more than 5 kg. The few that reported data from more than one time interval showed less impressive changes in HbA_{1c} level at 6 months than at 3 months, but weight loss continued.

A few posters reported on the use of exenatide in combination with insulin, which as stated earlier in this review, does seem a logical combination with basal insulin targeting fasting and other preprandial hyperglycaemia, and exenatide (or other GLP-1 agonist) targeting postprandial hyperglycaemia. One poster by Vithian *et al.* (2009)³⁰⁵ reported that half of 42 obese patients with type 2 diabetes, who were previously on insulin, could stop the insulin after a mean of 19 weeks on exenatide, and another 29% could reduce the dose by 50%. The fall in HbA_{1c} level was 0.75% and in weight, 5%.

Price *et al.* (2009)³⁰⁶ tried exenatide in 10 obese patients on over 100 units of insulin per day, and reported a mean fall in HbA_{1c} level of 1.2% and in BMI of 0.7% at 3 months. Median insulin dose per fell by 40 U/day, from a median at baseline of 201 U/day.

Brake *et al.* (2009)³⁰⁷ tried exenatide in a mixed group of 24 patients (some on insulin, some not) and found that amongst those on insulin, HbA_{1c} level fell by 1.55% by 3 months and weight by 9.6 kg.

So there seems to be sufficient evidence to justify larger trials of the combination of metformin, insulin and GLP-1 agonists.

Future trials are likely to use the long-acting version of exenatide. Its competitor, liraglutide, has already been tested in various trials in the LEAD studies,³⁰⁸ but some of these would be exclusions under our criteria. A long-acting form is now in Phase II studies.

It is unlikely that trials will be big enough or long enough to provide hard end points such as complications or mortality; they will provide intermediate outcomes such as HbA_{1c}, BMI, QoL, hypoglycaemia, postponement of need for insulin, and adherence (the last related to complexity of regimen). Trials should use strict definitions of the different forms of hypoglycaemia.

There may be trade-offs between efficacy and adherence.

We also need more data on the fracture problem with pioglitazone (just pioglitazone because rosiglitazone use is already in decline).

Present evidence on exenatide suggests that there is no long-term preservation of beta-cell capacity by a direct effect on the pancreas, but if weight loss continued over years, would that have an indirect effect by reducing insulin resistance?

It would be useful if evidence of beta-cell mass could be obtained directly, rather than by waiting for long-term deterioration in glycaemic control (for example, 9 years as in UKPDS 17). One option might be newer forms of imaging, if these could detect changes, or lack of changes, in only a few years. The methods have been reviewed by Meier (2008).³¹

This review, in line with the NICE guideline, has assumed a stepwise approach in the management of type 2 diabetes, with insulin as a late stage. We note the arguments for earlier use of insulin, but also the reality that in many patients, especially the more overweight, it often does not achieve good control.

However, recent research has suggested a radical approach to insulin treatment in type 2 diabetes. Weng *et al.* (2008)³⁰⁹ carried out a randomised trial in *newly-diagnosed* Chinese people with type 2 diabetes, of intensive insulin therapy [continuous subcutaneous insulin infusion (CSII) or multiple daily injection (MDI)] or oral agents for short periods, given for a few days (under 8 days in most) to achieve good glucose control, followed by 2 weeks of maintained normoglycaemia. Drug treatment was then stopped, and patients continued on diet and exercise alone. They were monitored for relapse.

At 12 months, 51% of the CSII group, 45% of the MDI group, and 27% of the OHA group were still in remission. Relapse was defined as fasting PG over 7.0 mmol/l or 2-hour postprandial PG more than 10 mmol/l.

These results suggest that a period of early tight control can produce lasting remission. It is possible that repeated short periods (say once a year) might be worthwhile.

This approach needs to be replicated in other populations. The results might not be applicable to other countries. The Chinese patients had a mean BMI of only 25 kg/m². There were some

weaknesses in the design, such as a weak method of randomisation by sealed envelopes, but the main design flaw was the absence of a diet-and-exercise-alone arm.

The results are in line with a few other smaller studies of intensive therapy in newly diagnosed type 2 diabetes, reviewed by Retnakaran and Drucker (2008)³¹⁰ in an editorial that accompanied the Lancet article by Weng *et al.* (2008).³⁰⁹

Cost-effectiveness studies

The main weakness in the literature is the number of studies funded by the manufacturers, although often carried out by commercial consultancies, which tend to find that their drug is cost-effective, often by being somewhat selective in underlying assumptions.

For assessing cost-effectiveness, we need better data on issues around the effects on QoL of changes in weight, nocturnal hypoglycaemia, and the fear of hypoglycaemia.

Alternatives to polypharmacy

Lastly, but perhaps most important of all, we need more studies of the type undertaken by Aas *et al.* (2005),²⁷ on intensive lifestyle intervention in people failing on oral agents.

Recent comments from other reviewers

The *Drug and Therapeutics Bulletin*³¹¹ took a fairly firm line on exenatide, sitagliptin and vildagliptin: 'While, on current evidence, we cannot recommend the routine use of these drugs, there may be individual circumstances in which they may be helpful. For example, exenatide may provide a useful alternative to insulin, particularly since it does not seem to cause weight gain. However exenatide frequently causes nausea and vomiting, and it is much more expensive than insulin therapy. There seem to be few convincing reasons for preferring sitagliptin or vildagliptin to other oral hypoglycaemic options'.

This seems a little harsh on the gliptins, as they also do not cause weight gain.

The Australian National Prescribing Service³¹² concluded that NPH should be the initial basal insulin therapy in type 2 diabetes, mentioning

concerns about the long-term safety of glargine and detemir.

One reviewer of the NICE guidelines issued in May 2008 noted the problems when new evidence was continually emerging. In an editorial, Winocour (2008)³¹³ commented: 'Sadly, I expect this one will have a very limited shelf life – almost by design – ... An organic web-based document, which is updated annually, could address the need for clinical guidelines where there is a rapidly progressive evidence base'.

The shelf-life was expected to be limited because NICE will issue an update early in 2009, which this TAR has been produced to support. However, we know that long-acting exenatide, liraglutide and two more gliptins will be arriving in the near future, and so the update will soon need to be updated.

Changes in costs will also change the cost-effectiveness ratios. For example, we would not recommend the use of rosiglitazone at present, because of its cardiovascular safety record and the

fact that it has no advantages over pioglitazone or the gliptins. But, if the cost of rosiglitazone dropped dramatically (perhaps because generic forms arrived), the equations would change, and we might well recommend rosiglitazone, despite the slightly increased risk, because lower expenditure on oral drugs could release considerable amounts of funds for other investments in diabetes care.

However, this illustrates a tension arising from the different perspectives of clinicians, seeking the best treatment for individual patients, and those such as policy-makers or programme managers who are trying to maximise the health gains which can be achieved with limited resources.

Conclusion

The new drugs – exenatide, the gliptins – and (the not so new) detemir are all clinically effective. Their cost-effectiveness is always relative, and depends on where they are used in the therapeutic pathways.



Acknowledgements

We thank the members of the NICE Short Guideline Development Group, their expert advisor (Professor Anthony Barnett) and the technical team at NICE for useful comments and information during the iterative process that produced this report. We thank Alastair Gray of Oxford for guidance on using the UKPDS model.

Contribution of authors

Norman Waugh led the review of clinical effectiveness of DPP-4 inhibitors, assisted with cost-effectiveness section, wrote the introduction and discussion and edited the whole report. Ewen Cummins carried out the review of economics literature, and did the de novo cost-effectiveness analysis. Pam Royle led the review of clinical effectiveness of GLP-1 agonists, carried out the literature searches, and helped with editing and checking of the final draft. Christine Clar led the review of clinical effectiveness of insulins and of adding pioglitazone to insulin regimens. Meaghan Marien assisted with the review of effectiveness of insulins. Bernd Richter contributed to the review of the clinical effectiveness of DPP-4 inhibitors. Sam Philip provided clinical advice and commented on drafts.

About the Aberdeen HTA Group

The Aberdeen Health Technology Assessment Group is part of the Institute of Applied Health Sciences (IAHS), which is part of the College of Medicine and Life Sciences of the University of Aberdeen. The IAHS is made up of discrete but methodologically related research groups. The HTA Group is drawn mainly from the Health Services Research Unit, the Department of Public Health, and the Health Economics Research Unit.

The HTA Group carries out independent health technology assessments, producing technology assessment reports (TARs) for the UK HTA Programme, which commissions TARs for NICE and other bodies, such as the National Screening

Committee. The group has produced previous TARs on diabetic topics, including:

- Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010;**14**(11).
- Screening for type 2 diabetes: literature review and economic modelling. *Health Technol Assess* 2007;**11**(17).
- Non-pharmacological prevention of diabetes in those with impaired glucose tolerance. In preparation.
- The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(33).

We also produce Cochrane reviews on diabetes topics.

About the CMED group

The Cochrane Metabolic and Endocrine Disorders Group (CMED) is one of the collaborative review groups of the Cochrane Collaboration. It is primarily concerned with the evaluation of health-care interventions for the prevention, treatment or management, and rehabilitation of metabolic, nutritional and endocrine disorders, such as diabetes.

The CMED Group aims to serve several groups of people, including:

- *health-care workers*, by providing high-quality, regularly updated and easily accessible summaries of scientific knowledge
- *patients* (present and potential) and relatives, directly by providing them with high-quality information; indirectly by supporting health-care workers and policy-makers
- *researchers and those who commission research*, by accurately summarising present knowledge identifying research gaps; also through development of methodology for systematic reviewing

- *policy-makers*, by producing accessible and reliable summaries, free of the biases that may be present in submissions by groups with a particular interest. Support to policy-makers may be indirect, via support to those who produce policy analyses for governments and
- others, such as health technology assessment units
 - *undergraduate and postgraduate students*, through the provision of concise reviews of difficult topics.



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Appendix I

Search strategies

Clinical effectiveness searches GLP-1 (exenatide and liraglutide) searches

MEDLINE (Ovid) (1990–April 2008)

1. exp Glucagon-Like Peptide 1/
2. (Glucagon-Like Peptide 1 or GLP-1).tw.
3. (exenatide or liraglutide).mp.
4. 1 or 2 or 3
5. randomized controlled trial.pt.
6. random\$.tw.
7. meta-analysis.pt.
8. review.pt.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to humans
12. limit 11 to yr = "1990 – 2008"

EMBASE (Ovid) (1990–April 2008)

1. exp Glucagon-Like Peptide 1/
2. (Glucagon-Like Peptide 1 or GLP-1).tw.
3. (exenatide or liraglutide).mp.
4. exp Glucagon-Like Peptide 1/
5. meta analysis/or randomized controlled trial/or "systematic review"/
6. random\$.tw.
7. 1 or 2 or 3 or 4
8. 5 or 6
9. 7 and 8
10. limit 11 to yr = "1990 – 2008"

Cochrane Library, Issue 2, 2008 (all sections)

(exenatide):ti,ab,kw or (liraglutide):ti,ab,kw or (GLP-1):ti,ab,kw

SCI (Science Citation Index) and ISI Proceedings (2000–April 2008)

TS = (exenatide or liraglutide) AND PY = (2000–2008)

DocType = Meeting Abstract; Language = All languages; Database = SCI-EXPANDED;

ADA (American Diabetes Association) meeting abstracts

<http://scientificsessions.diabetes.org/Abstracts/index.cfm?fuseaction=Locator.SearchAbstracts>

EASD (European Association for the Study of Diabetes) meeting abstracts

www.easd.org/easdwebfiles/annualmeeting/meetingmain.html#past-AM

FDA (US Food and Drug Administration)

www.fda.gov/cder/foi/nda/2005/021773_ByettaTOC.htm

EMA (European Medicines Evaluation Agency)

www.emea.europa.eu/

MHRA (Medicines and Healthcare Products Regulatory Agency)

www.mhra.gov.uk/index.htm

Manufacturers' websites

- Amylin (Exenatide and Exenatide LAR)
 - www.amylin.com/pipeline/byetta.cfm
 - www.byetta.com/index.jsp
 - www.amylin.com/pipeline/exenatidelar.cfm
- Novo Nordisk (Liraglutide)
 - www.novonordisk.com/

Contact with Novo Nordisk concerning the unpublished LEAD trials

DPP-4 inhibitors searches

Ovid MEDLINE(R) (1996–April 2008)

EMBASE (1996–April 2008)

1. dipeptidyl peptidase-4 inhibitor\$.mp.
2. dipeptidyl peptidase-IV inhibitor\$.mp.
3. dpp-iv inhibitor\$.mp.
4. dpp-4 inhibitor\$.mp.
5. (vildagliptin or sitagliptin or saxagliptin).mp.
[mp = title, original title, abstract, name of substance word, subject heading word]
6. 1 or 2 or 3 or 4 or 5
7. limit 6 to english language

SCI (meeting abstracts) 2005–8

dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dpp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin

Cochrane Library, Issue 2, 2008 (all sections)

(dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin):ti,ab,kw

ADA meeting abstracts

<http://scientificsessions.diabetes.org/Abstracts/index.cfm?fuseaction=Locator.SearchAbstracts>

EASD meeting abstracts

www.easd.org/easdwebfiles/annualmeeting/meetingmain.html#past-AM

FDA

www.fda.gov/cder/foi/nda/2005/021773_ByettaTOC.htm

EMEA

www.emea.europa.eu/

MHRA

www.mhra.gov.uk/index.htm

Insulins – glargine and detemir searches**Ovid MEDLINE(R) (1996–April 2008)****EMBASE (1996–April 2008)**

1. (glargine or detemir).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
2. Diabetes Mellitus, Type 2/
3. type 2 diabetes.tw.
4. 2 or 3
5. 1 and 4

Cochrane Library Issue 2, 2008 (all sections)

(glargine or detemir):ti,ab,kw and (type 2 diabetes):ti,ab,kw

ADA meeting abstracts

<http://scientificsessions.diabetes.org/Abstracts/index.cfm?fuseaction=Locator.SearchAbstracts>

EASD meeting abstracts

www.easd.org/easdwebfiles/annualmeeting/meetingmain.html#past-AM

FDA

www.fda.gov/cder/foi/nda/2005/021773_ByettaTOC.htm

EMEA

www.emea.europa.eu/

MHRA

www.mhra.gov.uk/index.htm

Manufacturers

- Detemir (Levemir) – Novo Nordisk
 - www.novonordisk.com/diabetes/levemir_splash.asp
- Glargine (Lantus) – sanofi-aventis
 - www.lantus.com/

Thiazolidinediones (rosiglitazone and pioglitazone) searches**Ovid MEDLINE(R) (1996–January, week 4, 2008)**

1. exp Thiazolidinediones/
2. rosiglitazone.tw.
3. pioglitazone.tw.
4. 1 or 2 or 3
5. randomized controlled trial.pt.
6. meta-analysis.pt.
7. (random\$or meta-analysis or systematic review).tw.
8. 5 or 6 or 7
9. 4 and 8

Ovid MEDLINE(R) (1996–January, week 4, 2008)

1. exp Thiazolidinediones/
2. rosiglitazone.tw.
3. pioglitazone.tw.
4. (risk or safety or adverse or harm or pharmacovigilance).tw.
5. (side-effect\$or precaution\$or warning\$or contraindication\$or contra-indication\$).tw.
6. exp Thiazolidinediones/ae [Adverse Effects]
7. 1 or 2 or 3
8. 4 or 5
9. 7 and 8
10. 6 or 9

EMBASE (1996–2008, week 18)

1. exp Thiazolidinediones/
2. rosiglitazone.tw.
3. pioglitazone.tw.
4. 1 or 2 or 3
5. (random\$or meta-analysis or systematic review).tw.
6. Randomized Controlled Trial/
7. exp “systematic review”/
8. Meta Analysis/
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to english language

EMBASE (1996–2008, week 18)

1. exp Thiazolidinediones/

2. rosiglitazone.tw.
3. pioglitazone.tw.
4. exp Rosiglitazone/ae [Adverse Drug Reaction]
5. exp Pioglitazone/ae [Adverse Drug Reaction]
6. (risk or safety or adverse or harm or pharmacovigilance).tw.
7. (side-effect\$or precaution\$or warning\$or contraindication\$or contra-indication\$).tw.
8. 6 or 7
9. 1 or 2 or 3
10. 8 and 9
11. 4 or 5 or 10

Cochrane Library 2008, Issue 2

(thiazolidinedione*):ti,ab,kw or
(pioglitazone):ti,ab,kw or (glitazone):ti,ab,kw

Searched web sites below for safety and adverse data information

ADA meeting abstracts

<http://scientificsessions.diabetes.org/Abstracts/index.cfm?fuseaction=Locator.SearchAbstracts>

EASD

www.easd.org/easdwebfiles/annualmeeting/meetingmain.html#past-AM

FDA

www.fda.gov/cder/foi/nda/2005/021773_ByettaTOC.htm

FDA MedWatch

www.fda.gov/medwatch/safety.htm

EMA

www.emea.europa.eu/

MHRA

www.mhra.gov.uk/index.htm

AutoAlerts

Ovid AutoAlerts were set-up for the clinical effectiveness for the rest of 2008 in order to retrieve new studies published after the initial searches (shown above) were run.

Economics searches

GLP-1 economics searches

Ovid MEDLINE (1996–May, week 1, 2008)

1. exp Glucagon-Like Peptides/
2. (Glucagon-Like Peptide 1 or GLP-1).tw.
3. (exenatide or byetta).mp. [mp = title, original title, abstract, name of substance word, subject heading word]

4. liraglutide.mp.
5. 1 or 2 or 3 or 4
6. “Costs and Cost Analysis”/
7. “cost of illness”/
8. exp Economics/
9. (pharmacoeconomic\$or pharmaco-economic\$or cost\$or economic\$).tw.
10. exp Health Status/
11. exp health status indicators/
12. exp “Quality of Life”/
13. exp quality-adjusted life years/
14. exp Patient Satisfaction/
15. (qaly\$or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
16. (markov or health utilit\$or hrql or hrqol or disabilit\$).tw.
17. (quality adj2 life).tw.
18. (decision adj2 model).tw.
19. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. 5 and 19
21. from 20 keep 29,38,49
22. from 21 keep 1–3

Total retrieved = 19

Ovid EMBASE (1996 to 2008, week 19)

1. (Glucagon-Like Peptide 1 or GLP-1).tw.
2. (exenatide or byetta).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. liraglutide.mp.
4. exp Glucagon Like Peptide 1/
5. exp health economics/
6. exp health status/
7. exp “quality of life”/
8. exp patient satisfaction/
9. (pharmacoeconomic\$or pharmaco-economic\$or cost\$or economic\$).tw.
10. (qaly\$or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
11. (markov or health utilit\$or hrql or hrqol or disabilit\$).tw.
12. (quality adj2 life).tw.
13. (decision adj2 model).tw.
14. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 1 or 2 or 3 or 4
16. 14 and 15

Total retrieved = 47

CRD databases [DARE (Database of Abstracts of Reviews of Effectiveness), NHS-EED (NHS Economic Evaluation Database) and HTA] (April 2008)

glp-1 OR liraglutide OR exenatide

Total retrieved = 9

SCI (1980–April 2008)

Topic = ((glp-1 or liraglutide or exenatide) and (cost* or economic* or pharmacoeconomic* or pharmaco-economic*.)

Total retrieved = 19

DPP-4 inhibitors – economics searches Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) [1950 to present (May, week 3, 2008)]

1. dipeptidyl peptidase-4 inhibitor\$.mp.
2. dipeptidyl peptidase-IV inhibitor\$.mp.
3. Dipeptidyl-Peptidase IV Inhibitors/
4. dpp-iv inhibitor\$.mp.
5. dpp-4 inhibitor\$.mp.
6. (vildagliptin* or sitagliptin* or saxagliptin*).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
7. 1 or 2 or 3 or 4 or 5 or 6
8. "Costs and Cost Analysis"/
9. "cost of illness"/
10. exp Economics/
11. (pharmacoeconomic\$or pharmaco-economic\$or cost\$or economic\$).tw.
12. exp Health Status/
13. exp health status indicators/
14. exp "Quality of Life"/
15. exp quality-adjusted life years/
16. exp Patient Satisfaction/
17. (qaly\$or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
18. (markov or health utilit\$or hrql or hrqol or disabilit\$).tw.
19. (quality adj2 life).tw.
20. (decision adj2 model).tw.
21. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 7 and 21

Total retrieved = 25

Ovid EMBASE (1980–2008, week 22)

1. dipeptidyl peptidase-4 inhibitor\$.mp.

2. dipeptidyl peptidase-IV inhibitor\$.mp.
3. dpp-iv inhibitor\$.mp.
4. dpp-4 inhibitor\$.mp.
5. (vildagliptin* or sitagliptin* or saxagliptin*).mp. [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. exp Dipeptidyl Peptidase IV Inhibitor/
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp health economics/
9. exp health status/
10. exp "quality of life"/
11. exp patient satisfaction/
12. (pharmacoeconomic\$or pharmaco-economic\$or cost\$or economic\$).tw.
13. (qaly\$or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
14. (markov or health utilit\$or hrql or hrqol or disabilit\$).tw.
15. (quality adj2 life).tw.
16. (decision adj2 model).tw.
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 7 and 17

Total retrieved = 180

NHS-EED (May 2008)

dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dpp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin

Total retrieved = 0

SCI database (searched on 2 May 2008)

Topic = ((dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dpp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin) and (cost* or economic* or pharmacoeconomic* or pharmaco-economic* or quality same life or QALY*))

Time span = All Years. Databases = SCI-EXPANDED, SSCI, A&HCI.

Total retrieved = 38

ISI Proceedings

Results Topic = ((dipeptidyl peptidase-4 inhibitor* OR dipeptidyl peptidase-IV inhibitor* OR dpp-iv inhibitor* OR dpp-4 inhibitor* OR vildagliptin or sitagliptin or saxagliptin)

and (cost* or economic* or pharmacoeconomic* or pharmaco-economic* or quality same life or QALY*))

Time span = All Years. Databases = STP.

Total retrieved = 5

Long-acting insulin analogues – economics searches
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) [1950 to present (week 4, April 2008)] and EMBASE (1996–2008, week 17)

1. (cost* or economic* or pharmacoeconomic* or pharmaco-economic*).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
2. (quality adj2 life).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3. (treatment adj2 satisfaction).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4. (glargine or detemir or levemir or lantus or NPH).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
5. 1 or 3 or 2
6. 4 and 5
7. limit 6 to yr = "2005 – 2008"

Total retrieved = 74 from MEDLINE and 294 from EMBASE

NHS-EED (30 May 2008)

glargine or detemir or levemir or lantus

Total retrieved = 22

SCI

Topic = ((glargine or detemir) and (cost* or economic* or pharmacoeconomic* or pharmaco-economic* or quality same life or satisfaction))

Time span = 2005–2008. Databases = SCI-EXPANDED, SSCI, A&HCI.

Total retrieved = 142

Glitazones – economics searches
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) [1950 to present (May, week 3, 2008)]

1. "Costs and Cost Analysis"/

2. "cost of illness"/
3. exp Economics/
4. (pharmacoeconomic\$or pharmaco-economic\$or cost\$or economic\$.tw.
5. exp Health Status/
6. exp health status indicators/
7. exp "Quality of Life"/
8. exp quality-adjusted life years/
9. exp Patient Satisfaction/
10. (qaly\$or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
11. (markov or health utilit\$or hrql or hrqol or disabilit\$.tw.
12. (quality adj2 life).tw.
13. (decision adj2 model).tw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Thiazolidinediones/
16. (Thiazolidinedione\$or pioglitazone\$or rosiglitazone\$.tw.
17. 15 or 16
18. 14 and 17

Total retrieved = 234

Ovid EMBASE 1996 to 2008 Week 22

1. pioglitazone/or rosiglitazone/
2. (Thiazolidinedione\$or rosiglitazone\$or pioglitazone\$.tw.
3. 1 or 2
4. exp health economics/
5. exp health status/
6. exp "quality of life"/
7. exp patient satisfaction/
8. (pharmacoeconomic\$or pharmaco-economic\$or cost\$or economic\$.tw.
9. (qaly\$or EQ5D or EQ-5D or well-being or wellbeing or health status or satisfaction or euroqol or euro-qol or SF-36 or SF36 or hrql or hrqol).tw.
10. (markov or health utilit\$or hrql or hrqol or disabilit\$.tw.
11. (quality adj2 life).tw.
12. (decision adj2 model).tw.
13. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. 3 and 13

Total retrieved = 936

NHS EED (30 May 2008)

thiazolidinedione* or rosiglitazone* or pioglitazone*

Total retrieved = 18

Web of Science®

Topic = ((thiazolidinedione* or rosiglitazone* or pioglitazone*) and (pharmacoeconomic* or pharmaco-economic* or cost* or economic* or quality same life))

Time span = All Years. Databases = SCI-EXPANDED, SSCI, A&HCI.

Refined by: Document Type = (MEETING ABSTRACT)

Total retrieved = 45

Appendix 2

Characteristics of included trials – GLP-I receptor agonists

Study	Methods	Participants	Interventions	Outcomes
Barnett (2007) ⁵⁰	<p>TRIAL DESIGN: Open-label, crossover</p> <p>DURATION OF INTERVENTION: 16 weeks</p> <p>DURATION OF FOLLOW-UP: 16 weeks</p> <p>RUN-IN PERIOD: Not reported</p> <p>RANDOMISATION PROCEDURE: Computer-generated central randomisation table</p> <p>BLINDING: Open label</p> <p>OVERALL RISK OF BIAS: ++</p> <p>SOURCE OF FUNDING: Eli Lilly</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes</p> <p>INCLUSION CRITERIA: Type 2 diabetes, equal to or more than 30 years of age, receiving treatment with either a stable dose of immediate- or extended-release MET equal to or greater than 1500 mg/day or an optimally effective dose of SFU for 3 months, HbA_{1c} level equal to, or more than, 7.1% and equal to, or less than, 11%, BMI more than 25 kg/m² and less than 40 kg/m², stable body weight (not varying by more than 10% for at least 3 months prior to screening)</p> <p>EXISTING THERAPY: Failing on MET or SFUs</p> <p>EXCLUSION CRITERIA: Not reported</p> <p>NUMBERS: 141</p> <p>AGE: Mean 54 years (SD 9)</p> <p>DURATION OF DIABETES: EXEN first 6.5 years (4.9), INSULIN first 8.2 years (6.0)</p> <p>HbA_{1c}: 8.9% (SD 1.1)</p> <p>GENDER: EXEN first 52.7% males, INSULIN first 45.8% males</p> <p>ETHNIC GROUP: Not reported</p> <p>COMORBIDITIES: Not stated</p> <p>COMEDICATIONS: Patients continued prestudy dose of MET or SFU</p>	<p>NUMBER OF STUDY CENTRES: 26 sites</p> <p>SETTING: Unclear</p> <p>INTERVENTION: EXEN, subcutaneous injection, 10 µg/day for 4 weeks then 20 µg/day for 12 weeks, administered twice daily</p> <p>CONTROL: Insulin glargine (INSULIN), titrated to FBG ≤5.6 mmol/l, initiated at 10IU and increased weekly, four times daily</p> <p>TREATMENT BEFORE STUDY:</p> <ul style="list-style-type: none"> - Patients had been receiving treatment with either a stable dose of immediate- or extended-release MET 1500 mg/day or an optimally effective dose of SFU for 3 months - Patients continued on prestudy dose of MET or SFU 	<p>PRIMARY OUTCOMES: HbA_{1c} (change from baseline to end of treatment)</p> <p>SECONDARY OUTCOMES: Target HbA_{1c}; bodyweight, fasting serum glucose, fasting serum lipids, 7-point SMBG, PPG excursions; safety assessment; adverse events, including hypoglycaemia</p>

Study	Methods	Participants	Interventions	Outcomes
Davis (2007) ⁵¹	<p>TRIAL DESIGN: Parallel, open-label trial</p> <p>DURATION OF INTERVENTION: 16 weeks</p> <p>DURATION OF FOLLOW-UP: 16 weeks</p> <p>RUN-IN PERIOD: Not reported</p> <p>RANDOMISATION PROCEDURE: Not reported in detail; 2:1 EXENATIDE-INSULIN</p> <p>BLINDING: None</p> <p>SETTING: Five centres</p> <p>COUNTRY: USA</p> <p>ITT ANALYSIS: No. Results are only for patients with sufficient data for primary efficacy analysis ($n = 45$ compared with $n = 49$ ITT)</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Inadequate; numbers vary in tables</p> <p>SAMPLE SIZE CALCULATION: Yes; however, powered to 'verify probability of observing > 60% success in Exenatide group' (?)</p> <p>OVERALL RISK OF BIAS: +</p> <p>SOURCE OF FUNDING: Not specified but some authors declared as employees of Amylin Pharmaceuticals and/or Eli Lilly</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes</p> <p>INCLUSION CRITERIA: Between 30 and 75 years; diagnosed within 2 years, treated with one of the following for equal to or more than 3 months to 12 years: once- or twice-daily NPH insulin; once-daily glargine; once daily or three times daily ultralente insulin or insulin mixture. All patients on immediate or extended-release MET and/or SFU for at least 3 months prior to screening; or fixed-dose SFU/MET combination therapy. At time of screening: HbA_{1c} level equal to or less than 10.5; BMI > 27 and < 40 kg/m²; history of stable body weight</p> <p>EXISTING THERAPY: Insulin and oral agents</p> <p>EXCLUSION CRITERIA: > three episodes of severe hypoglycaemia within 6 months prior to screening, used any prescription drug to promote weight loss within 3 months, previously received EXEN or GLP-1 analogues</p> <p>NUMBERS: 49 (51 were randomised; one discontinued before receiving study drug and one withdrawn as found not to have type 2 diabetes)</p> <p>AGE: Mean – EXEN 54 years (SD 8), INSULIN 52 (SD 8)</p> <p>DURATION OF DIABETES: Mean EXEN 10.4 years (SD 6.2), INSULIN 11.9 years (SD 7.4)</p> <p>HbA_{1c}: Mean EXEN 8% (SD 1.2), INSULIN 8.3% (SD 0.9)</p> <p>GENDER: EXEN 46% males, INSULIN 50% males</p> <p>ETHNIC GROUPS: Not reported</p>	<p>INTERVENTION: EXEN, s.c., 10 µg/day for 4 weeks and 20 g/day for 12 weeks, before morning and evening meals</p> <p>CONTROL: Usual insulin (INSULIN) regimen for 16 weeks</p> <p>OTHER TREATMENT: Both groups continued oral medication and instructed to continue diet and exercise regimen</p>	<p>PRIMARY OUTCOMES:</p> <ol style="list-style-type: none"> 1. HbA_{1c} <p>*Mean HbA_{1c} (%) change from baseline to 16 weeks</p> <ol style="list-style-type: none"> 2. Fasting serum glucose <p>*Mean fasting serum glucose (mmol/l) at baseline and 16 weeks</p> <p>SECONDARY OUTCOMES:</p> <ol style="list-style-type: none"> 1. Blood chemistries 2. Fasting serum lipids 3. Fasting C-peptide 4. Body weight <p>*Mean change in body weight from baseline to 16 weeks</p> <ol style="list-style-type: none"> 5. Point SMBG <p>OTHER OUTCOMES:</p> <ol style="list-style-type: none"> 1. Adverse events defined as any untoward medical occurrence, without regard to the possibility of a causal relationship

Study	Methods	Participants	Interventions	Outcomes
DeFronzo (2005) ³⁸	<p>TRIAL DESIGN: RCT</p> <p>DURATION OF INTERVENTION: 30 weeks</p> <p>DURATION OF FOLLOW-UP: 30 weeks</p> <p>RUN-IN PERIOD: 4 weeks single-blind with twice-daily s.c. injections of placebo</p> <p>RANDOMISATION PROCEDURE: Stratified according to screening HbA_{1c} values (< 9% and ≥ 9%)</p> <p>BLINDING: Triple blinded. Except for lead-in period (single blind) and MIN or MAX SFU dose (not blinded)</p> <p>SETTING: 91 sites (82, DeFronzo at 30 weeks; 54, Ratner; at 82 weeks)</p> <p>COUNTRY: USA</p> <p>ITT ANALYSIS: Yes</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate</p> <p>SAMPLE SIZE CALCULATION: Yes; powered for primary outcome HbA_{1c}</p> <p>OVERALL RISK OF BIAS: +</p> <p>SOURCE OF FUNDING: Amylin Pharmaceuticals and Eli Lilly</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes treated with MET and a SFU (those taking a SFU were excluded in DeFronzo study)</p> <p>INCLUSION CRITERIA: 22–77 years of age (19–78 in DeFronzo), type 2 diabetes, treated with MET, screening FPG of < 13.3 mmol/l, BMI 27–45 kg/m², HbA_{1c} 7.5 (7.1 in DeFronzo study) to 11%, MET dose equal to or more than 1500 mg/day for 3 months before screening, and SFU dose at least maximum effective dose for 3 months before screening; weight stable for 3 months before screening; no clinically significant abnormal laboratory test values, females postmenopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing throughout study</p> <p>EXISTING THERAPY: Failing MET</p> <p>EXCLUSION CRITERIA: Use of meglitinides, TZDs, alpha-glucosidase inhibitors, exogenous insulin therapy, weight-loss drugs, any investigational drug, or evidence of clinically significant comorbid conditions</p> <p>NUMBERS: 733</p> <p>AGE: EXEN10, 55 years (SD 9); EXEN20, 55 years (SD 10); PLACEBO, 56 years (SD 10)</p> <p>DURATION OF DIABETES: EXEN10, 8.7 years (SD 5.9); EXEN20, 8.7 years (SD 6.1); PLACEBO, 9.4 years (SD 6.1)</p> <p>HbA_{1c}: EXEN10, 8.5 (SD 1); EXEN20, 8.5 (SD 1.1); PLACEBO 8.5 (SD 1)</p> <p>GENDER: EXEN10, 59.2% males; EXEN20, 59.3% males; PLACEBO, 55.9% males</p> <p>ETHNIC GROUPS: EXEN10 – white 69%, black 10.2%, Hispanic 15.9%; EXEN20 – white 66.4%, black 11.6%, Hispanic 16.6%; PLACEBO – white 68.4%, black 12.1%, Hispanic 15.8%</p>	<p>INTERVENTION: EXEN s.c., 10 µg/day, morning and evening for 30 weeks</p> <p>INTERVENTION: EXEN s.c., 10 µg/day for 4 weeks, increasing to 20 µg/day for 26 weeks, morning and evening</p> <p>CONTROL: Placebo s.c. twice daily</p> <p>OTHER TREATMENT: All participants continued current regimen of MET. No variation of SFU dose permitted after week 12; unblinded randomisation to either maximally effective or minimum recommended doses of SFU</p>	<p>PRIMARY OUTCOMES:</p> <ol style="list-style-type: none"> HbA_{1c} <p>*Mean HbA_{1c} change from baseline</p> <ol style="list-style-type: none"> Safety <p>Treatment-emergent adverse events defined as those occurring upon or after receiving the first randomised dose</p> <p>SECONDARY OUTCOMES:</p> <ol style="list-style-type: none"> HbA_{1c} <p>*Number (%) of patients achieving HbA_{1c} ≤ 7% by week 30 (of ITT subjects with baseline HbA_{1c} > 7%)</p> <p>Change in HbA_{1c} at 30 weeks stratified by baseline A_{1c}</p> <ol style="list-style-type: none"> Effect of EXEN on fasting and postprandial (meal cohort only) PG concentrations Body weight <p>*Change in body weight (kg) from baseline to 30 weeks</p> <ol style="list-style-type: none"> Fasting and postprandial concentrations of blood insulin Fasting proinsulin Lipids

Study	Methods	Participants	Interventions	Outcomes
Heine (2005) ⁵³	<p>TRIAL DESIGN: Randomised parallel open label</p> <p>DURATION OF INTERVENTION: 26 weeks</p> <p>DURATION OF FOLLOW-UP: 26 weeks</p> <p>RUN-IN PERIOD: No details of any run-in period</p> <p>RANDOMISATION PROCEDURE: Central randomisation table administered by interactive voice-response system; randomisation stratified by investigative size (block of four)</p> <p>BLINDING: Open label</p> <p>SETTING: 82 centres</p> <p>COUNTRY: 13 countries</p> <p>ITT ANALYSIS: Yes</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate</p> <p>SAMPLE SIZE CALCULATION: Yes, powered for primary outcome HbA_{1c}</p> <p>OVERALL RISK OF BIAS: ++</p> <p>SOURCE OF FUNDING: Eli Lilly and Amylin Pharmaceuticals</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes</p> <p>INCLUSION CRITERIA: 30–75 years of age, treated with stable and maximally effective doses of MET and a SFU for at least 3 months before screening, HbA_{1c} ranging from 7% to 10%, BMI ranging from 25 to 45 kg/m²</p> <p>EXISTING THERAPY: MET and SFU</p> <p>EXCLUSION CRITERIA: Had more than three episodes of severe hypoglycaemia within 6 months before screening; had been treated with insulin within 3 months before screening, with TZDs, within 4 months before screening, with alpha-glucosidase inhibitors within 3 months before screening, or with meglitinides within 3 months before screening</p> <p>NUMBERS: 551</p> <p>AGE: EXEN 55 years, INSULIN 56.6 years</p> <p>DURATION OF DIABETES: 9.5 years</p> <p>HbA_{1c}: EXEN 8.2% (SD 1), INSULIN 8.3% (SD 1)</p> <p>GENDER: EXEN 55% males INSULIN 56.5 males</p> <p>ETHNIC GROUPS: EXEN – white 79.8%, black 0.7%, Hispanic 15.6%; INSULIN – white 80.5%, black 1.1%, Hispanic 15%</p>	<p>INTERVENTION: EXEN 20 µg/day s.c., morning and evening</p> <p>CONTROL: Insulin glargine (INSULIN), s.c., titrated to BG level < 5.6 mmol/l</p> <p>OTHER TREATMENT: MET and SFUs fixed at prestudy levels</p>	<p>PRIMARY OUTCOMES:</p> <ol style="list-style-type: none"> 1. HbA_{1c} <p>*Mean HbA_{1c} change from baseline to 26 weeks</p> <p>*Percentage patients who achieved target HbA_{1c} level ≤ 7% (for ITT patients with HbA_{1c} level > 7% at baseline)</p> <p>SECONDARY OUTCOMES:</p> <ol style="list-style-type: none"> 1. Body weight <p>*Mean change in body weight from baseline to 26 weeks</p> <ol style="list-style-type: none"> 2. FPG <p>*Reduction in FPG from baseline to 26 weeks</p> <p>*Percentage of patients achieving FPG < 5.6 mmol/l</p> <ol style="list-style-type: none"> 3. Blood glucose <p>*Mean change in SMBG from baseline to 26 weeks</p> <ol style="list-style-type: none"> 4. Patient-reported health outcome measures (Secnik Boye)

Study	Methods	Participants	Interventions	Outcomes
<p>Kendall (2005)⁵⁹</p>	<p>TRIAL DESIGN: RCT, double-blind, parallel</p> <p>DURATION OF INTERVENTION: 30 weeks</p> <p>DURATION OF FOLLOW-UP: 30 weeks</p> <p>RUN-IN PERIOD: 4 weeks</p> <p>RANDOMISATION PROCEDURE: Randomisation stratified according to HbA_{1c} values; no details reported</p> <p>BLINDING: Double blind</p> <p>SETTING: 91 centres</p> <p>COUNTRY: USA</p> <p>ITT ANALYSIS: Yes</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate</p> <p>SAMPLE SIZE CALCULATION: Yes, powered for primary outcome HbA_{1c}</p> <p>OVERALL RISK OF BIAS: +</p> <p>SOURCE OF FUNDING: Amylin Pharmaceuticals and Eli Lilly</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes, treated with MET and SFU</p> <p>INCLUSION CRITERIA: 22–77 years of age, screening FPG < 13.3 mmol/l; BMI 27–45 kg/m²; HbA_{1c} 7.5–11%.</p> <p>MET dose was ≥ 1500 mg/day and SFU dose at least maximum effective dose for 3 months before screening. Weight stable for 3 months before screening; no clinically significant abnormal lab test values (> 25% outside normal lab values). Female subjects postmenopausal, surgically sterile, or using contraceptives for 3 months before screening and continuing through study</p> <p>EXISTING THERAPY: MET and a SFU</p> <p>EXCLUSION CRITERIA: Use of meglitinides, TZDs, alpha-glucosidase inhibitors, exogenous insulin therapy, weight-loss drugs, corticosteroids, drugs known to affect GI motility, transplantation medications or any investigational drug or evidence of clinically significant comorbid conditions for 3 months before screening</p> <p>DIAGNOSTIC CRITERIA: Not reported</p> <p>NUMBERS: 733</p> <p>AGE: EXEN 10 µg, 55 years (SD 9); EXEN 20 µg, 55 years (SD 10); PLACEBO, 56 years (SD 10)</p> <p>DURATION OF DIABETES: EXEN 10 µg, 8.7 years (SD 5.9), EXEN 20 µg, 8.7 years (SD 6.4), PLACEBO, 9.4 years (SD 6.2)</p> <p>HbA_{1c}: EXEN 10 µg 8.5% (SD 1); EXEN 20 µg, 8.5% (SD 1.1); PLACEBO 8.5% (SD 1)</p> <p>GENDER: EXEN 10 µg, 59.2% males; EXEN 20 µg, 59.3% males; PLACEBO, 55.9% males</p> <p>ETHNIC GROUPS: EXEN 10 µg, white 69%, black 10.2%, Hispanic 15.9%; EXEN 20 µg, white 66.4%, black 11.6%, Hispanic 16.6%; PLACEBO, 68.4%, black 12.1%, Hispanic 15.8%</p>	<p>INTERVENTION: EXEN10 10 µg/day, subcutaneous, morning and evening</p> <p>INTERVENTION: EXEN20 20 µg/day, subcutaneous, morning and evening</p> <p>CONTROL: Subcutaneous, titrated to BG level < 5.6 mmol/l</p> <p>OTHER TREATMENT: MET and SFU fixed at pre-study levels</p>	<p>PRIMARY OUTCOMES:</p> <ol style="list-style-type: none"> HbA_{1c} Mean HbA_{1c} change from baseline to 30 weeks Percentage of patients who achieved target HbA_{1c} level ≤ 7% (for ITT patients with HbA_{1c} level > 7% at baseline) <p>SECONDARY OUTCOMES:</p> <ol style="list-style-type: none"> Body weight Mean change in body weight from baseline to 30 weeks FPG Reduction in FPG from baseline to 30 weeks Percentage of patients achieving FPG < 5.6 mmol/l Blood glucose Mean change in self-monitored blood glucose from baseline to 26 weeks Fasting plasma lipids Exenatide pharmacokinetics <p>ADDITIONAL PUBLISHED OUTCOMES:</p> <p>Safety:</p> <ol style="list-style-type: none"> Treatment emergent adverse events Hypoglycaemic events Clinical laboratory tests Physical examination 12-lead ECG Vital signs Titration of anti-EXEN antibodies

Study	Methods	Participants	Interventions	Outcomes
Nauck (2007) ¹²²	<p>TRIAL DESIGN: RCT</p> <p>DURATION OF INTERVENTION: 52 weeks</p> <p>DURATION OF FOLLOW-UP: 52 weeks</p> <p>RANDOMISATION PROCEDURE: Procedure not reported. Stratified by site, based on screening values of HbA_{1c}</p> <p>BLINDING: Not reported</p> <p>SETTING: Multicentre (number not reported)</p> <p>COUNTRY: 13 countries</p> <p>ITT ANALYSIS: Yes</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Yes</p> <p>SAMPLE SIZE CALCULATION: Yes</p> <p>OVERALL RISK OF BIAS: ++</p> <p>SOURCE OF FUNDING: Not specified but authors declared as consultants or employees of Amylin Pharmaceuticals and/or Eli Lilly</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes</p> <p>INCLUSION CRITERIA: Between 30 and 75 years of age; had suboptimal glycaemic control despite receiving optimally effective MET and SFU therapy for at least 3 months; HbA_{1c} levels $\geq 7\%$ and $\leq 11\%$; BMI ≥ 25 and ≤ 40 kg/m², and a history of stable body weight</p> <p>EXISTING THERAPY: MET and SFU</p> <p>EXCLUSION CRITERIA: More than three episodes of severe hypoglycaemia within 6 months prior to screening, had been treated with insulin, TZDs, alpha-glucosidase inhibitors or meglitinides for longer than 2 weeks within 3 months</p> <p>NUMBERS: 501 in ITT sample</p> <p>AGE: EXEN 59 years (SD 9), INSULIN 58 (SD 9)</p> <p>DURATION OF DIABETES: EXEN, 9.8 years (SD 6.3); INSULIN, 10 years (SD 6.2)</p> <p>HbA_{1c}: EXEN, 8.6% (SD 1), INSULIN, 8.6 (SD 1.1)</p> <p>GENDER: EXEN 53% males, INSULIN 49% males</p> <p>ETHNIC GROUPS: Not reported</p>	<p>INTERVENTION: EXEN, s.c., 10 µg/day for 4 weeks then 20 µg for 48 weeks (morning and evening doses)</p> <p>CONTROL: INSULIN ASPART 30/70, s.c., morning and evening doses</p> <p>OTHER TREATMENT: Maintenance of optimally effective prestudy MET and SFU doses</p>	<p>PRIMARY OUTCOMES:</p> <ol style="list-style-type: none"> HbA_{1c} <p>*Mean change in HbA_{1c} from baseline to week 52</p> <p>SECONDARY OUTCOMES</p> <ol style="list-style-type: none"> Body weight <p>*Mean reduction in body weight from baseline to week 52</p> <ol style="list-style-type: none"> FSG <p>*Mean change in fasting serum glucose from baseline to week 52</p> <ol style="list-style-type: none"> SMBG Beta-cell function <p>*Mean change in beta-cell function from baseline to 52 weeks (HOMA-B)</p> <ol style="list-style-type: none"> Insulin sensitivity <p>*Mean change in insulin sensitivity from baseline to 52 weeks (HOMA-S)</p> <ol style="list-style-type: none"> HDL cholesterol and fasting lipids <p>OTHER OUTCOMES</p> <ol style="list-style-type: none"> Treatment-emergent adverse events

Study	Methods	Participants	Interventions	Outcomes
Zinman (2007) ⁶⁰	<p>TRIAL DESIGN: RCT</p> <p>DURATION OF INTERVENTION: 16 weeks</p> <p>DURATION OF FOLLOW-UP: 16 weeks</p> <p>RUN-IN PERIOD: 2-week single-blind placebo run-in</p> <p>RANDOMISATION PROCEDURE: Central randomisation table; automated interactive voice-response system administered assignment; stratified by site and current treatment (TZD alone or TZD plus MET)</p> <p>BLINDING: Double-blind. Prefilled disposable injection pens or cartridges containing indistinguishable EXEN and placebo solutions used</p> <p>SETTING: 49 research clinics, hospitals and primary facilities</p> <p>COUNTRY: USA, Canada, Spain</p> <p>ITT ANALYSIS: Yes</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Yes</p> <p>SAMPLE SIZE CALCULATION: Yes</p> <p>OVERALL RISK OF BIAS: ++</p> <p>SOURCE OF FUNDING: Eli Lilly and Amylin Pharmaceuticals</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes</p> <p>INCLUSION CRITERIA: Adults; treated with stable dose of TZD for at least 4 months before screening; patients received TZD therapy alone or in combination with a stable dosage of MET for 30 days; HbA_{1c} value between 7.1% and 10% at screening; BMI between 25 kg/m² and 45 kg/m², and a history of stable body weight (≤ 10% variation) for at least 3 months before screening</p> <p>EXISTING THERAPY: TZD alone or TZD with MET</p> <p>EXCLUSION CRITERIA: Not reported</p> <p>NUMBERS: 233</p> <p>AGE: EXEN, 55.6 years (SD 10.8); PLACEBO 56.6 years (SD 10.2)</p> <p>DURATION OF DIABETES: EXEN, 7.3 years (SD 4.9); PLACEBO, 8.2 years (SD 5.8)</p> <p>HbA_{1c}: EXEN 7.9% (SD 0.9); PLACEBO 7.9 (SD 0.8)</p> <p>GENDER: EXEN 53.7% males; PLACEBO 57.1% males</p> <p>ETHNIC GROUPS: EXEN, white 85.1%; PLACEBO white 82.1%</p>	<p>INTERVENTION (ROUTE, TOTAL DOSE/DAY, FREQUENCY): EXEN, s.c., 10 µg/day for 4 weeks and 20 µg/day for 12 weeks, morning and evening doses</p> <p>CONTROL (ROUTE, TOTAL DOSE/DAY, FREQUENCY): Placebo, s.c., morning and evening doses</p> <p>OTHER TREATMENT: Doses of TZD and MET constant throughout study</p>	<p>PRIMARY OUTCOMES:</p> <ol style="list-style-type: none"> 1. Changes HbA_{1c} <p>*Mean reduction in HbA_{1c} from baseline to 16 weeks</p> <p>*Percentage of patients who achieved a target HbA_{1c} level ≤7% (of those patients with HbA_{1c} level >7% at baseline)</p> <p>*Percentage of patients who achieved a target HbA_{1c} level ≤6.5%</p> <p>SECONDARY OUTCOMES:</p> <ol style="list-style-type: none"> 1. Body weight <p>*Mean reduction in body weight from baseline to 16 weeks</p> <ol style="list-style-type: none"> 2. FSG <p>*Mean reduction in fasting serum glucose from baseline to 16 weeks</p> <ol style="list-style-type: none"> 3. SMBG 4. HOMA levels
<p>ECG, electrocardiogram; EXEN, exenatide; FSG, fasting serum glucose; HOMA, homeostatic model assessment; MET, metformin; SFU, sulfonylurea; SMBG, self-monitoring of blood glucose; TZD, thiazolidinedione.</p>				

Appendix 3

Characteristics of included trials – DPP-4 inhibitors

Study	Methods	Participants	Interventions	Outcomes
Bolli (2008) ²³	<p>TRIAL DESIGN: RCT</p> <p>DURATION OF INTERVENTION: 24 weeks</p> <p>DURATION OF FOLLOW-UP: 24 weeks</p> <p>RUN-IN PERIOD: None reported</p> <p>RANDOMISATION PROCEDURE: Not reported</p> <p>BLINDING: Reported as 'double-blind'</p> <p>SETTING: Not clear</p> <p>COUNTRY: Multinational – Germany, UK, USA, Spain, Italy, Switzerland, Austria, South Africa, Australia</p> <p>ITT ANALYSIS: No, per-protocol analysis</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate</p> <p>SAMPLE SIZE CALCULATION: Yes, and adequately powered per protocol</p> <p>OVERALL RISK OF BIAS: +</p> <p>SOURCE OF FUNDING: Novartis</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes inadequately controlled with prior MET monotherapy</p> <p>INCLUSION CRITERIA: 18–77 years of age, type 2 diabetes, treated with MET \geq 1500 mg per day, screening HbA_{1c} 7.5–11.0%, non-fertile or using a medically approved birth control method, BMI 22–45 kg/m², FPG < 15 mmol/l</p> <p>EXISTING THERAPY: Failing MET</p> <p>EXCLUSION CRITERIA: History of type 1 diabetes or secondary forms of diabetes, acute metabolic diabetic complications, MI, unstable angina or coronary artery bypass surgery within the previous 6 months, congestive heart failure (NYHA I–IV) and liver disease such as cirrhosis or chronic active hepatitis. Also specific abnormal lab</p> <p>NUMBERS: 576 randomised</p> <p>AGE: VILDA 100 mg + MET, 56.3 years (SD 9.3); PIO 30 mg + MET, 57.0 years (SD 9.7)</p> <p>DURATION OF DIABETES: VILDA 100 mg + MET, 6.4 years (SD 4.9); PIO 30 mg + MET, 6.4 years (SD 5.2)</p> <p>HbA_{1c}: VILDA 100 mg + MET 8.4% (SD 1.0); PIO 30 mg + MET 8.4% (SD 0.9)</p> <p>GENDER: VILDA 100 mg + MET 61.7% males and PIO 30 mg + MET 64.1% males</p> <p>ETHNIC GROUPS: VILDA 100 mg + MET, white 82.4%, Hispanic or Latino 8.5%, Asian (non-Indian subcontinent) 4.1%, black 3.0%, other 2.0%; PIO 30 mg + MET, white 81.9%, Hispanic or Latino 10.3%, Asian (non-Indian subcontinent) 3.9%, black 2.5%, other 1.4%</p> <p>COMORBIDITIES: Not reported</p> <p>COMEDICATIONS: Not reported</p>	<p>INTERVENTION: VILDA 100 mg daily, two equally divided doses</p> <p>CONTROL: PIO 30 mg once daily</p> <p>OTHER TREATMENT: Assumed that participants continued current regimen of MET</p>	<p>PRIMARY:</p> <ol style="list-style-type: none"> 1. HbA_{1c} 2. Percentage of patients responsive to treatment (HbA_{1c} < 7%, \leq 6.5%, reduction \geq 1%, \geq 0.7%, \geq 0.5%, meeting at least one criterion) <p>SECONDARY:</p> <ol style="list-style-type: none"> 1. FPG 2. Fasting lipids 3. Body weight <p>*Change in body weight (kg) from baseline to 24 weeks</p> <p>Safety</p>

Study	Methods	Participants	Interventions	Outcomes
Hermansen (2007) ¹²⁴	<p>TRIAL DESIGN: RCT</p> <p>DURATION OF INTERVENTION: 24 weeks</p> <p>DURATION OF FOLLOW-UP: 24 weeks</p> <p>RUN-IN PERIOD: Up to 14 weeks</p> <p>RANDOMISATION PROCEDURE: Not reported but 1:1</p> <p>BLINDING: Reported as 'double-blind'</p> <p>SETTING: Not clear</p> <p>COUNTRY: Reported as 'multinational'</p> <p>ITT ANALYSIS: Yes, with LOCF</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate</p> <p>SAMPLE SIZE CALCULATION: Yes, but not reported if numbers achieved</p> <p>OVERALL RISK OF BIAS: +</p> <p>SOURCE OF FUNDING: Merck</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes</p> <p>INCLUSION CRITERIA: 18–75 years of age, type 2 diabetes, taking either glimepiride (any dose) alone or in combination with MET (any dose), or taking another oral hypoglycaemic drug mono, dual or triple therapy or not taking any oral hypoglycaemic drug during the previous 8 weeks</p> <p>EXISTING THERAPY: If taking glimepiride alone or with MET, entered placebo run-in. If other regime and depending on HbA_{1c} control, discontinued and started treatment with glimepiride alone or with MET, dose titrated for 4 weeks, then run-in period 10 weeks, with placebo run-in period if HbA_{1c} $\geq 7.5\%$ and $\leq 10.5\%$. Entered for randomisation if adherence $\geq 75\%$</p> <p>EXCLUSION CRITERIA: History of type 1 diabetes, treated with insulin in prior 8 weeks, renal dysfunction, history of hypersensitivity, intolerance or contraindications to glimepiride, SFUs, MET or PIO</p> <p>NUMBERS: 441 randomised – SIT 100 mg + MET + SU, 116; PLACEBO + MET + SU, 113</p> <p>AGE: SIT 100 mg + MET + SU, 56.5 years (SD 9.6); PLACEBO + MET + SU, 57.7 years (SD 8.9)</p> <p>DURATION OF DIABETES: SIT 100 mg + MET + SU, 9.3 years (SD 5.7); PLACEBO + MET + SU, 10.6 years (SD 6.8)</p> <p>HbA_{1c}: SIT 100 mg + MET + SU, 8.27% (SD 0.73); PLACEBO + MET + SU 8.26% (SD 0.68)</p> <p>GENDER: SIT 100 mg + MET + SU 52.6% males; PLACEBO + MET + SU 59% males</p> <p>ETHNIC GROUPS: SIT 100 mg + MET + SU, white 64.7%, black 6.6%, Hispanic 24.5%, Asian 5.7%, other 5.7%; PLACEBO + MET + SU, white 71.7%, black 8.0%, Hispanic 6.2%, Asian 11.5%, other 2.7%</p> <p>COMORBIDITIES: Not reported</p> <p>COMEDICATIONS: Not reported</p>	<p>INTERVENTION: SIT 100 mg once daily</p> <p>CONTROL: Placebo</p> <p>OTHER TREATMENT: Continued stable doses of glimepiride and MET (as established in the run-in period). Also given rescue therapy of PIO 30 mg/day (open label) if FPG not meeting specific, and progressively lower, goals after randomization. Discontinued from study if rescue therapy for more than 4 weeks and FPG still high</p> <p>NOTE: Only reported details for relevant comparator arms</p>	<p>PRIMARY:</p> <ol style="list-style-type: none"> HbA_{1c} *Mean HbA_{1c} change from baseline. If significant then assessed treatment effects by strata <p>SECONDARY:</p> <ol style="list-style-type: none"> FPG Fasting lipids – TC, LDL-C, TG, HDL-C Beta-cell function Changes in insulin resistance Safety and tolerability

Study	Methods	Participants	Interventions	Outcomes
Nauck (2007) ¹²²	<p>TRIAL DESIGN: RCT</p> <p>DURATION OF INTERVENTION: 52 weeks</p> <p>DURATION OF FOLLOW-UP: 52 weeks</p> <p>RUN-IN PERIOD: 2 week single-blind placebo</p> <p>RANDOMISATION PROCEDURE: Not reported, 1:1 ratio</p> <p>BLINDING: Double blinded, except for lead-in period (single blind)</p> <p>SETTING: Not clear</p> <p>COUNTRY: Described as 'multinational'</p> <p>ITT ANALYSIS: Per-protocol and all-patients-treated analysis</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate</p> <p>SAMPLE SIZE CALCULATION: Not reported</p> <p>OVERALL RISK OF BIAS: –</p> <p>SOURCE OF FUNDING: Merck</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes with inadequate control on MET</p> <p>INCLUSION CRITERIA: 18–78 years of age, type 2 diabetes, treated with MET (eligible if not taking any oral therapy, any oral therapy as monotherapy, any oral therapy with MET, then titrated to MET monotherapy over 8-week period)</p> <p>EXISTING THERAPY: Failing MET</p> <p>EXCLUSION CRITERIA: History of type 1 diabetes, insulin use within 8 weeks of screening, renal function impairment inconsistent with use of MET, FPG at or prior to randomisation > 15.0 mmol/l</p> <p>NUMBERS: 1172 randomised</p> <p>AGE: SIT + MET, 56.8 years (SD 9.3); SU + MET 56.6 years (SD 9.8)</p> <p>DURATION OF DIABETES: SIT + MET, 6.5 years (SD 6.1); SU + MET, 6.2 years (SD 5.4)</p> <p>HbA_{1c}: SIT + MET, 7.7 (SD 0.9); SU + MET, 7.6 (SD 0.9)</p> <p>GENDER: SIT + MET 57.1% males, SU + MET 61.3%</p> <p>ETHNIC GROUPS: SIT + MET, white 73.5%, black 7.0%, Hispanic 7.3%, Asian 8.5%, other 3.7%; SU + MET, white 74.3%, black 6.0%, Hispanic 7.3%, Asian 8.4%, other 3.4%</p> <p>COMORBIDITIES: Not reported</p> <p>COMEDICATIONS: Allowed lipid lowering, antihypertensive, thyroid, medications and HRT, birth control – but expected to remain at stable doses. Other treatments for hyperglycaemia not allowed</p> <p>PHARMACONAIVE: SIT + MET 4.3%, SU + MET 4.8% at screening</p>	<p>INTERVENTION: SIT 100 mg once daily</p> <p>CONTROL: Glipizide, initial dose of 5 mg with up-titration according to protocol specifications to maximum of 20 mg/day</p> <p>OTHER TREATMENT: Assumed that all participants continued stable regimen of MET</p>	<p>PRIMARY:</p> <ol style="list-style-type: none"> I. HbA_{1c} *Mean HbA_{1c} change from baseline <p>SECONDARY:</p> <ol style="list-style-type: none"> I. HbA_{1c} *Number (%) of patients achieving HbA_{1c} ≤ 7% or 6.5% change in HbA_{1c} stratified by baseline A_{1c} <p>Safety and tolerability:</p> <p>Adverse experiences, lab safety parameters, body weight, vital signs, ECG data</p> <p>Compliance</p> <p>Tablet count</p>

Study	Methods	Participants	Interventions	Outcomes
Scott (2007) ¹²⁰	<p>TRIAL DESIGN: RCT</p> <p>DURATION OF INTERVENTION: 18 weeks</p> <p>DURATION OF FOLLOW-UP: 18 weeks</p> <p>RUN-IN PERIOD: 2 week single-blind placebo</p> <p>RANDOMISATION PROCEDURE: Not reported, 1:1:1 ratio</p> <p>BLINDING: Double blinded, except for lead-in period (single blind)</p> <p>SETTING: Not clear</p> <p>COUNTRY: Described as 'multinational'</p> <p>ITT ANALYSIS: All-patients-treated analysis</p> <p>DESCRIPTION OF WITHDRAWALS AND LOSSES TO FOLLOW-UP: Adequate</p> <p>SAMPLE SIZE CALCULATION: Not reported</p> <p>OVERALL RISK OF BIAS: +</p> <p>SOURCE OF FUNDING: Merck</p>	<p>WHO PARTICIPATED: Patients with type 2 diabetes treated with MET</p> <p>INCLUSION CRITERIA: 18–75 years of age, type 2 diabetes, treated with MET at stable dose of at least 1500 mg/day for at least 10 weeks prior to screening, HbA_{1c} 7–11%</p> <p>EXISTING THERAPY: Failing MET</p> <p>EXCLUSION CRITERIA: Type 1 diabetes, insulin use within 8 weeks of screening, impaired renal function, contraindications for TZDs or MET</p> <p>NUMBERS: 273 randomised</p> <p>AGE: SIT 100, 55.2 years (SD 9.8); ROS18, 54.8 years (SD 10.5); PLACEBO 55.3 years (SD 9.3)</p> <p>DURATION OF DIABETES: SIT 100, 4.9 years (SD 3.5); ROS18, 4.6 years (SD 4.0); PLACEBO 5.4 years (SD 3.7)</p> <p>HbA_{1c}: SIT 100, 7.8 (SD 1.0); ROS18, 7.37 (SD 0.8); PLACEBO 7.7 (SD 0.9)</p> <p>GENDER: SIT 100 55% males, ROS18 63% males, PLACEBO 59% males</p> <p>ETHNIC GROUPS: SIT 100, Caucasian 61%, Asian 38%, others 1%; ROS18, Caucasian 59%, Asian 38%, other 3%; PLACEBO, Caucasian 61%, Asian 39%, other 0%</p> <p>COMORBIDITIES: 59% hypertension, 42% hyperlipidaemia/dyslipidaemia</p> <p>COMEDICATIONS: Not reported</p> <p>PHARMACONAIVE: N/A</p>	<p>INTERVENTION: SIT 100 mg once daily</p> <p>INTERVENTION: ROS 8 mg once daily</p> <p>CONTROL: Placebo once daily</p> <p>OTHER TREATMENT: All participants continued current regimen of MET. All patients received counselling on exercise and a weight-maintaining diet</p>	<p>PRIMARY:</p> <ol style="list-style-type: none"> 1. HbA_{1c} *1. Mean HbA_{1c} change from baseline 2. Beta-cell function <p>Proinsulin–insulin ratio and HOMA-beta</p> <ol style="list-style-type: none"> 3. Meal tolerance test <p>SECONDARY:</p> <ol style="list-style-type: none"> 1. Adverse experiences 2. Physical examinations 3. Vital signs 4. Body weight

FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; HRT, hormone replacement therapy; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward; MET, metformin; N/A, not applicable; NYHA, New York Heart Association; PIO, pioglitazone; ROS, rosiglitazone; SIT, sitagliptin; TC, total cholesterol; TG, triglyceride; TZD, thiazolidinedione; VILDA, vildagliptin.

Appendix 4

Characteristics of included reviews – long-acting insulin analogues

Review	Inclusion criteria and methodology	Included studies	Quality
<p>Duckworth (2007)¹⁴⁰</p> <p>Focus: Clinical evidence for insulin glargine vs NPH insulin</p> <p>Funding: Industrial (Sanofi-aventis USA)</p>	<p>INCLUSION CRITERIA:</p> <p>Study design: Not specified</p> <p>Participants: Patients with type 2 diabetes</p> <p>Interventions: Insulin glargine vs NPH insulin</p> <p>Outcomes: HbA_{1c}, FPG, incidence of hypoglycaemia, other safety assessments</p> <p>METHODOLOGY:</p> <p>Search strategy: PubMed 1996–2005; search terms reported; English language only</p> <p>Study selection: Not described</p> <p>Quality assessment: Not described</p> <p>Data extraction: Not described</p> <p>Meta-analysis: No</p> <p>Data analysis: Not described</p> <p>Subgroups/sensitivity analyses: None</p>	<p>Number of included trials: eight</p> <p>Number of participants: 3379 (range 100–756)</p> <p>TRIALS:</p> <p>Design: All open-label RCTs</p> <p>Duration: 4 weeks to 1 year</p> <p>Quality: Not reported</p> <p>Origin: Not reported</p> <p>Funding: Many of the included trials supported by Sanofi-aventis (no further details)</p> <p>PARTICIPANTS:</p> <p>Age: Not reported</p> <p>Gender: Not reported</p> <p>BMI: Not reported</p> <p>Diabetes duration: Not reported</p> <p>HbA_{1c}: Mean 8.5–9.7%</p> <p>Previous medication: See below, some limited details given</p> <p>INTERVENTIONS:</p> <p>Two trials in patients with previous insulin therapy; five trials in insulin-naïve patients on oral therapy; one trial included patients on oral therapy plus insulin; dose titration targets 80–140 mg/dl (4.5–7.8 mmol/l) in two trials, 72–126 mg/dl (4–7 mmol/l) in one trial, 120 mg/dl (6.7 mmol/l) in two trials, ≤ 100 mg/dl (5.6 mmol/l) in three trials; in trials with previous oral agents – four trials continued existing oral therapy, in one trial existing oral therapy was replaced by 3 mg glimepiride, in one trial fixed dose of 2 g MET</p> <p>OUTCOMES:</p> <p>HbA_{1c}, FPG, hypoglycaemia, safety, percentage reaching target</p> <p>HbA_{1c}/FBG</p> <p>Number of included trials: Seven RCTs insulin glargine vs NPH (six analysed, see below), two RCTs insulin detemir vs NPH</p> <p>Number of participants (in analysed trials): 3151 for glargine trials (range 110–764), 980 for detemir trials (505 and 475)</p> <p>TRIALS:</p> <p>Design: All studies were parallel trials; two had a superiority design, one and equivalence and two a non-inferiority design; in none of the trials were participants or caregivers blinded</p> <p>Duration: 6–12 months</p>	<p>Appropriate and clearly focused question: Adequately addressed</p> <p>Inclusion/exclusion criteria described: Poorly addressed</p> <p>Literature search sufficiently rigorous to identify all relevant studies: Poorly addressed</p> <p>Study selection described: Not reported</p> <p>Data extraction described: Not reported</p> <p>Study quality assessed and taken into account: Not reported</p> <p>Study flow shown: Not reported</p> <p>Study characteristics of individual studies described: Adequately addressed</p> <p>Quality of individual studies given: Not reported</p> <p>Results of individual studies shown: Adequately addressed</p> <p>Enough similarities between studies selected to make combining them reasonable: Not applicable</p> <p>How well was study done to minimise bias: (–)</p> <p>What is the likely direction in which bias might affect study results? Less effect than reported</p>
<p>Horvath (2007)¹⁴¹</p> <p>Focus: Effects of long-term treatment with long-acting insulin analogues (insulin glargine and insulin detemir) compared with NPH insulin in patients with type 2 diabetes</p> <p>Funding: Non-industrial</p>	<p>INCLUSION CRITERIA:</p> <p>Study design: RCTs with parallel or crossover design, blinded or open-label, with a duration of 24 weeks or longer</p> <p>Participants: Patients with type 2 diabetes</p> <p>Interventions: Long-acting insulin analogues (glargine or detemir) vs NPH insulin; in case of combination with oral agents, the antihyperglycaemic agent had to be part of each treatment arm; s.c. applications for insulin only</p>	<p>Number of included trials: Seven RCTs insulin glargine vs NPH (six analysed, see below), two RCTs insulin detemir vs NPH</p> <p>Number of participants (in analysed trials): 3151 for glargine trials (range 110–764), 980 for detemir trials (505 and 475)</p> <p>TRIALS:</p> <p>Design: All studies were parallel trials; two had a superiority design, one and equivalence and two a non-inferiority design; in none of the trials were participants or caregivers blinded</p> <p>Duration: 6–12 months</p>	<p>Appropriate and clearly focused question: Well covered</p> <p>Inclusion/exclusion criteria described: Well covered</p> <p>Literature search sufficiently rigorous to identify all relevant studies: Well covered</p> <p>Study selection described: Well covered</p> <p>Data extraction described: Well covered</p>

Review	Inclusion criteria and methodology	Included studies	Quality
<p>Outcomes: <i>Primary:</i> overall, severe and nocturnal hypoglycaemia; glycaemic control (HbA_{1c}); <i>secondary:</i> mortality, cardiovascular morbidity, diabetic late complications, QoL, adverse events, costs</p> <p>METHODOLOGY:</p> <p>Search strategy: databases searched: Cochrane Library, MEDLINE, EMBASE, CRD databases; electronic search strategy shown; citation searches of included trials and reviews; additional internet searches listed; information on unpublished trials sought from Sanofi-aventis and Novo Nordisk</p> <p>Study selection: Two reviewers independently screened titles and abstracts; full articles obtained for citations that appeared to fulfil the inclusion criteria (or in case of disagreement); if disagreement persisted, resolved by a third party</p> <p>Quality assessment: Independent assessment of quality by two reviewers; differences in opinion resolved by discussion with a third reviewer; quality parameters assessed: randomisation, allocation concealment, blinding, description of withdrawals and dropouts, ITT analysis, blinding of outcome assessors</p> <p>Data extraction: Done independently by two reviewers using data extraction sheets; differences in data extraction resolved by consensus; information extracted listed</p> <p>Meta-analysis: Yes</p> <p>Data analysis: WMDs or odd ratios calculated, random effects model used; heterogeneity assessed using chi-squared test</p> <p>Subgroups/sensitivity analyses: Planned but not carried out</p>	<p>Quality: All studies rated as being of insufficient methodological quality (rating C); reporting of randomisation poor in most trials, adequate allocation concealment in five trials; discontinuation rates 1.6–10.2%; all main analyses used ITT approach</p> <p>Origin: Four trials Europe, two North America, one Europe and South Africa, one Latin America</p> <p>Funding: Five trials were commercially funded, unclear for the rest</p> <p>PARTICIPANTS:</p> <p>Age: Mean age 55–62 years</p> <p>Gender: Numbers given but partially unclear if they refer to men or women, distribution looks balanced</p> <p>BMI: Mean 27–33 kg/m²</p> <p>Diabetes duration: Mean 8–14 years</p> <p>HbA_{1c}: Mean 7.9–9.5%</p> <p>Previous medication: No details, none of the trials was performed with pharmaco-naive patients (i.e. controlled on diet/exercise only)</p> <p>INTERVENTIONS:</p> <p>Six studies used combinations with oral antidiabetic drugs (five glargine and one detemir), two with a short-acting insulin (one glargine and one detemir), and one with both (detemir); one study required an upward titration of insulin glargine with a target of a fraction of 50% of the basal insulin requirement while the fraction of NPH on the total insulin requirement was left unchanged, thus introducing a difference in the treatments, and the study was therefore not considered further; one study compared morning or evening glargine with evening NPH, in all other studies glargine or NPH were injected at bedtime (one study choice of bedtime or twice daily); two studies (glargine) changed from previous oral antihyperglycaemic treatment to glimepiride during run-in</p> <p>OUTCOMES:</p> <p>Glycaemic control (HbA_{1c}), hypoglycaemia, FBG, BG profiles, percentage reaching target HbA_{1c}, insulin doses, weight change, adverse events</p>	<p>Study quality assessed and taken into account: Well covered</p> <p>Study flow shown: Well covered</p> <p>Study characteristics of individual studies described: Well covered</p> <p>Quality of individual studies given: Well covered</p> <p>Results of individual studies shown: Well covered</p> <p>Enough similarities between studies selected to make combining them reasonable: Well covered</p> <p>How well was study done to minimise bias: (++)</p> <p>What is the likely direction in which bias might affect study results? No likely bias</p>	

Review	Inclusion criteria and methodology	Included studies	Quality
<p>Tran (2007)⁴² Focus: Clinical and cost-effectiveness of long-acting insulin analogues (insulin glargine and insulin detemir) for the treatment of diabetes (both type 1 and type 2 diabetes) Funding: Canadian Agency for Drugs and Technology in Health</p>	<p>INCLUSION CRITERIA: Study design: RCTs Participants: Patients with diabetes (type 1, type 2 or gestational – only type 2 considered here) Interventions: Long-acting insulin analogues (insulin glargine or detemir) vs conventional human insulin or OAD agents Outcomes: Glycaemic control (BG, HbA_{1c}), QoL, hypoglycaemic episodes, adverse events, complications of diabetes, mortality METHODOLOGY: Search strategy: Databases searched – MEDLINE, BIOSIS Previews, PASCAL, EMBASE, PubMed, Cochrane Database of Systematic Reviews from 1990 onwards; electronic search strategy given; alert searches; grey literature obtained by searching listed websites; manufacturers were asked to provide relevant information Study selection: Two reviewers independently selected trials for inclusion; differences in decision resolved by consensus Quality assessment: Jadad scale; allocation concealment; blinding of assessors, ITT analysis Data extraction: One reviewer extracted data into a structured form, another reviewer checked the extraction Meta-analysis: Yes Data analysis: Fixed and random effects models; heterogeneity assessed using Higgins' I²-value; WMDs, relative risks and risk differences computed Subgroups/sensitivity analyses: None</p>	<p>Number of included trials: Nine RCTs insulin glargine, two RCTs insulin detemir (type 2 diabetes) Number of participants: 4729 (range 110–756) TRIALS: Design: All open-label parallel trials; 10 full publications, two abstracts/posters; most studies described as multicentre Duration: 4–52 weeks Quality: For full reports, mean Jadad score 2.4 (SD 0.7), allocation concealment adequate in four studies (unclear in remainder), 90% reported ITT analysis Origin: Four trials Europe, four trials North America, two trials Europe and South Africa, one trial international Funding: Industrial (where reported) PARTICIPANTS: Age: Mean 53–61 years (where reported) Gender: 36–49% female (where reported) BMI: Mean 27–35 kg/m² Diabetes duration: Mean 8.5–13.8 years (where reported) HbA_{1c}: Mean 8.4–9.8% Previous medication: See below INTERVENTIONS: Seven studies including various combinations of oral antihyperglycaemic medications, one study morning vs evening glargine vs evening NPH, one study combination with insulin aspart OUTCOMES: No specific details given – results reported for: glycaemic control, 8-point glucose profiles, hypoglycaemia, adverse events, mortality, QoL</p>	<p>Appropriate and clearly focused question: Well covered Inclusion/exclusion criteria described: Well covered Literature search sufficiently rigorous to identify all relevant studies: Well covered Study selection described: Well covered Data extraction described: Adequately addressed Study quality assessed and taken into account: Well covered Study flow shown: Well covered Study characteristics of individual studies described: Well covered Quality of individual studies given: Well covered Results of individual studies shown: Well covered Enough similarities between studies selected to make combining them reasonable: Yes How well was study done to minimise bias: (++) What is the likely direction in which bias might affect study results? No likely bias</p>

Review	Inclusion criteria and methodology	Included studies	Quality
<p>Warren (2004)¹⁴</p> <p>Focus: Clinical and cost-effectiveness of insulin glargine in its licensed basal bolus indication (both type 1 and type 2 diabetes)</p> <p>Funding: NICE, UK</p>	<p>INCLUSION CRITERIA:</p> <p>Study design: Methodology including at least one of: (1) systematic review; (2) RCT; (3) economic evaluations; study duration at least 4 weeks</p> <p>Participants: Patients with type 1 or type 2 diabetes, requiring insulin for glycaemic control (only type 2 considered here)</p> <p>Interventions: Insulin glargine vs other long-acting basal insulin</p> <p>Outcomes: Glycaemic control (BG, HbA_{1c}); incidence and severity of hypoglycaemic episodes</p> <p>METHODOLOGY:</p> <p>Search strategy: Databases searched: Biological Abstracts, CINAHL, Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, EBM Reviews, EMBASE, HTA Database, MEDLINE, NHS Economic Evaluations Database, OHE Health Economic Evaluations Database, PREMEDLINE, Science Citation Index, Social Sciences Citation Index; electronic search strategies given; searching of reference lists of relevant publications; 45 health services research related resources searched via the internet (list given); citation searches of key papers; no date, language, study or publication type restrictions; list provided by Aventus of peer-reviewed articles of glargine primary research</p> <p>Study selection: Titles and abstracts screened; full copies of primary research reports, reviews and abstracts obtained; no further details</p> <p>Quality assessment: Jadad scale; blinding of outcome assessment</p> <p>Data extraction: Done by one reviewer using customised data extraction sheets</p> <p>Meta-analysis: No</p> <p>Data analysis: Text and tables</p> <p>Subgroups/sensitivity analyses: None</p>	<p>Number of included trials: Five RCTs for type 2 diabetes</p> <p>Number of participants: 1399 (range 100–518)</p> <p>TRIALS:</p> <p>Design: All prospective, three clearly described as RCTs, none double-blind, design not clearly documented for two trials; two full publications, three abstracts; most studies described as multicentre</p> <p>Duration: 4 to 52 weeks</p> <p>Quality: Assessment only possible for two articles reported in full; both scored 2 (of 3) on Jadad scale; blinding of patients not possible; none of the studies specified blinded outcome assessment</p> <p>Origin: One trial Europe, four trials USA</p> <p>Funding: Not reported</p> <p>PARTICIPANTS:</p> <p>Age: ~59 years (where reported)</p> <p>Gender: 47–38% female (where reported)</p> <p>BMI: Mean 29 to 31 kg/m² (where reported)</p> <p>Diabetes duration: 10–14 years (where reported)</p> <p>HbA_{1c}: Mean 8.5–9.1% (where reported)</p> <p>Previous medication: See below, no details</p> <p>INTERVENTIONS: Two studies of two formulations of insulin glargine compared with each other and to NPH, three studies of glargine compared with NPH; two studies of patients previously on insulin; three studies of patients previously on oral medication (and continuing oral medication); insulin doses individually titrated to achieve target FBG levels; titration periods of varying durations</p> <p>OUTCOMES: Glycaemic control, hypoglycaemia, FBG, diurnal BG, percentage reaching target FBG</p>	<p>Appropriate and clearly focused question: Well covered</p> <p>Inclusion/exclusion criteria described: Well covered</p> <p>Literature search sufficiently rigorous to identify all relevant studies: Well covered</p> <p>Study selection described: Adequately addressed</p> <p>Data extraction described: Not adequately addressed</p> <p>Study quality assessed and taken into account: Well covered</p> <p>Study flow shown: Poorly addressed</p> <p>Study characteristics of individual studies described: Well covered</p> <p>Quality of individual studies given: Well covered</p> <p>Results of individual studies shown: Well covered</p> <p>Enough similarities between studies selected to make combining them reasonable: Not applicable</p> <p>How well was study done to minimise bias: (+)</p> <p>What is the likely direction in which bias might affect study results? No likely bias</p>

Review	Inclusion criteria and methodology	Included studies	Quality
<p>Wang (2003)¹⁴³</p> <p>Focus: Efficacy and tolerability of insulin glargine</p> <p>Funding: Not reported</p>	<p>INCLUSION CRITERIA:</p> <p>Study design: Clinical trials, ≥ 100 participants; includes pharmacodynamic studies, only clinical efficacy trials considered here</p> <p>Participants: Type 1 or type 2 diabetes, only type 2 diabetes considered here</p> <p>Interventions: Insulin glargine (no details)</p> <p>Outcomes: HbA_{1c}, FPG, FBG, incidence of hypoglycaemia, measures of tolerability</p> <p>METHODOLOGY:</p> <p>Search strategy: MEDLINE/PubMed, EMBASE (1966–2002), Premedline (November 2002); search words given; searching of reference lists of relevant publications</p> <p>Study selection: Not described</p> <p>Quality assessment: Not described</p> <p>Data extraction: Not described</p> <p>Meta-analysis: No</p> <p>Data analysis: Not described</p> <p>Subgroups/sensitivity analyses: None</p>	<p>Number of included trials: Seven RCTs for efficacy, one RCT for QoL</p> <p>Number of participants: 2856 (range 100 to 756)</p> <p>TRIALS:</p> <p>Design: All trials multicentre, open-label, randomised trials</p> <p>Duration: 4–52 weeks</p> <p>Quality: Inconsistent reporting of mean or adjusted mean changes in primary and secondary efficacy end points within and between treatment groups; studies were typically statistically underpowered (only three studies included power analysis); five studies only available in abstract form</p> <p>Origin: Europe and USA</p> <p>Funding: Unclear, some industrial, indicated that for most studies authors may have had conflicts of interest</p> <p>PARTICIPANTS:</p> <p>Age: ~59 years</p> <p>Gender: Not reported</p> <p>BMI: Reported for only two studies, mean 29 to 32 kg/m²</p> <p>Diabetes duration: Not reported</p> <p>HbA_{1c}: Mean 8.4–9.0% (where reported)</p> <p>Previous medication: See below, no details</p> <p>INTERVENTIONS: Insulin doses individually titrated to achieve target FBG level of ≤ 120 mg/dl (6.7 mmol/l) (≤ 100 mg/dl in Fritsche 2003 and Riddle 2003); two trials comparing two formulations of insulin glargine (containing 30 or 80 µg/ml of zinc); three trials of patients not receiving OADs with previous once- or twice-daily NPH insulin with or without short-acting insulin for postprandial control; four studies comparing once-daily insulin glargine with once-daily NPH insulin in previously insulin-naïve patients also taking OAD agents</p> <p>OUTCOMES: HbA_{1c}, FPG, self-monitored FBG levels, incidence of hypoglycaemia</p>	<p>Appropriate and clearly focused question: Adequately addressed</p> <p>Inclusion/exclusion criteria described: Poorly addressed</p> <p>Literature search sufficiently rigorous to identify all relevant studies: Adequately addressed</p> <p>Study selection described: Not reported</p> <p>Data extraction described: Not reported</p> <p>Study quality assessed and taken into account: Poorly addressed</p> <p>Study flow shown: Not reported</p> <p>Study characteristics of individual studies described: Adequately addressed</p> <p>Quality of individual studies given: Poorly addressed</p> <p>Results of individual studies shown: Adequately addressed</p> <p>Enough similarities between studies selected to make combining them reasonable: Not applicable</p> <p>How well was study done to minimise bias: (–)</p> <p>What is the likely direction in which bias might affect study results? Less effect than reported</p>
			<p>FBG, fasting blood glucose; FPG, fasting plasma glucose; ITT, intention to treat; MET, metformin; NPH, Neutral Protamine Hagedorn; OAD, oral antidiabetic drugs; s.c., subcutaneous; TZD, thiazolidinedione; WMD, weighted mean difference.</p>

Appendix 5

Characteristics of included trials – long-acting insulin analogues

Study	Design	Participants	Interventions	Outcome measures
<p>Insulin-naive, oral antihyperglycaemics – glargine vs NPH insulin</p> <p>Pan (2007) (LEAD study)¹⁷⁹ China, France, Korea</p>	<p>Focus: Effect of insulin glargine vs NPH insulin on metabolic control and safety in Asian patients with type 2 diabetes, inadequately controlled on OHAs</p> <p>Design: Non-inferiority study; open-label, parallel group randomised trial, multicentre</p> <p>Duration: 24 weeks</p> <p>Follow-up: No postintervention follow-up</p> <p>Funding: Sanofi-aventis, Korea</p>	<p>Total number: 443</p> <p>N glargine: 220; 198 completed the trial</p> <p>N NPH: 223; 201 completed the trial</p> <p>Inclusion criteria: Insulin-naive – Asian; aged ≥ 40 and ≤ 80 years; type 2 diabetes according to WHO criteria plus specified BG criteria; poorly controlled on oral hypoglycaemic agents for ≥ 3 months before study entry; BMI 20–35 kg/m²; HbA_{1c} ≥ 7.5 and $\leq 10.5\%$, FBG levels > 120 mg/dl (> 6.7 mmol/l)</p> <p>Exclusion criteria: Pregnancy; history of ketoacidosis; likelihood of requiring treatment with drugs prohibited by the protocol (e.g. non-selective beta-blockers, systemic corticosteroids)</p> <p>Age: Glargine, 55.6 (SD 8.4 years); NPH, 56.6 (SD 8.7 years)</p> <p>Gender: Glargine 59.6% female, NPH 55.6% female</p> <p>BMI: Glargine, 24.8 (SD 3.1) kg/m²; NPH, 25.1 (SD 3.3) kg/m²</p> <p>Ethnicity: $n = 126$ China, 26 Hong Kong, 19 Indonesia, 112 South Korea, 16 Malaysia, 36 Pakistan, 24 Philippines, 32 Taiwan, 48 Thailand, 4 Singapore</p> <p>Diabetes duration: Glargine, 10.3 (SD 6.3 years); NPH, 10.0 (SD 5.4 years)</p> <p>Previous medication: Not reported, duration of treatment with OHAs: glargine, 9.1 (SD 6.0 years); NPH, 8.6 (SD 5.2 years)</p> <p>Comorbidities: Not reported</p> <p>Subgroups: None</p>	<p>Glargine: Insulin glargine once daily at bedtime (21.00–23.00 hours), once-daily glimepiride (3 mg) in the morning (07.00–09.00 hours)</p> <p>NPH: NPH insulin once daily at bedtime (21.00–23.00 hours), once-daily glimepiride (3 mg) in the morning (07.00–09.00 hours)</p> <p>Both: Insulin glargine/NPH insulin titrated to a target FBG ≤ 120 mg/dl (≤ 6.7 mmol/l), starting at insulin dose of 0.15 U/kg/day</p> <p>Cointerventions: None</p> <p>Adherence assessment: No</p> <p>Screening phase: 3–4 weeks, oral treatments standardised to 3 mg glimepiride, patients were given training in self-administration of insulin and SMBG</p>	<p>Primary: Change in HbA_{1c} level from baseline to end point</p> <p>HbA_{1c}: HbA_{1c}, proportion of patients with HbA_{1c} $< 7.5\%$, proportion of combined responders (both HbA_{1c} $< 7.5\%$ and FBG levels ≤ 120 mg/dl)</p> <p>Hypoglycaemia: Proportion of patients with hypoglycaemia; severe hypoglycaemia (symptoms consistent with hypoglycaemia, BG < 50 mg/dl or prompt recovery after oral carbohydrate, intravenous glucose or glucagons administration and the requirement of third-party assistance); nocturnal hypoglycaemia (while patient was asleep)</p> <p>Glycaemic excursions: Yes, blood glucose profiles</p> <p>Total daily dose: Yes</p> <p>Weight change: BMI</p> <p>Complication rates: No</p> <p>Adverse events: Yes</p> <p>Health-related QoL: No</p> <p>Other: None</p> <p>Timing of assessment: Baseline, 2, 4, 6, 8, 12, 16, 20 and 24 weeks after randomisation</p>

Study	Design	Participants	Interventions	Outcome measures
Wang (2007) ⁶⁵ China	<p>Focus: Effect of insulin glargine as basal insulin replacement vs NPH insulin in patients with type 2 diabetes, in whom BG was not well controlled with SFUs</p> <p>Design: RCT, single centre</p> <p>Duration: 12 weeks</p> <p>Follow-up: No postintervention follow-up</p> <p>Setting: Unclear</p> <p>Funding: Not reported</p>	<p>Total number: 24</p> <p>N glargine: 16</p> <p>N NPH: 8</p> <p>Inclusion criteria: Type 2 diabetes for 6 months; age 30–70 years; BG not well controlled (FBG ≥ 7.0 mmol/l and < 13.0 mmol/l); treatment with SFU (equivalent to 7.5 mg/day glibenclamide) or combination treatment with oral agents for > 3 months</p> <p>Exclusion criteria: Obvious renal, liver or heart disease</p> <p>Age: Glargine 57 years (SD 6), NPH 56 years (SD 8)</p> <p>Gender: Glargine 43.8% female, NPH 50% female</p> <p>BMI: Glargine: 24.2 (SD 2.8 kg/m²); NPH: 24.6 (SD 2.5 kg/m²)</p> <p>Ethnicity: Not reported, presumably all Chinese</p> <p>Diabetes duration: Glargine 10.4 (SD 4.3 years); NPH 9.5 (SD 4.9 years)</p> <p>Previous medication: Not reported</p> <p>Comorbidities: Not reported</p> <p>Subgroups: None</p>	<p>Glargine: Insulin glargine plus extended-release glipizide (glucotrol XL)</p> <p>NPH: NPH insulin plus glucotrol XL</p> <p>Both: Extended-release glipizide (glucotrol XL) 5 mg/day before breakfast; glargine or NPH injected at bedtime, initial dose 0.15 IU/kg/day; dose titrated every 3 days by the patient with instructions from researchers until FBG was < 6.7 mmol/l</p> <p>Cointerventions: None</p> <p>Adherence assessment: No</p> <p>Screening phase: Diabetes education; previous oral antihyperglycaemic therapy stopped and patients treated with glipizide 5 mg/day before breakfast for 2 weeks</p>	<p>Primary: Unclear</p> <p>HbA_{1c}: HbA_{1c}</p> <p>Hypoglycaemia: Yes; hypoglycaemic event defined as a sensor glucose value of < 3.5 mmol/l for > 15 minutes</p> <p>Glycaemic excursions: Yes, continuous glucose-monitoring system</p> <p>Total daily dose: Yes</p> <p>Weight change: Yes; weight and BMI</p> <p>Complication rates: No</p> <p>Adverse events: No</p> <p>Health-related QoL: No</p> <p>Other: None</p> <p>Timing of assessment: Baseline and week 12</p>

Study	Design	Participants	Interventions	Outcome measures
Previous insulin – detemir vs NPH insulin				
Montanana (2007)¹⁷⁸ (PREDICTIVE-BMI trial) Spain	<p>Focus: Weight change caused by detemir or NPH used as part of basal bolus regimen in already overweight type 2 diabetes patients</p> <p>Design: Open parallel-group RCT; multicentre</p> <p>Duration: 26 weeks</p> <p>Follow-up: No postintervention follow-up</p> <p>Setting: Unclear</p> <p>Funding: Novo Nordisk</p>	<p>Total number: 271</p> <p>N detemir: 126; 125 completed the trial</p> <p>N NPH: 151; 146 completed the trial</p> <p>Inclusion criteria: Men or women \geq 18 years; type 2 diabetes, had been receiving two daily doses (at least one pre-mix) for \geq 3 months; HbA_{1c} between 7.5% and 11%; BMI between 25 and 40 kg/m²</p> <p>Exclusion criteria: Patients receiving oral glucose-lowering drugs (other than MET); daily insulin dose \geq 2 IU/kg; any condition rendering the patient unsuitable to participate; anticipated changes in concomitant medications known to interfere with glucose metabolism; proliferative retinopathy or maculopathy requiring acute treatment in the preceding 6 months; uncontrolled hypertension; pregnancy and breastfeeding</p> <p>Age: Detemir, 62.1 years (SD 9.3); C, 61.8 years (SD 8.3)</p> <p>Gender: Detemir 62.4% female, C, 56.8% female</p> <p>BMI/weight: Detemir, 31.6 kg/m² (SD 4.3)/79.5 kg (SD 11.9); C, 32.0 kg/m² (SD 4.2)/82.2 kg (SD 12.2)</p> <p>Ethnicity: 99% white</p> <p>Diabetes duration: Detemir, 16.2 years (SD 8.7); C, 16.4 years (SD 7.4)</p> <p>Previous medication: Detemir, 50.4% MET use; C, 57.5% MET use</p> <p>Comorbidities: Not reported</p> <p>Subgroups: None</p>	<p>Detemir: Once daily (evening)</p> <p>NPH: Once daily (evening)</p> <p>Both: Basal insulin continually and individually titrated, aiming for pre-breakfast PG of \leq 6.1 mmol/l without levels of hypoglycaemia considered unacceptable to the patient</p> <p>Cointerventions: All patients received insulin aspart at main meals (individually titrated aiming for postprandial glucose levels of \leq 10.0 mmol/l); concomitant treatment with MET also allowed</p> <p>Adherence assessment: Not reported</p>	<p>Primary: Weight change</p> <p>HbA_{1c}: Yes</p> <p>Hypoglycaemia: Yes; all major (third-party assistance required), minor (self-managed, PG confirmed \leq 3.0 mmol/l), nocturnal hypoglycaemic events</p> <p>Glycaemic excursions: No</p> <p>Total daily dose: Yes</p> <p>Weight change: Yes</p> <p>Complication rates: No</p> <p>Adverse events: Yes</p> <p>Health-related QoL: No</p> <p>Other: None</p> <p>Timing of assessment: Five clinic visits after randomisation</p>
Insulin-naïve – detemir vs NPH insulin				
Philis-Tsimikas (2006)¹⁸⁰ Denmark, France, Italy, Netherlands, Norway, Spain, USA	<p>Focus: Effectiveness and tolerability of detemir vs NPH once daily with one or more oral antidiabetic in people with poorly controlled type 2 diabetes</p> <p>Design: Multicentre, randomised, open-label, three-arm parallel trial</p>	<p>Total number: 504 enrolled, 498 in ITT analysis</p> <p>N morning detemir: 165, 149 completed the trial</p> <p>N evening detemir: 169, 154 completed the trial</p> <p>N evening NPH: 164, 149 completed the trial</p> <p>Inclusion criteria: Age \geq 18 years, BMI \leq 40 kg/m², diagnosis of type 2 diabetes since at least 12 months, insulin naïve, HbA_{1c} between 7.5% and 11% after at least 3 months' treatment with one or more OAD agents; OAD therapy was therapy with MET or an insulin secretagogue or a combination of the two, at least half the recommended maximum dose; at US centres, concomitant treatment with TZDs was permitted throughout study period, at</p>	<p>N morning detemir: Insulin detemir once daily before breakfast</p> <p>N evening detemir: Insulin detemir once daily in the evening (= interval 1 hour before last meal until bedtime)</p> <p>N evening NPH: Human NPH insulin once daily in the evening</p>	<p>Primary: HbA_{1c}</p> <p>HbA_{1c}: Yes</p> <p>Hypoglycaemia: Yes; major episodes (requiring third-party assistance), confirmed episodes (PG reading $<$ 3.1 mmol/l, patients able to self-manage the event), nocturnal hypoglycaemia (between 23.00 and 06.00 hours)</p>

Study	Participants	Interventions	Outcome measures
<p>Design</p> <p>Duration: 20 weeks</p> <p>Follow-up: No postintervention follow-up</p> <p>Setting: Outpatient clinic</p> <p>Funding: Novo Nordisk</p>	<p>European centres TZD was to be discontinued before initiation of insulin treatment; use of alpha-glucosidase inhibitor was permitted but only in combination with another OAD agent</p> <p>Exclusion criteria: Proliferative retinopathy/maculopathy requiring treatment, hypoglycaemia unawareness or recurrent major hypoglycaemia, use or anticipated use of \geq one drug likely to affect BG regulation (e.g. systemic steroids, non-selective beta-blockers, monoamine oxidase inhibitors), OAD treatment not adhering to approved labelling in the respective country; any disease or condition that would make patient unsuitable for participation (e.g. renal, hepatic, cardiac disease), uncontrolled hypertension, any psychological incapacity or language barrier precluding adequate understanding or cooperation</p> <p>Age: Morning detemir, 58.3 years (SD 10.4); evening detemir, 58.7 years (SD 10.2); NPH insulin, 58.4 years (SD 11.0)</p> <p>Gender: Morning detemir, 40.6% female; evening detemir, 46.2% female; NPH insulin, 42.7% female</p> <p>BMI: Morning detemir, 29.8 kg/m² (SD 5.0); evening detemir, 29.7 kg/m² (SD 5.1); NPH insulin, 30.4 kg/m² (SD 4.8)</p> <p>Ethnicity: Not reported</p>	<p>All groups: insulin injected via pen device, participants advised to keep time of injection constant and to inject insulin subcutaneously, preferably in the thigh, but to rotate sites; initial dose of treatment was 10 IU (U), doses were titrated at clinic visits or by telephone at least once every 4 weeks, based on the mean of three PG levels measured on receiving detemir; in patients the dose was titrated to aim for pre-dinner PG concentration of \leq 6.0 mmol/l; in patients receiving detemir or NPH in the evening, titration was aimed to achieve pre-breakfast PG concentration of \leq 6.0 mmol/l</p> <p>Cointerventions: OAD therapy and dose was to remain unchanged; other cointerventions (similar between groups); \sim 21% used acetylsalicylic acid, \sim 19% simvastatin, \sim 15% atorvastatin</p> <p>Adherence assessment: Not reported</p>	<p>Glycaemic excursions: 9-point self-measured PG profiles (using capillary blood and plasma-calibrated monitor); immediately before and 90 minutes after main meals, bedtime, 03.00 hours; additional measurements when patients experienced symptoms indicative of hypoglycaemia</p> <p>Total daily dose: Yes</p> <p>Weight change: Yes (calibrated scales)</p> <p>Complication rates: No</p> <p>Adverse events: Adverse events, standard laboratory analyses, funduscopy, physical examination</p> <p>Health-related QoL: No</p> <p>Other: None</p> <p>Timing of assessment: At least nine telephone contacts and six clinic visits (including screening and randomisation)</p>

Diabetes duration: Morning detemir, 10.5 years (SD 7.6); evening detemir, 10.5 years (SD 7.0); NPH insulin, 10.0 years (SD 6.9)

Previous medication: Morning detemir, 26.1% OAD monotherapy (9.7% MET, 16.4% secretagogues), 73.9% combination therapy (56.4% MET + 1 or 2 secretagogues, 5.5% MET + secretagogue + TZD, 6.7% 2 secretagogues, 1.8% secretagogue + TZD); evening detemir, 21.3% OAD monotherapy (8.3% MET, 13.0% secretagogue), 78.7% combination therapy (53.8% MET + 1 or 2 secretagogues, 8.9% MET + secretagogue + TZD, 7.7% 2 secretagogues, 1.2% secretagogue + TZD); NPH insulin, 24.4% OAD monotherapy (9.8% MET, 14.6% secretagogue), 75.6% combination therapy (53.0% MET + 1 or 2 secretagogues, 6.1% MET + secretagogue + TZD, 9.1% 2 secretagogues, 1.2% secretagogue + TZD)

Comorbidities: \sim 56% hypertension, \sim 29% hypercholesterolaemia, \sim 12% dyslipidaemia, \sim 1% diabetic retinopathy; similar occurrence in treatment groups

Subgroups: None

Study	Design	Participants	Interventions	Outcome measures
Insulin-naive – glargine vs detemir Rosenstock (2008) ¹⁷⁷ Europe, USA	Focus: Comparison of clinical outcomes following supplementation of oral glucose-lowering drugs with basal insulin analogues detemir and glargine in patients with type 2 diabetes Design: Open-label, parallel group randomised controlled non-inferiority trial, multicentre Duration: 52 weeks Follow-up: No postintervention follow-up Setting: Unclear Funding: Novo Nordisk	Total number: 582 N detemir: 291, 231 completed the trial N NPH: 291, 252 completed the trial Inclusion criteria: Insulin-naive men or women ≥ 18 years, type 2 diabetes with ≥ 12 months' disease duration; HbA _{1c} between 7.5% and 10%; BMI ≤ 40 kg/m ² ; had been receiving one or two oral agents (MET, insulin secretagogues, alpha-glucosidase inhibitors) ≥ 4 months on at least half of maximum recommended dose Exclusion criteria: Treatment with TZDs; use of more than two oral agents within 6 months; hypoglycaemic unawareness; other medical conditions likely to interfere with trial conduct; withdrawal criteria included pregnancy, HbA _{1c} $> 11\%$ after the first 12 weeks of treatment, initiation of medication interfering with glucose metabolism Age: Detemir, 58.4 years (SD 10.2); glargine, 59.4 years (SD 9.6) Gender: Detemir 43% female, glargine 41.2% female BMI/weight: Detemir, 30.6 kg/m ² (SD 4.8)/87.4 kg (SD 16.6); glargine, 30.5 kg/m ² (SD 4.6)/87.4 kg (SD 17.4) Ethnicity: Detemir, 86% white, 7.6% black, 2.4% Asian-Pacific Islanders, 4% other; glargine, 90.4% white, 4.1% black, 2.4% Asian-Pacific Islanders, 3.1% other Diabetes duration: Detemir, 9.1 years (SD 6.1); glargine, 9.1 years (SD 6.4) Previous medication: Detemir – monotherapy 25% (11% MET, 14% insulin secretagogues), combination therapy 75% (97% MET + secretagogue); glargine – monotherapy 24% (11% MET, 13% insulin secretagogues), combination therapy 76% (97% MET + secretagogue) Comorbidities: Not reported Subgroups: None	Detemir: Once daily (evening) detemir or twice daily (morning and evening) (55% used twice-daily injections) Glargine: Once daily (evening) Both: Basal insulin initiated at once daily (evening) 12 U and titrated according to a structured treatment algorithm; people on detemir were allowed to receive an additional morning dose if pre-dinner PG was > 7.0 mmol/l, but only if pre-breakfast PG was < 7.0 mmol/l or nocturnal hypoglycaemia (major episode or PG ≤ 4.0 mmol/l) precluded the achievement of the FPG target; injection of insulin using pen injector; FPG target ≤ 6.0 mmol/l in the absence of hypoglycaemia Cointerventions: Oral glucose-lowering therapy, diet and physical activity recommended to remain stable during the study; no mealtime insulin allowed Adherence assessment: Not reported	Primary: HbA _{1c} HbA _{1c} : Yes; proportion of participants achieving HbA _{1c} $\leq 7.0\%$ with and without hypoglycaemia Hypoglycaemia: Yes; major (assistance from another person required), minor (confirmed by PG < 3.1 mmol/l) symptoms only (PG ≥ 3.1 mmol/l or no measurement made), nocturnal Glycaemic excursions: Within-participant variation in PG; 10-point self-measured PG profiles Total daily dose: Yes Weight change: Yes Complication rates: No Adverse events: Yes Health-related QoL: No Other: FPG Timing of assessment: 16 scheduled visits, during first 12 weeks contact with weekly investigator
FBG, fasting blood glucose; FPG, fasting plasma glucose; ITT, intention to treat; MET, metformin; NPH, Neutral Protamine Hagedorn; TZD, thiazolidinedione.				

Appendix 6

Characteristics of included trials – insulin + pioglitazone vs insulin

Study	Design	Participants	Interventions	Outcome measures
Asnani (2006) ²³⁸ USA	<p>Focus: Effect of PIO on vascular reactivity in patients with insulin-treated type 2 diabetes</p> <p>Design: Randomised, double-blind, placebo-controlled trial, single centre</p> <p>Duration: 4 months</p> <p>Follow-up: No postintervention follow-up</p> <p>Funding: Takeda, NIH</p>	<p>Total number: 20</p> <p>N PIO + Ins: 10; 8 completed the trial</p> <p>N P + Ins: 10; 8 completed the trial</p> <p>Inclusion criteria: Age 18–75 years, insulin-treated type 2 diabetes (with or without OAD agents), poor glycaemic control ($HbA_{1c} > 7.5\%$)</p> <p>Exclusion criteria: Active liver disease, pregnant or breastfeeding women, history or recent MI within last 6 months, recent major surgery within last 6 months</p> <p>Age: PIO + Ins: 59 years (SD 6); P + Ins: 57 years (SD 5)</p> <p>Gender: Not reported</p> <p>BMI: Not reported</p> <p>Ethnicity: Not reported</p> <p>Diabetes duration: Not reported</p> <p>Previous medication: Not reported</p> <p>Comorbidities: Not reported</p> <p>Subgroups: None</p>	<p>PIO + Ins: PIO 30 mg at breakfast, insulin continued as before</p> <p>P + Ins: Placebo, insulin continued as before</p> <p>Cointerventions: Stable lipid-lowering (statins) and antihypertensive therapy (including ACE inhibitors in all); not changed during therapy</p> <p>Adherence assessment: Not reported</p> <p>Screening/titration phase: Unclear</p>	<p>Primary: Flow-mediated dilatation</p> <p>HbA_{1c}: Yes</p> <p>Hypoglycaemia: No</p> <p>Glycaemic excursions: No</p> <p>Total daily dose: No</p> <p>Weight change: No</p> <p>Complication rates: No</p> <p>Adverse events: No</p> <p>Health-related QoL: No</p> <p>Other: Brachial artery reactivity; laboratory assessments, lipid profile</p> <p>Timing of assessment: Baseline, 4 months</p>

Study	Design	Participants	Interventions	Outcome measures
<p>Berhanu (2007)²³¹ USA</p>	<p>Focus: Safety and efficacy of PIO administered alone or in combination with MET in reducing insulin dosage requirements for improved glycaemic control in patients with type 2 diabetes</p> <p>Design: Randomised, double-blind, placebo-controlled trial, multicentre</p> <p>Duration: 20 weeks</p> <p>Follow-up: No postintervention follow-up</p> <p>Funding: Takeda Global R&D Centre</p>	<p>Total number: 222</p> <p>N PIO + Ins: 110; 96 completed the trial</p> <p>N P + Ins: 112; 102 completed the trial</p> <p>Inclusion criteria: Patients with documented type 2 diabetes; age 18–80 years; could self-monitor BG; previous combination therapy failed (HbA_{1c} ≥ 8.0%) ≤ 3 months before screening</p> <p>Combination therapy = SFU plus MET, insulin plus MET after failed SFU, or insulin alone after failed combination therapy with MET and SFU (> 50% maximum SFU and ≥ 2000 mg/day MET required); C-peptide ≥ 0.7 ng/ml; FPG > 120 mg/dl</p> <p>Exclusion criteria: TZDs use < 30 days or insulin treatment > 30 months before screening; BMI < 20 or > 45 kg/m²; history of MI, acute cardiovascular event, or cerebrovascular accident < 6 months before screening; cardiac rhythm disturbance; significant cardiovascular disease including NYHA class III or IV; uncontrolled hypertension; LDL ≥ 175 mg/dl, triglycerides > 500 mg/dl; ALT > 1.5 times upper limit of normal; diabetic neuropathy or anaemia</p> <p>Age: PIO + Ins, 52.9 years (SD 11.33); P + Ins, 52.5 years (SD 11.07)</p> <p>Gender: PIO + Ins, 56.4% female; P + Ins, 58.9% female</p> <p>BMI: PIO + Ins, 30.7 kg/m² (SD 6.09); P + Ins, 31.8 kg/m² (SD 6.2)</p> <p>Ethnicity: PIO + Ins, Hispanic 50.0%, non-Hispanic white 34.9%, non-Hispanic black 12.7%, other 2.7%; P + Ins, Hispanic 58.9%, non-Hispanic white 25.9%, non-Hispanic black 11.6%, other 3.6%</p> <p>Diabetes duration: PIO + Ins, 7.7 years (SD 6.15); P + Ins: 8.5 years (SD 5.43)</p> <p>Previous medication: PIO + Ins, SFUs plus MET 90.0%, insulin plus MET 8.2%, insulin only 1.8%; P + Ins, SFUs plus MET 92.9%, insulin plus MET 5.4%, insulin only 1.8%</p> <p>Comorbidities: Not reported</p> <p>Subgroups: None</p>	<p>PIO + Ins: PIO titrated to 45 mg/day during first 4 weeks of treatment, plus insulin as below</p> <p>P + Ins: Identical placebo plus insulin as below</p> <p>Both groups: All patients received one or multiple daily injections of Humalog, Humulin 70/30 or Humulin N; insulin adjusted to achieve FPG < 140 mg/dl while avoiding hypoglycaemia</p> <p>Cointerventions: Excluded medications before and during study; hydrochlorothiazide (at doses > 25 mg/day), glucocorticoids, steroid injections for joints, niacin; concurrent use of weight-loss agents and antidiabetic medications not included in the study were not permitted; patients maintained stable MET and, as applicable, previous statin use for duration of study; 98.2% in both groups used MET; 30.9% in PIO group and 28.6% in placebo group used statins</p> <p>Adherence assessment: Pill counts (99.1–99.4% adherence)</p> <p>Screening/titration phase: 1 week screening; instructions on insulin use and up to 1 week SFU discontinuation as applicable; insulin initiated and titrated to achieve FPG < 140 and > 70 mg/dl for 4 additional weeks; after titration period, insulin type, dose and administration schedule were left to the discretion of the clinical investigator; during titration period, instructions regarding diabetes, hypoglycaemia, nutrition, exercise; patients were randomised if FPG < 140 mg/dl achieved during titration</p>	<p>Primary: Change in insulin dosage from baseline to study end</p> <p>HbA_{1c}: Yes</p> <p>Hypoglycaemia: Hypoglycaemic events (SMBG < 60 mg/dl or laboratory value < 70 mg/dl, more than two simultaneous hypoglycaemia symptoms relieved by oral glucose-containing substance, or resulting in needing assistance for simple tasks)</p> <p>Glycaemic excursions: No</p> <p>Total daily dose: Yes</p> <p>Weight change: Weight</p> <p>Complication rates: No</p> <p>Adverse events: Yes; clinical examinations; ECG; ALT</p> <p>Health-related QoL: No</p> <p>Other: Lipid parameters, C-peptide</p> <p>Timing of assessment: Visits every 2 weeks for the first month, once per month thereafter</p>

Study	Design	Participants	Interventions	Outcome measures
Fernandez (2008) ²³² USA	<p>Focus: Relationship between glycaemic control, vascular reactivity and inflammation in type 2 diabetes</p> <p>Design: Double-blind, placebo-controlled RCT, single centre</p> <p>Duration: 36 weeks</p> <p>Follow-up: No</p> <p>postintervention follow-up</p> <p>Funding: ADA, Takeda Pharmaceuticals</p>	<p>Total number: 30</p> <p>N PIO + Ins: 10</p> <p>N P + Ins: 10</p> <p>N ramipril + Ins: 10 (not considered here)</p> <p>Inclusion criteria: Adult Mexican-Americans with type 2 diabetes requiring insulin therapy (HbA_{1c} > 8.0% despite optimised oral therapy); patients on insulin combination therapy with MET, SFUs or meglitinides included</p> <p>Exclusion criteria: Insulin combination therapy with TZDs</p> <p>Age: Mean age ~46 years (no details)</p> <p>Gender: Overall ~60% female (no details)</p> <p>BMI: Overall ~31–33 kg/m² (no details)</p> <p>Ethnicity: Mexican-American</p> <p>Diabetes duration: 6.2–8.4 years</p> <p>Previous medication: Use of OAD medications similar between groups</p> <p>Comorbidities: Not reported</p> <p>Subgroups: None</p>	<p>PIO + Ins: PIO 45 mg/day; started at 15 mg daily and then increased to 30 mg daily in week 2, and to 45 mg daily in week 4</p> <p>P + Ins: Placebo</p> <p>Ramipril + Ins: Ramipril 10 mg/day (not considered here)</p> <p>All groups: Three-day comprehensive diabetes education and nutritional programme; patients could select between insulin therapy using multiple daily injections (basal bolus therapy using combination of insulin glargine at bedtime plus premeal insulin aspart) or continuous s.c. infusion (Meditronic/Minimed or Animas pump using basal infusion and premeal boluses of insulin aspart); insulin dose adjusted to achieve the following glycaemic goals: fasting and pre-meal capillary BG 80–120 mg/dl, 2-hour postmeal glucose < 160 mg/dl, bedtime glucose < 140 mg/dl</p> <p>Cointerventions: Patients on ACE-inhibitors or angiotensin II receptor blockade were switched to alpha-methyl dopa (at least 2 months before study) and the dose adjusted to re-establish blood pressure control (< 130/80 mmHg) before enrolment; other medication allowed if stable for at least 3 months; nearly half the patients were using a statin and one-third were on antihypertensive therapy</p> <p>Adherence assessment: Compliance with treatment ascertained during each visit (no details)</p> <p>Screening phase: No</p>	<p>Primary: Vascular analyses</p> <p>HbA_{1c}: Yes</p> <p>Hypoglycaemia: Yes (symptomatic hypoglycaemia requiring glucose ingestion)</p> <p>Glycaemic excursions: No</p> <p>Total daily dose: Yes</p> <p>Weight change: Yes</p> <p>Complication rates: No</p> <p>Adverse events: Yes</p> <p>Health-related QoL: No</p> <p>Other: Euglycaemic-hyperinsulinaemic clamp; vascular studies; lipid parameters</p> <p>Timing of assessment: Clinic visits at 2- to 4-week intervals during first 3 months, every 2 months thereafter</p>

Study	Design	Participants	Interventions	Outcome measures
<p>Mattoo (2005)²³³ Worldwide</p>	<p>Focus: Effect of PIO plus insulin vs placebo plus insulin on glycaemic control, serum lipid profile, and selected cardiovascular risk factors in patients with type 2 diabetes whose disease was inadequately controlled with insulin therapy alone, despite efforts to intensify the treatment</p> <p>Design: Randomised double-blind, placebo-controlled parallel group trial, multicentre</p> <p>Duration: 6 months</p> <p>Follow-up: No postintervention follow-up</p> <p>Funding: Eli Lilly, Takeda Europe</p>	<p>Total number: 289</p> <p>N PIO + Ins: 142; 128 completed the trial</p> <p>N P + Ins: 147; 135 completed the trial</p> <p>Inclusion criteria: Type 2 diabetes diagnosed according to WHO criteria, use of insulin therapy (with or without oral antihyperglycaemic medication) for ≥ 3 months, $HbA_{1c} \geq 7.5\%$ at screening, ≥ 30 years at diagnosis</p> <p>Exclusion criteria: Type 1 diabetes, clinical signs or symptoms of any chronic systemic condition (defined), signs or symptoms of drug or alcohol abuse; previous therapy with TZDs, systemic glucocorticoid therapy, nicotinic acid at > 500 mg/day, or therapy for malignancy other than basal cell or squamous skin cancer; women breastfeeding or pregnant, women of childbearing potential without active birth control</p> <p>Age: PIO + Ins, 58.8 years (SD 7.4); P + Ins, 58.9 years (SD 6.9)</p> <p>Gender: PIO + Ins, 56.3% female; P + Ins, 57.1% female</p> <p>BMI: PIO + Ins, 32.5 kg/m² (SD 4.8); P + Ins: 31.8 kg/m² (SD 5.0)</p> <p>Ethnicity: Not reported</p> <p>Diabetes duration: PIO + Ins, 163.4 months (SD 81.0); P + Ins, 160.9 months (SD 73.7)</p> <p>Previous medication: 149 patients previously on oral agents (MET $n = 109$, SFU $n = 19$, MET plus SFU $n = 17$, other $n = 4$)</p> <p>Comorbidities: Not reported</p> <p>Subgroups: None</p>	<p>PIO + Ins: 30 mg PIO plus insulin</p> <p>P + Ins: Identical placebo plus insulin</p> <p>Both: All patients received diabetes education, including dietary and exercise guidelines, and were instructed to maintain their individual diet and exercise regimens throughout the study; patient diaries for SMBG; insulin dose reduced by 10% at randomisation to avoid hypoglycaemia and adjusted thereafter based on SMGB levels</p> <p>Cointerventions: Patients were allowed to use other medication as required, except another OAD agent, systemic glucocorticoid therapy, or nicotinic acid (> 500 mg/day)</p> <p>Adherence assessment: Capsule count (compliance rate $\geq 97.2\%$)</p> <p>Screening phase: Up to 14 days lead-in phase, patients remained on prescribed insulin therapy regimen, as monotherapy or with OHA; patients with $HbA_{1c} \geq 7.5\%$ then proceeded to insulin intensification period (3 months); insulin dose and number of injections adjusted to achieve fasting and preprandial BG < 5.5 mmol/l and 2-hour postprandial BG < 7.5 mmol/l; patients with $HbA_{1c} \geq 7.0\%$ after insulin intensification were randomised to PIO plus insulin or placebo plus insulin</p>	<p>Primary: Change in HbA_{1c} level from baseline to end point</p> <p>HbA_{1c}: HbA_{1c}</p> <p>Hypoglycaemia: Yes (1. subjective symptoms only, 2. subjective symptoms with SMBG ≥ 2.8 mmol/l, 3. subjective symptoms with SMBG < 2.8 mmol/l, 4. SMBG < 2.8 mmol/l without symptoms)</p> <p>Glycaemic excursions: No</p> <p>Total daily dose: Yes</p> <p>Weight change: Yes</p> <p>Complication rates: No</p> <p>Adverse events: Yes: adverse events, laboratory testing, physical examination</p> <p>Health-related QoL: No</p> <p>Other: Lipid parameters</p> <p>Timing of assessment: Five visits between randomisation and end of study</p>

Study	Design	Participants	Interventions	Outcome measures
Raz (2005) ^{23,4} Worldwide	Focus: Efficacy and safety of biphasic insulin aspart 30/70 (BIAsp 30) plus PIO vs glibenclamide plus PIO and BIAsp 30 monotherapy in type 2 diabetes Design: Randomised, open-label, parallel group trial, multicentre Duration: 18 weeks Follow-up: No postintervention follow-up Funding: Novo Nordisk	Total number: 283 N PIO + Ins: 93; 73 completed the trial N PIO + glibenclamide: 93; 56 completed the trial (not considered here) N Ins mono: 97; 75 completed the trial Inclusion criteria: Male and female patients with type 2 diabetes; age \geq 18 years; BMI \leq 40 kg/m ² ; treatment with SFU (monotherapy or combination therapy) \geq 3 months before screening; insufficient glycaemic control (HbA _{1c} 7.4–14.7%) Exclusion criteria: Significant disease or conditions likely to affect trial or health outcomes (including history of drug or alcohol dependence, impaired hepatic function, cardiac disease) Age: PIO + Ins, 56.7 years (SD 10.5); Ins mono, 55.2 years (SD 9.1) Gender: PIO + Ins, 47% female; Ins mono, 35% female BMI: PIO + Ins, 29.4 kg/m ² (SD 4.6); Ins mono, 29.5 kg/m ² (SD 4.9) Ethnicity: Not reported Diabetes duration: PIO + Ins, 9.2 years (SD 5.3); Ins mono, 10.0 years (SD 5.8) Previous medication: Patients taking other oral agents with SFU: PIO + Ins – none 14.0%, acarbose 9.7%, meglitinides 3.2%, MET 83.9%, TZDs 7.5%; ins mono – none 13.4%, acarbose 12.4%, meglitinides 1.0%, MET 80.4%, TZDs 4.1% Comorbidities: Not reported Subgroups: None	PIO + Ins: 30 mg PIO once daily after breakfast plus biphasic insulin aspart 30/70 (BIAsp 30). BIAsp 30 initiated at a dose of 0.2 U/kg/day PIO + glibenclamide: 30 mg PIO once daily after breakfast plus glibenclamide (starting dose 5 mg in patients already on glibenclamide, equivalent dose not exceeding 10 mg in patients previously on other SFUs) (not considered here) Ins mono: BIAsp 30 initiated at a dose of 0.3 U/kg/day Insulin therapy: Biphasic insulin aspart 30/70 (30% rapid-acting soluble insulin aspart, 70% intermediate-acting protamine-crystallised insulin aspart); BIAsp 30 injected immediately (within 5 minutes) before breakfast (50% of dose) and before dinner (50% of dose); BIAsp 30 titrated individually by patients using SMBG to achieve target BG values of 5–8 mmol/l for fasting, preprandial and night-time measurements, and 5–10 mmol/l for postprandial readings; BIAsp 30 injections with NovoPen 3; all dose titrations completed within 8 weeks of treatment Cointerventions: Any patient treated with insulin sensitiser other than PIO was told to stop treatment 14 days before randomisation; no manipulation of lipid-lowering regimens Adherence assessment: Checking patient diaries Screening phase: None	Primary: End of trial HbA _{1c} HbA _{1c} : Yes Hypoglycaemia: Major hypoglycaemic episodes (patient unable to self-treat, BG < 50 mg/dl, or when symptoms remitted after administration of intravenous glucose or intramuscular glucagons after food intake); minor hypoglycaemic episodes (BG < 50 mg/dl, patient handled the event without assistance from others); symptomatic episodes (hypoglycaemic symptoms present but not confirmed by BG measurement, assistance from others not required) Glycaemic excursions: Yes, BG profiles (7 and 8 point) Total daily dose: Yes Weight change: Weight Complication rates: No Adverse events: Yes Health-related QoL: No Other: Lipid profiles Timing of assessment: Screening, 8 weeks, end of trial (HbA _{1c}); baseline, 4, 8, 12, 18 weeks (lipids)

Study	Design	Participants	Interventions	Outcome measures
Rosenstock (2002) ²³⁵ (PIO 014 study group) USA	<p>Focus: Effect of two doses of PIO (15 or 30 mg) in combination with a stable insulin regimen to improve glycaemic control in patients whose type 2 diabetes is poorly controlled despite current insulin therapy</p> <p>Design: Double-blind, placebo-controlled RCT, multicentre</p> <p>Duration: 16 weeks</p> <p>Follow-up: No postintervention follow-up</p> <p>Funding: Takeda Pharmaceuticals</p>	<p>Total number: 566</p> <p>N PIO15 + Ins: 191; 161 completed the trial</p> <p>N PIO30 + Ins: 188; 172 completed the trial</p> <p>N P + Ins: 187; 164 completed the trial</p> <p>Inclusion criteria: 30–75 years, type 2 diabetes; insulin treatment for ≥ 30 units/day for ≥ 4 months, with stable dosage for at least 30 days; at screening HbA_{1c} $\geq 8.0\%$, fasting C-peptide $> 0.7 \mu\text{g/L}$</p> <p>Exclusion criteria: History of ketoacidosis, unstable or rapidly progressive diabetic retinopathy, nephropathy or neuropathy; impaired hepatic function (AST, ALT, total bilirubin or alkaline phosphatase > 2.5 times upper limit of normal); impaired kidney function (serum creatinine $> 1.8 \text{ mg/dl}$); anaemia; unstable or symptomatic cardiovascular or cerebrovascular conditions (defined)</p> <p>Age: PIO15 + Ins, 56.9 years (SE 10.4); PIO30 + Ins, 57.5 years (SE 9.9); P + Ins, 56.7 years (SE 9.4)</p> <p>Gender: PIO15 + Ins, 53.9% female; PIO30 + Ins, 49.5% female; P + Ins, 54.5% female</p> <p>BMI: PIO15 + Ins, 33.2 kg/m² (SE 5.4); PIO30 + Ins, 34.3 kg/m² (SE 6.2); P + Ins, 33.2 kg/m² (SE 5.2)</p> <p>Ethnicity: PIO15 + Ins, 74.9% Caucasian; PIO30 + Ins, 73.4% Caucasian; P + Ins: 71.1% Caucasian</p> <p>Diabetes duration: Not reported</p> <p>Previous medication: 88% insulin monotherapy; 12% combination with oral agents (8% MET, 2% glyburide, 2% glipizide); 134 patients receiving serum lipid-reducing agent (classes approximately evenly distributed across groups)</p> <p>Comorbidities: Not reported</p> <p>Subgroups: None</p>	<p>N PIO15 + Ins: 15 mg PIO plus usual insulin regimen</p> <p>N PIO30 + Ins: 30 mg PIO plus usual insulin regimen</p> <p>N P + Ins: Placebo plus usual insulin regimen</p> <p>All: Insulin dose could be decreased in response to hypoglycaemia; maximum permitted decrease in insulin dose at any one time: 10% of patient's current total daily dosage; reduced dose remained fixed unless new occurrences of hypoglycaemia warranted another 10% decrease</p> <p>Cointerventions: Lipid-lowering medications allowed, provided patient had been taking stable dose for > 60 days and regimen was continued without alteration throughout the study; no dietary intervention/modification</p> <p>Adherence assessment: No</p> <p>Screening phase: 2 weeks – patients on OHA in addition to insulin discontinued oral agent at beginning of screening period; screening followed by one week (for patients on stable insulin monotherapy) or 4 weeks (for patients previously on insulin plus oral agents) single-blind placebo treatment period (stable insulin regimen in combination with placebo)</p>	<p>Primary: Unclear, presumably HbA_{1c} at study end point</p> <p>HbA_{1c}: Yes</p> <p>Hypoglycaemia: Yes; defined as FPG $\leq 100 \text{ mg/dl}$ (5.6 mmol/l) on two occasions symptoms of hypoglycaemia not explained by other conditions</p> <p>Glycaemic excursions: No</p> <p>Total daily dose: Yes</p> <p>Weight change: Yes</p> <p>Complication rates: No</p> <p>Adverse events: Yes; laboratory values, vital signs, ECGs, any adverse events</p> <p>Health-related QoL: No</p> <p>Other: Serum lipid measurements (triglycerides and cholesterol)</p> <p>Timing of assessment: Patients seen every 4 weeks</p>

Study	Design	Participants	Interventions	Outcome measures
<p>Scheen (2006)^{23,6}</p> <p>19 European countries</p> <p>Part of PROactive trial (investigating only patients concomitantly treated with insulin)</p> <p>Abstract only</p>	<p>Focus: Effects of PIO on the secondary prevention of macrovascular events in type 2 diabetes</p> <p>Design: Randomised double-blind outcome study, multicentre</p> <p>Duration: Mean 34.5 months</p> <p>Follow-up: No postintervention follow-up</p> <p>Funding: Takeda Europe, Eli Lilly</p>	<p>Total number: 1760</p> <p>N PIO + Ins: 864</p> <p>N P + Ins: 896</p> <p>Inclusion criteria: Male or female with type 2 diabetes; age 35–75 years; HbA_{1c} level above the upper limit of normal (local equivalent of 6.5% for a DCCT-traceable assay), despite management of diabetes with diet alone or with oral BG-lowering agents; increased risk of macrovascular disease as defined in the trial; insulin allowed if given in combination with oral agents</p> <p>Exclusion criteria: Current use of PIO or any other TZDs; signs of type 1 diabetes; insulin as sole therapy for diabetes; planned revascularisation; symptomatic heart failure; leg ulcers, gangrene, or pain at rest; haemodialysis; significantly impaired hepatic function (serum ALT > 2.5 times upper limit of normal)</p> <p>Age: Not reported for subgroup on insulin therapy</p> <p>Gender: Not reported for subgroup on insulin therapy</p> <p>BMI: Not reported for subgroup on insulin therapy</p> <p>Ethnicity: Not reported for subgroup on insulin therapy</p> <p>Diabetes duration: Not reported for subgroup on insulin therapy</p> <p>Previous medication: At baseline, insulin combined with MET monotherapy in 53%, SFU monotherapy in 24%, dual therapy with MET and SFU 12%</p> <p>Comorbidities: Not reported</p> <p>Subgroups: Abstract reports subgroup of larger trial – in the main trial only about one-third of patients received concomitant insulin therapy</p>	<p>PIO + Ins: PIO plus previous treatment; forced titration phase in the first 2 months of treatment, with stepwise increase of PIO dose from 15 to 30 mg and then up to 45 mg, to maintain patients at maximum tolerated dose; dose could be adjusted at any time within 15 to 45 mg range, based on tolerability</p> <p>P + Ins: Placebo plus previous treatment</p> <p>Both: Investigators encouraged to maintain glycaemia at < 6.5%</p> <p>Cointerventions: Proportion of concomitant oral therapy remained similar: PIO + Ins, MET alone 47%, SFU alone 16%, MET plus SFU 10%; P + Ins, MET alone 52%, SFU alone 16%, MET plus SFU 11%</p> <p>Adherence assessment: No</p> <p>Screening phase: Not reported</p>	<p>Primary: (of PROactive trial) Time from randomisation to any of (composite end point): all-cause mortality, non-fatal MI, acute coronary syndrome, cardiac intervention (including coronary artery bypass graft or percutaneous coronary intervention), stroke, major leg amputation (above ankle), bypass surgery; or revascularisation in the leg</p> <p>HbA_{1c}: Yes</p> <p>Hypoglycaemia: Yes (but undefined)</p> <p>Glycaemic excursions: No</p> <p>Total daily dose: Yes</p> <p>Weight change: No</p> <p>Complication rates: Not reported here</p> <p>Adverse events: Yes</p> <p>Health-related QoL: No</p> <p>Other: None (in this abstract)</p> <p>Timing of assessment: Unclear</p>

Study	Design	Participants	Interventions	Outcome measures
Shah (2007) ²³⁷ USA Abstract only	<p>Focus: Effects of a PIO and insulin combination vs insulin therapy alone on body fat distribution</p> <p>Design: Randomised double-blind placebo-controlled trial, single centre</p> <p>Duration: 12–16 weeks</p> <p>Follow-up: No postintervention follow-up</p> <p>Setting: Unclear</p> <p>Funding: Not stated</p>	<p>Total number: 25</p> <p>N PIO + Ins: 12</p> <p>N P + Ins: 13</p> <p>Inclusion criteria: Insulin-treated, obese type 2 diabetes patients</p> <p>Exclusion criteria: Not reported</p> <p>Age: Not reported</p> <p>Gender: Not reported</p> <p>BMI: 36.5 kg/m²</p> <p>Ethnicity: Not reported</p> <p>Diabetes duration: Not reported</p> <p>Previous medication: Not reported</p> <p>Comorbidities: Not reported</p> <p>Subgroups: None</p>	<p>PIO + Ins: PIO (30 mg titrated to 45 mg) and insulin</p> <p>P + Ins: Placebo and insulin</p> <p>Cointerventions: Not reported</p> <p>Adherence assessment: Not reported</p>	<p>Primary: Body fat distribution</p> <p>HbA_{1c}: HbA_{1c}</p> <p>Hypoglycaemia: No</p> <p>Glycaemic excursions: No</p> <p>Total daily dose: No</p> <p>Weight change: Yes</p> <p>Complication rates: No</p> <p>Adverse events: No</p> <p>Health-related QoL: No</p> <p>Other: Subcutaneous adipose tissue, visceral adipose tissue (abdominal CT scans)</p> <p>Timing of assessment: Not reported</p>
				<p>ACE, angiotensin-converting enzyme; ADA, American Diabetes Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIAsp, biphasic insulin aspart; DCCT, Diabetes Control and Complications Trial; ECG, electrocardiogram; FPG, fasting plasma glucose; Ins, insulin; LDL, low-density lipoprotein; MET, metformin; OAD, oral antidiabetic; P, placebo; PIO, pioglitazone; SMBG, self-monitoring of blood glucose; s.c., subcutaneous; SFU, sulfonyleurea; TZD, thiazolidinedione.</p>

Appendix 7

Characteristics of included trials – pioglitazone + insulin vs pioglitazone

Study	Design	Participants	Interventions	Outcome measures
Raskin (2006) ^{242,243} USA Abstract only	Focus: Safety and efficacy of BIAsp 30 (30% soluble and 70% protaminated insulin aspart) in insulin-naive type 2 diabetes patients taking any two OAD agents Design: Randomised, parallel group trial, single/multicentre unclear Duration: 34 weeks Follow-up: No postintervention follow-up Funding: Novo Nordisk	Total number: 181 N BIAsp 30 + MET + PIO: 93 N MET + PIO: 88 Inclusion criteria: Insulin naive, type 2 diabetes; HbA _{1c} 7.5–12%, taking any two OAD agents Exclusion criteria: Not reported Age: Not reported Gender: Not reported BMI: Not reported Ethnicity: Not reported Diabetes duration: Not reported Previous medication: Not reported Comorbidities: Not reported Subgroups: None	BIAsp 30 + MET + PIO: BIAsp 30 (30% soluble and 70% protaminated insulin aspart) added to an optimised treatment of MET and PIO; BIAsp 30 initiated at 6 U twice a day (pre-breakfast and pre-supper) and titrated to target BG (4.4–6.1 mmol/l) by an algorithm-directed forced titration MET + PIO: Optimised treatment of MET and PIO without insulin Cointerventions: Not reported Adherence assessment: Not reported Run-in phase: 8-week run-in – treatment changed to MET (2500 mg/day) and PIO (30 or 45 mg/day)	Primary: HbA _{1c} (presumably) HbA _{1c} : Yes Hypoglycaemia: Minor hypoglycaemia (BG <3.1 mmol/l) Glycaemic excursions: No Total daily dose: No Weight change: Weight Complication rates: No Adverse events: Yes Health-related QoL: No Other: None Timing of assessment: Not reported
	BIAsp, biphasic insulin aspart; MET, metformin; OAD, oral antidiabetic; PIO, pioglitazone.			

Appendix 8

Pair-wise comparisons

Male BMI 30

	No comparison			With comparison		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
Comparison 1: EXE_GLA vs GLA						
UKPDS QALYs	8.607	8.538	0.069	8.394	8.331	0.063
Total QALYs	8.567	8.464	0.103	8.354	8.258	0.096
Direct drug cost (£)	8813	7939	875	8592	7727	865
Total cost (£)	18,953	18,258	696	19,469	18,778	691
ICER			6755			7180
	No comparison			With comparison		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
Comparison 2: SIT vs ROSI						
UKPDS QALYs	8.566	8.549	0.017	8.347	8.342	0.005
Total QALYs	8.479	8.447	0.032	8.263	8.242	0.021
Direct drug cost (£)	5793	5938	-145	5628	5779	-151
Total cost (£)	16,083	16,277	-194	16,650	16,853	-203
ICER			-6055			-9849
	No comparison			With comparison		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
Comparison 3: VIL vs PIO						
UKPDS QALYs	8.561	8.590	-0.029	8.353	8.378	-0.025
Total QALYs	8.468	8.479	-0.011	8.262	8.269	-0.007
Direct drug cost (£)	5371	5824	-453	5220	5665	-445
Total cost (£)	15,731	16,180	-449	16,309	16,756	-446
ICER			39,846			66,799

	No comparison			With comparison		
	Glargine	NPH	Net	Glargine	NPH	Net
Comparison 4: GLA vs NPH						
UKPDS QALYs	8.538	8.540	-0.002	8.331	8.333	-0.003
Total QALYs	8.464	8.457	0.007	8.258	8.253	0.006
Direct drug cost (£)	7939	6111	1828	7727	5946	1780
Total cost (£)	18,258	16,402	1855	18,778	16,980	1798
ICER			281,349			320,029
	No comparison			With comparison		
	Detemir	NPH	Net	Detemir	NPH	Net
Comparison 5: DET vs NPH						
UKPDS QALYs	8.530	8.540	-0.010	8.316	8.333	-0.018
Total QALYs	8.472	8.457	0.015	8.259	8.253	0.006
Direct drug cost (£)	8826	6111	2715	8585	5946	2638
Total cost (£)	19,128	16,402	2726	19,621	16,980	2641
ICER			187,726			417,625

Male BMI 30 but no weight changes within UKPDS Outcomes Model

Comparison 1: EXE_GLA vs GLA	No comparison			With comparison		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	8,599	8,547	0.053	8,386	8,338	0.048
Total QALYs	8,559	8,472	0.087	8,347	8,265	0.082
Direct drug cost (£)	8808	7945	863	8587	7732	856
Total cost (£)	18,999	18,222	777	19,513	18,740	773
ICER			8967			9449
Comparison 2: SIT vs ROSI						
Comparison 2: SIT vs ROSI	No comparison			With comparison		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
UKPDS QALYs	8,562	8,562	0.000	8,354	8,353	0.001
Total QALYs	8,476	8,460	0.015	8,269	8,253	0.016
Direct drug cost (£)	5790	5947	-157	5632	5787	-154
Total cost (£)	16,089	16,272	-183	16,670	16,848	-178
ICER			-11,878			-11,011
Comparison 3: VIL vs PIO						
Comparison 3: VIL vs PIO	No comparison			With comparison		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	8,562	8,603	-0.041	8,354	8,389	-0.035
Total QALYs	8,469	8,492	-0.023	8,263	8,279	-0.017
Direct drug cost (£)	5371	5833	-461	5221	5672	-451
Total cost (£)	15,745	16,191	-446	16,325	16,763	-438
ICER			19,477			26,270

	No comparison			With comparison		
Comparison 4: GLA vs NPH						
UKPDS QALYs	Glargine	NPH	Net	Glargine	NPH	Net
Total QALYs	8,547	8,550	-0.004	8,338	8,341	-0.003
Direct drug cost (£)	8,472	8,468	0.005	8,265	8,261	0.005
Total cost (£)	7945	6118	1826	7732	5952	1780
ICER	18,222	16,389	1833	18,740	16,958	1782
			387,629			379,631
Comparison 5: DET vs NPH						
UKPDS QALYs	Detemir	NPH	Net	Detemir	NPH	Net
Total QALYs	8,535	8,550	-0.015	8,329	8,341	-0.012
Direct drug cost (£)	8,477	8,468	0.009	8,272	8,261	0.012
Total cost (£)	8831	6118	2713	8598	5952	2646
ICER	19,132	16,389	2743	19,638	16,958	2680
			303,770			226,163

Female BMI 30

	No comparison			With comparison		
Comparison 1: EXE_GLA vs GLA						
UKPDS QALYs	Exenatide	Glargine	Net	Exenatide	Glargine	Net
Total QALYs	9,468	9,397	0.071	9,210	9,148	0.062
Direct drug cost (£)	9,423	9,318	0.105	9,167	9,071	0.096
Total cost (£)	9394	8385	1010	9140	8143	997
ICER	19,436	18,598	838	19,969	19,138	831
			7970			8653
Comparison 2: SIT vs ROSI						
UKPDS QALYs	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
Total QALYs	9,436	9,402	0.034	9,175	9,153	0.022
Direct drug cost (£)	9,344	9,294	0.050	9,085	9,047	0.038
Total cost (£)	6244	6379	-135	6053	6195	-142
ICER	16,415	16,568	-153	17,003	17,178	-175
			-3079			-4604
Comparison 3: VIL vs PIO						
UKPDS QALYs	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
Total QALYs	9,428	9,427	0.000	9,175	9,176	-0.001
Direct drug cost (£)	9,328	9,310	0.019	9,078	9,061	0.017
Total cost (£)	5824	6265	-441	5646	6082	-437
ICER	15,959	16,502	-543	16,581	17,112	-531
			-29,027			-30,976

	No comparison			With comparison		
Comparison 4: GLA vs NPH						
	Glargine	NPH	Net	Glargine	NPH	Net
UKPDS QALYs	9.397	9.395	0.002	9.148	9.147	0.002
Total QALYs	9.318	9.308	0.010	9.071	9.061	0.010
Direct drug cost (£)	8385	6497	1887	8143	6308	1835
Total cost (£)	18,598	16,742	1856	19,138	17,341	1797
ICER			177,940			179,074
Comparison 5: DET vs NPH						
	Detemir	NPH	Net	Detemir	NPH	Net
UKPDS QALYs	9.398	9.395	0.002	9.146	9.147	-0.001
Total QALYs	9.335	9.308	0.027	9.085	9.061	0.024
Direct drug cost (£)	9310	6497	2812	9039	6308	2732
Total cost (£)	19,538	16,742	2796	20,048	17,341	2706
ICER			102,007			113,988

Male BMI 35

	No comparison		With comparison		
Comparison 1: EXE_GLA vs GLA					
UKPDS QALYs	Exenatide	Glargine	Exenatide	Glargine	Net
Total QALYs	8,533	8,448	8,328	8,252	0.076
Direct drug cost (£)	8,493	8,375	8,289	8,180	0.109
Total cost (£)	9,958	9,863	9,703	9,612	91
ICER	20,311	20,360	20,787	20,844	-57
					-522
Comparison 2: SIT vs ROSI					
UKPDS QALYs	Sitagliptin	Rosiglitazone	Sitagliptin	Rosiglitazone	Net
Total QALYs	8,485	8,473	8,285	8,274	0.011
Direct drug cost (£)	8,399	8,371	8,201	8,174	0.027
Total cost (£)	6619	6767	6438	6586	-147
ICER	17,165	17,363	17,712	17,906	-194
					-7254
Comparison 3: VIL vs PIO					
UKPDS QALYs	Vildagliptin	Pioglitazone	Vildagliptin	Pioglitazone	Net
Total QALYs	8,490	8,504	8,288	8,302	-0.014
Direct drug cost (£)	8,397	8,393	8,198	8,194	0.004
Total cost (£)	6111	6552	5937	6374	-436
ICER	16,717	17,095	17,264	17,656	-392
					-98,356

	No comparison			With comparison		
Comparison 4: GLA vs NPH						
UKPDS QALYs	Glargine	NPH	Net	Glargine	NPH	Net
Total QALYs	8,448	8,443	0.005	8,252	8,250	0.002
Direct drug cost (£)	8,375	8,361	0.013	8,180	8,169	0.010
Total cost (£)	9863	7349	2514	9612	7162	2450
ICER	20,360	17,857	2503	20,844	18,415	2429
			189,400			233,187
Comparison 5: DET vs NPH						
UKPDS QALYs	Detemir	NPH	Net	Detemir	NPH	Net
Total QALYs	8,445	8,443	0.001	8,249	8,250	-0.001
Direct drug cost (£)	8,387	8,361	0.025	8,192	8,169	0.023
Total cost (£)	11,084	7349	3734	10,803	7162	3641
ICER	21,579	17,857	3722	22,043	18,415	3627
			146,632			157,478

Female BMI 35

Comparison 1: EXE_GLA vs GLA	No comparison			With comparison		
	Exenatide	Glargine	Net	Exenatide	Glargine	Net
UKPDS QALYs	9.391	9.306	0.085	9.143	9.069	0.074
Total QALYs	9.346	9.227	0.119	9.099	8.991	0.108
Direct drug cost (£)	10,645	10,388	257	10,350	10,100	249
Total cost (£)	20,907	20,781	126	21,396	21,289	107
ICER			1058			988
Comparison 2: SIT vs ROSI						
Comparison 2: SIT vs ROSI	No comparison			With comparison		
	Sitagliptin	Rosiglitazone	Net	Sitagliptin	Rosiglitazone	Net
UKPDS QALYs	9.350	9.329	0.021	9.105	9.087	0.018
Total QALYs	9.258	9.222	0.037	9.015	8.981	0.034
Direct drug cost (£)	7138	7282	-144	6925	7069	-144
Total cost (£)	17,542	17,769	-227	18,121	18,335	-214
ICER			-6205			-6315
Comparison 3: VIL vs PIO						
Comparison 3: VIL vs PIO	No comparison			With comparison		
	Vildagliptin	Pioglitazone	Net	Vildagliptin	Pioglitazone	Net
UKPDS QALYs	9.347	9.343	0.003	9.103	9.100	0.004
Total QALYs	9.248	9.226	0.021	9.007	8.985	0.022
Direct drug cost (£)	6627	7065	-439	6424	6856	-433
Total cost (£)	16,988	17,458	-470	17,598	18,047	-449
ICER			-21,965			-20,618

	No comparison			With comparison		
Comparison 4: GLA vs NPH	Glargine	NPH	Net	Glargine	NPH	Net
UKPDS QALYs	9,306	9,303	0.003	9,069	9,065	0.003
Total QALYs	9,227	9,216	0.012	8,991	8,980	0.012
Direct drug cost (£)	10,388	7796	2592	10,100	7576	2524
Total cost (£)	20,781	18,208	2572	21,289	18,792	2497
ICER			219,805			212,009
	No comparison			With comparison		
Comparison 5: DET vs NPH	Detemir	NPH	Net	Detemir	NPH	Net
UKPDS QALYs	9,313	9,303	0.010	9,071	9,065	0.006
Total QALYs	9,250	9,216	0.034	9,010	8,980	0.030
Direct drug cost (£)	11,663	7796	3867	11,336	7576	3760
Total cost (£)	22,135	18,208	3926	22,592	18,792	3800
ICER			114,229			125,938

DET, detemir; EXE, exenatide; GLA, glargine; ICER, incremental cost-effectiveness ratio; NPH, Neutral Protamine Hagedorn; PIO, pioglitazone; QALY, quality-adjusted life-year; ROSI, rosiglitazone; SIT, sitagliptin; UKPDS, United Kingdom Prospective Diabetes Study; VIL, vildagliptin.

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We look forward to hearing from you.