NICE National Institute for Health and Care Excellence

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes

Assessment Report

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Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation.

Warwick Evidence

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Pamela Royle did literature searches, generated the list of references and edited and formatted the final report.
Christine Clar, Rachel Court, Bee Tan and Saran Shantikumar extracted data from the trials in Chapter 2. Christine Clar drafted the clinical effectiveness section. Bee Tan drafted the section on UTIs and GTIs.
Christine Clar and Jill Colquitt extracted data for the network meta-analysis which was carried out by Olakan Uthman.
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List of Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACEI	Angiotensin-Converting Enzyme Inhibitor
ADOPT	A Diabetes Outcome Progression Trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AG	Assessment Group
AHA	Anti-Hyperglycaemic Agents
ARB	Angiotensin-Receptor Blocker
BDR	Background Diabetic Retinopathy
BMI	Body Mass Index
BNF	British National Formulary
BNP	B-type Natriuretic Peptides
BP	Blood Pressure
CANTATA-M	CANagliflozin Treatment and Trial Analysis - Monotherapy
CDM	CARDIFF Diabetes Model
CEAC	Cost-Effectiveness Acceptability Curve
CG	Clinical Guideline
CHF	Congestive Heart Failure
CI	Confidence Interval
CKD	Chronic Kidney Disease
CODE-2	Cost of Diabetes in Europe – Type 2
CPRD	Clinical Practice Research Datalink
CrI	Credible Interval
CSII	Continuous Subcutaneous Insulin Infusion
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complications Trial
DIC	Deviation Information Criterion
DKA	Diabetic ketoacidosis
DPP4	Dipeptidyl peptidase-4
DURATION-1	Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly
ECHO-T2DM	Economic and Health Outcomes Model for Type 2 Diabetes Mellitus
EDICT	Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EMPA-REG BASAL	Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin
EMPA-REG METSU	Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes

EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
EMPA-REG RENAL	Efficacy and Safety of Empagliflozin in Patients With Type 2 Diabetes and Renal Impairment
EQ-5D	European Quality of Life-5 Dimensions
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GDG	Guideline Development Group
GLP-1	Glucagon-like peptide-1
GPRD	General Practice Research Database
GTI	Genital Tract Infection
GUIDE	GlUcose control in type 2 diabetes: Diamicron MR vs. glimEpiride
HbA1c	Glycated haemoglobin (A1c)
HDL	High-Density Lipoprotein
HFS	Hypoglyceamic Fear Survey
HOPE	Heart Outcomes Prevention Evaluation Study
ICERs	Incremental Cost-Effectiveness Ratio
IHD	Ischaemic Heart Disease
IQR	Interquartile range
ITT	Intention-to-treat
LOCF	Last observation carried forward
MCMC	Markov Chain Monte Carlo
MD	Mean Difference
MDI	Multiple Daily Injections
MO	Macular Oedema
MHRA	Medicines & Healthcare products Regulatory Agency
MI	Myocardial Infarction
MR	Modified Release
MS	Manufacturer Submission
NAFLD	Non-alcoholic fatty liver disease
NMA	Network Meta-Analysis
NPH	Neutral Protamine Hagedorn
OLS	Ordinary Least Squares
OM1	UKPDS Outcomes Model v1
PDR	Proliferative diabetic retinopathy
PPARG	Peroxisome proliferator-activated receptor gamma
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVD	Peripheral Vascular Disease
QALY	Quality-Adjusted Life Year

QoL	Quality of Life
QWB	Quality of Wellbeing
RCT	Randomised Controlled Trial
RR	Risk Ratio
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGLT1	Sodium-Glucose coTransporter 1
SGLT2	Sodium-glucose co-transporter-2
SIGN	Scottish Intercollegiate Guidelines Network
SLC5A2	Solute Carrier family 5 (sodium/glucose cotransporter), member 2
SMBG	Self monitoring of blood glucose
SmPC	Summary of Product Characteristics
SU	Sulphonylurea or Sulfonylurea
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TC	Total Cholesterol
THIN	The Health Improvement Network
TTO	Time Trade-Off
TZDs	Thiazolidinediones
UKPDS	United Kingdom Prospective Diabetes Study
UTI	Urinary Tract Infection
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy
WMD	Weighted Mean Difference
YHPHO	York and Humber Public Health Observatory

Summary

The prevalence of type 2 diabetes has been increasing in the UK, and over 3.5 million people in England have the disease. It has at times been described as “mild” diabetes, in contrast to type 1 (insulin-dependent) diabetes, but this term was incorrect since people with type 2 diabetes are also at risk of complications of diabetes, including visual loss, renal failure and neuropathy, and an excess risk of cardiovascular disease, particularly coronary artery disease.

Most people with type 2 diabetes are overweight, so treatment starts with lifestyle advice, aimed at reducing weight and increasing physical activity. Even modest amounts of weight loss can improve control of blood glucose.

If drug treatment is necessary, the drug of first choice is metformin. However some people cannot tolerate metformin. It causes troublesome diarrhoea in 5-10% of people. There is also a contraindication to using metformin in people with renal impairment.

If drug treatment is required to control high blood glucose levels when metformin cannot be used, the other options suggested in the NICE guideline include;

- Sulfonylureas
- Pioglitazone
- The DPP4 inhibitors
- Repaglinide

All of these are oral medications and licensed for use in monotherapy. The sulfonylureas have been used for decades and are available in inexpensive generic forms. Gliclazide costs around £30 a year, or around £60-80 a year for the modified release form. Their safety record is well established. They can cause weight gain and hypoglycaemia.
Pioglitazone is also available in inexpensive generic form, costing around £21 a year. It has rather more adverse effects, including weight gain, oedema, heart failure and fractures. There has been concern over an increased risk of bladder cancer but this is unproven, and recent research is reassuring.

The DPP4 inhibitors, such as sitagliptin, are a more recent group, with no generic forms, and cost around £430 a year. They have been approved by NICE for use in combination therapy. They are very well tolerated, and have the advantage of being weight neutral.

The newest group of drugs to be licensed for monotherapy are the sodium-glucose co-transporter 2 (SGLT2) inhibitors. These inhibit a mechanism in the kidney that conserves glucose by reabsorbing it from the urine. This means that glucose is lost in the urine, which reduces the blood glucose level and also leads to a loss of calories, which leads to weight loss. They also act like a mild diuretic and have a modest blood pressure lowering effect. They cost around £470 a year.

The purpose of this report is to review the clinical effectiveness and cost-effectiveness of three SGLT2 inhibitors, dapagliflozin, canagliflozin and empagliflozin, in monotherapy in people who cannt take metformin. All three drugs have previously been approved by NICE for use in combination treatment, which is therefore not addressed in this report.

Methods

Searches were carried out in Medline and Embase, looking for randomised controlled trials lasting 24 weeks or more. The trials were then critically appraised and summarised. Submissions from the three manufacturers were checked for any additional trials – none were found. For adverse events, a wider range of studies were used, including trials of combinations. A network meta-analysis was carried out involving the three SGLT2 inhibitors and key comparators. Cost-effectiveness modelling was done using the UKPDS Outcome model, version 1, because the Assessment Group was unable to obtain access to version 2 in time.

Results

Seven relevant trials were obtained, three of dapagliflozin and two each for canagliflozin and empagliflozin. All these trials were of good quality. The canagliflozin and dapagliflozin trials compared them with placebo, but the two empagliflozin trials included active comparators, one sitagliptin and one linagliptin. All three drugs were shown to be effective in improving glycaemic control, promoting weight loss and lowering blood pressure. The main outcome was glycaemic control as reflected in reductions in HbA1c, where a reduction of 0.5% or more is regarded as clinically useful.

In the three trials of dapagliflozin 10mg daily, HbA1c was reduced by 0.39%, 0.66% and 0.82% more than on placebo. The trial with the smallest reduction had the lowest baseline HbA1c, of 7.5%. Generally speaking the higher the baseline HbA1c, the greater the reduction seen. On dapagliflozin 10mg daily, patients lost between 1.1kg and 2kg in weight more than in the placebo groups, though it is worth noting that two trials were carried out in China and Japan where starting BMIs were around 26. The placebo groups lost between 0.27 kg and 2.2 kg, and also improved their HbA1cs (by 0.23%, 0.29% and 0.06%), and some of this might have been due to the circumstances of being in a trial, so

the differences due to dapagliflozin might be greater in routine care. Systolic blood pressure fell by 2.7 to 3.1 mmHg.

One canagliflozin trial was carried out in Japan and the other in 17 countries. On canagliflozin 100mg daily, HbA1c was reduced by 0.91% and 1.01% more than on placebo, from baselines of 8.0%. One trial also used a dose of 300mg, which reduced HbA1c by 1.17%. On 100mg daily, weight loss was around 2kg, and systolic blood pressure by 3.7 and 5.2 mm Hg. On 300mg daily, weight loss was 2.9kg. In both the canagliflozin trials, the placebogroup HbA1c rose (by 0.14% and 0.29%).

One empagliflozin trial was carried out in 197 centres in 22 countries, and the other in 124 centres in 9 countries, mainly western countries but including China, India and Japan. Compared to placebo, empagliflozin 10 mg reduced HbA1c by 0.74% and empagliflozin 25 mg by 0.86%. Weight loss was about 2 kg, and SBP was reduced by 2.6 and 3.4 mm Hg.

The only significant adverse effects reported in the trials were increases in urinary and genital tract infections, mainly in women. Both UTIs and GTIs occurred in about 4% to 9% in women.

Long-term cardiovascular outcome studies are being carried out on all three drugs, but the only one to report is the empagliflozin outcomes trial, in September 2015. This recruited 7020 patients in 42 countries, randomised to empagliflozin 10mg and 25mg, and placebo, added to the diabetes medications they were already on. Half were on insulin-containing regimens. They were selected as being at high risk of cardiovascular disease. Other glucose-lowering drugs could be added and this occurred in 31.5% of the placebo group and 19.5% of the empagliflozin groups. The mean HbA1cs at week 206 were 7.81% in the empagliflozin group and 8.16% in the placebo group.
All-cause mortality at a median of 3 years was 8.3% in the placebo group and 5.7% in the pooled empagliflozin group.This was mainly due to differences in cardiovascular deaths – 5.9% and 3.7%. The primary outcome was a composite of death from cardiovascular causes, non-fatal MI and non-fatal stroke, and this occurred in 12.1% of the placebo group and 10.5% of the empagliflozin group, giving a hazard ratio of 0.86 (95% CI 0.74-0.99). There were no significant differences in death from MI or in non-fatal MI. The proportions of MIs reported as fatal were surprisingly low at 4.0% and 4.4% for placebo and empagliflozin respectively. The difference in cardiovascular mortality was mainly due to sudden death (1.6% and 1.1%), heart failure (0.8% and 0.2%) and an ill-defined category of “other cardiovascular deaths” (2.4% and 1.6%). Subgroup analyses showed that the primary outcome only reached statistical significance in Asians. The Kaplan-Meier curves for deaths separate after a few months. They show a curious acceleration in the placebo group after 42 months.

Over the years, UTIs were no more frequent in the empagliflozin group than the placebo one, but GTIs were about three times as frequent. However in some trials the untreated controls might also have had an increased risk of UTIs due to poor control and hence glycosuria.

Network meta-analysis

We included the three SGLT2 inhibitors, pioglitazone, gliclazide, sitagliptin, vildagliptin and linagliptin in an NMA using placebo as a common comparator as far as possible. Compared to placebo, reductions in HbA1c were;

Canagliflozin 300mg	1.19%
Canagliflozin 100mg	0.95%
Empagliflozin 25mg	0.88%
Empagliflozin 10mg	0.76%
Dapagliflozin 10mg	0.59%

A caveat is necessary regarding the effects of the larger doses of canagliflozin and empagliflozin, which is that according to the licences, the larger doses should only be used in people who have tolerated the starting doses but have had an insufficient response. Those who do not respond well to the starting dose might not achieve the same effects as did people in the trials randomised to the larger disease from the start.

Only one dose of dapagliflozin is used, despite larger effects being reported with larger doses such as 20mg daily. In considering the smaller effect size with dapagliflozin 10mg, the improvements in the placebo groups in the dapagliflozin trials should be noted.

The reductions in HbA1c with pioglitazone and gliclazide were 1.13% and 0.95%.

A caveat is required regarding effect sizes in NMAs. Many trials recruit patients with quite high HbA1c levels, and the reductions seen in HbA1c may be much larger than would be seen in patients managed according to NICE guidelines with frequent monitoring and prompt intensification once their HbA1c exceeded 7.5%.

Cost effectiveness

Janssen, Astrazeneca and Boehringer Ingelheim each submitted cost effectiveness modelling exercises. Boehringer Ingelheim submitted four modelling exercises. The following summary concentrates upon the Boehringer Ingelheim lifetime modelling, the model B, which compared empagliflozin with pioglitazone, repaglinide, gliclazide and sitagliptin. The other three Boehringer Ingelheim models are summarised in the main body of the AG report.

All the company submissions apply the old £608 annual cost for canagliflozin 300mg, rather than the price reduction in August 2015 to the same £477 annual price for canagliflozin 100mg. As a

consequence, the summary of cost effectiveness results of the companies concentrates upon the canagliflozin 100mg results.

Janssen stands out for having used the ECHO-T2DM model. Astrazeneca, Boehringer Ingelheim and the AG used models based upon either the UKPDS68 or upon a combination of the UKPDS68 and the UKPDS82.

The Janssen model assumed that after an initial treatment effect HbA1c would increase at a constant rate. This rate was treatment specific. As a consequence, the annual rate of increase in HbA1c associated with a treatment could be as important as the initial treatment effect upon HbA1c.

Due in part to the assumed slow annual increase in HbA1c with pioglitazone, Janssen estimated that it has the lowest total lifetime costs of £20,264 and yields an average 9.998 QALYs. Gliclazide was estimated to be somewhat more expensive than pioglitazone with total costs of £20,956 and to yield 9.949 QALYs so is dominated by pioglitazone. Sitagliptin was also more expensive with a total cost of £23,442 and to yield a total of 9.981 per QALY so was dominated by pioglitazone, though has a cost effectiveness estimate compared to gliclazide of £6,969 per QALY.

Janssen estimated that canagliflozin 100mg has total costs of £23,525 and yields 10.039 QALYs which implies a cost effectiveness estimate of £79,537 per QALY compared to pioglitazone. The cost effectiveness estimate compared to gliclazide was £3,377 per QALY, this being largely due to the higher costs in the gliclazide arm (using the modified release form) compared to pioglitazone. Canagliflozin 100mg was estimated to dominate empagliflozin 10mg, empagliflozin 25mg and dapagliflozin 10mg.

The Janssen cost effectiveness estimates for the flozins compared to sitagliptin were £1,414 per QALY for canagliflozin 100mg, £1,977 per QALY for empagliflozin 25mg, £4,724 per QALY for empagliflozin 10mg and £6,040 per QALY for sitagliptin.

If the annual rate of increase in HbA1c was equalised between the treatments and repaglinide was included as a comparator it appears that this worsened the cost effectiveness estimate for canagliflozin compared to repaglinide to £189k per QALY. The cost effectiveness estimates for canagliflozin 100mg compared to gliclazide and sitagliptin worsened to £21,580 per QALY and £21,470 per QALY respectively. Applying the UKPDS68 evolution of HbA1c across all treatments resulted in broad clinical equivalence between canagliflozin 100mg and gliclazide, but the costs of canagliflozin 100mg are £744 greater.

The Astrazeneca submission used the CARDIFF diabetes model (CDM) which has been revised to use the equations of UKPDS68 to evolve the risk factors and the equations of UKPDS82 to calculate the probabilities of events and death. The UKPDS82 is a partial update of the UKPDS68.

Astrazeneca pooled the flozins into a class effect. Given this pioglitazone was estimated to be the least costly with total costs of £26,067 and to yield 13.111 QALYs. The sulfonylureas were estimated to have a total cost of £26,582 so £515 higher than pioglitazone, and to yield 13.179 QALYs so have a cost effectiveness estimate of £7,574 per QALY compared to pioglitazone. The gliptins were estimated to have a total cost of £27,873 and to yield 13.188 QALYs or only 0.009 QALYs more than the sulfonylureas, hence have a cost effectiveness compared to the sulfonylureas of £143k per QALY. The flozins were only £106 more expensive than the glitpins and yielded an additional 0.018 QALYs so had a cost effectiveness compared to the gliptins of £5,904 per QALY. But the flozins cost effectiveness compared to the sulfonylureas was poor at £52,047 per QALY.

Astrazeneca sensitivity analyses showed results were sensitive to the HbA1c intensification threshold and to the assumptions around the evolution of weight.

The Boehringer Ingelheim submission built a visual basic front and back end to the UKPDS OM1 model. The OM1 model uses the UKPDS68 equations for the evolution of the risk factors and the calculation of the probability of events.

Boehringer Ingelheim estimates that pioglitazone is the least expensive treatment with a total cost of [redacted] and yields [redacted] QALYs. Only repaglinide is close to being cost effective compared to pioglitazone, yielding an additional 0.025 QALYs at an additional cost of £635 hence a cost effectiveness estimate of £25,349 per QALY. Boehringer include costs ([redacted]) of self-monitoring of blood glucose for both repaglinide and pioglitazone whereas it would be unnecessary with pioglitazone. Empagliflozin 25mg and empagliflozin 10mg are estimated to be £2,834 and £2,834 more expensive than pioglitazone to yield an additional 0.061 and 0.056 QALYs, so have cost effectiveness estimates of £46,480 per QALY and £50,892 per QALY compared to pioglitazone. The cost effectiveness estimates for empagliflozin 25mg and 10mg compared to sitagliptin were somewhat better. The net costs are estimated to be [redacted] and [redacted] with additional patient gains of [redacted] and [redacted], resulting in cost effectiveness estimates of around £7,333 per QALY and £8,325 per QALY respectively.

The intention specified within the protocol was for the AG to use the UKPDS OM2. In common with the updated CDM, the OM2 uses the equations of UKPDS68 to evolve the risk factors and the equations of UKPDS82 to calculate the probabilities of events and death. But the OM2 was not made

available to the AG. As a consequence and as also specified in the protocol, the AG fell back upon writing a visual basic front and back end to the UKPDS OM1 model.

The AG modelling suggests that gliclazide is the least expensive with total costs of £27,314. Repaglinide and pioglitazone have similar total costs of £27,413 and £27,543 respectively. The increased costs for pioglitazone are due in part to the AG including a £72 allowance for annual BNP monitoring. Costs increase quite markedly with sitagliptin at a total cost of £32,358, and increase further with the flozins being clustered between £32,676 and £32,866. Sitagliptin is estimated to be £5,045 more expensive than gliclazide, and the flozins between £5,362 and £5,553 more expensive than gliclazide.

If there are no direct quality of life impacts from weight changes gliclazide is estimated to yield 10.392 QALYs. This is the highest total QALYs for this BMI scenario and as a consequence gliclazide dominates all the other treatments.

Including direct quality of life impacts from weight changes and assuming that the weight changes associated with the monotherapies persist indefinitely results in repaglinide now being superior to gliclazide by 0.030 QALYs and so having a cost effectiveness estimate of £3,331 per QALY. Repaglinide formally dominates pioglitazone and sitagliptin, but canagliflozin yields an additional 0.177 QALYs at an additional cost of £5,262 so has a cost effectiveness estimate of £44,994 per QALY compared to repaglinide. If weight losses associated with treatment tend to rebound at either one year or at treatment intensification the cost effectiveness estimate for canagliflozin compared to repaglinide worsens to £192k per QALY and £119k per QALY respectively.

Canagliflozin is estimated to be around £100 less expensive than empagliflozin and £200 less expensive than dapagliflozin. With no direct quality of life effects from weight changes it is estimated to be marginally more effective by 0.002 QALYs than empagliflozin and more effective by 0.013 QALYs than dapagliflozin. Including the effects of weight upon quality of life increases these net gains to 0.034 QALYs and 0.046 QALYs if weight changes persist indefinitely. If they rebound after one year these gains fall to 0.007 QALYs and 0.019 QALYs, while if they rebound at treatment change they fall to 0.014 QALYs and 0.026 QALYs.
These very small differences in QALY gains lead to ICERs that can vary widely.

Both canagliflozin and empagliflozin have reasonable cost effectiveness estimates compared to sitagliptin of £12,623 per QALY and £18,341 per QALY even if there are no quality of life impacts from weight changes. Including these effects improves their cost effectiveness estimates compared to sitagliptin.

Dapagliflozin fares slightly worse compared to sitagliptin. It costs an additional £508 but only yields an additional 0.013 QALYs if there are no direct quality of life impacts from weight changes, so has a cost effectiveness estimate of £40,383 per QALY compared to sitagliptin. This improves to £6,632 per QALY if weight changes have a quality of life impact and are assumed to persist indefinitely. If they only persist for one year the cost effectiveness estimate worsens to a little over £30,000 per QALY, but if they persist until treatment change the cost effectiveness estimate worsens but only to a little under £20,000 per QALY.

The base case applied the baseline HbA1c values for those starting a monotherapy of the NICE CG which had a mean of 8.4% (s.d. 1.8%). This differs from some of the companies' modelling, which assumed a common baseline HbA1c of 7.5%. As would be expected this both improved patient outcomes and lowered total costs. It did not alter the patterns of dominance, and while the cost effectiveness estimates for the flozins compared to repaglinide worsened the effect was not major.

Of more interest was that the cost effectiveness estimates of the flozins compared to sitagliptin worsened. With no direct quality of life impacts from weight these worsened to £24,939 per QALY for canagliflozin, £30,150 per QALY for empagliflozin and £54,863 per QALY for dapagliflozin. With the monotherapy BMI effects persisting for the patient lifetime these cost effectiveness estimates improve to £3,717 per QALY, £6,042 per QALY and £7,442 per QALY respectively. Weight loss rebound after one year reduces the improvements to £14,961 per QALY, £21,643 per QALY and £38,256 per QALY, while weight loss rebound at treatment change reduces the improvements to £8,237 per QALY, £13,310 per QALY, and £19,902 per QALY respectively.

Making the HbA1c treatment effect a function of patients' baseline HbA1c had little practical impact upon the cost effectiveness estimates for the flozins compared to gliclazide, repaglinide and pioglitazone. But it improved the cost effectiveness estimates for canagliflozin compared to sitagliptin by around one third. The impact for empagliflozin is less, and there was little impact for dapagliflozin. This is as would be expected given the greater HbA1c effect for canagliflozin compared to sitagliptin, the slightly greater effect for empagliflozin and broad equivalence between dapagliflozin and sitagliptin.

Janssen applied linear evolutions of HbA1c with the annual rate of change being treatment specific, and slower on pioglitazone. Applying the same annual rates of change within the AG modelling reduced total costs and increased total QALYs quite considerably. It also caused pioglitazone to be estimated as the cheapest treatment, with it dominating gliclazide. Pioglitazone also dominated repaglinide if there were no direct quality of life impacts from weight changes. Including these with

no rebound for weight gains caused the cost effectiveness of repaglinide compared to pioglitazone to improve to £15,633 per QALY. The pattern of dominance was not otherwise altered.

The linear HbA1c evolutions still saw the flozins dominated unless there were direct quality of life impacts from weight changes. Given these, the cost effectiveness estimates for canagliflozin compared to repaglinide were surprisingly similar to those of the base case, though the higher cost effectiveness estimates varied more due to the divisions by small net QALY gains.

Assuming that adding gliclazide at the 1st intensification causes only a -0.47% reduction in HbA1c (based on starting it at HbA1c of just over 7.5%) compared to the -1.01% reduction of the base case has little to no impact for gliclazide and repaglinide as patients will not use this intensification. But it increases costs and reduces QALYs in the other arms, so worsening the cost effectiveness estimates for the flozins. The cost effectiveness estimates for the flozins compared to sitagliptin are not particularly affected, though those for dapagliflozin do worsen slightly.

Assuming that the UTI and GTI rates apply throughout the modelling rather than just for the first cycle has little practical impact upon results.

Overall, the flozins are not cost-effective compared to gliclazide and pioglitazone, but can compete with sitagliptin.
The average costs per QALY will apply to the "average patient" and there will be instances where patients may be more susceptible to adverse effects. For example, the risks of fracture with pioglitazone will be greater in women with reduced bone density.

Research needs.
The main research need is for long-term data on cardiovascular outcomes for canagliflozin and dapagliflozin. Large studies are underway.

Conclusions
Dapagliflozin, canagliflozin and empagliflozin are effective in reducing hyperlycaemia and improving glycaemic control, with added benefits of some reductions in blood pressure and weight. The only common adverse effects are increases in urinary and genital tract infections, but in a small proportion of users. Only empagliflozin has long-term cardiovascular outcomes reported yet, showing a reduction in mortality. In monotherapy, the three drugs do not appear cost-effective compared to gliclazide or pioglitazone, but may be competitive against sitagliptin.

Plain English Summary

In type 2 diabetes, it is important to try to get blood glucose levels back down to as near normal as possible to reduce the risk of long-term complications such as damage to eyesight and kidneys, and heart disease. The SGLT2 inhibitors are the newest type of oral drugs. They work by increasing the amount of glucose in the urine, which leads to calorie loss, leading to some weight loss. However they are much more expensive than older drugs such as gliclazide and pioglitazone.

The NHS has to decide whether a new treatment is good value. There is only one NHS budget and this needs to be spent so as to get the most benefit for patients as a whole. If a new treatment is adopted this means that savings must be made elsewhere and other treatments reduced or stopped. A new treatment may result in patient gains. If these patient gains are more than those that are lost when the other treatments are reduced, patients as a whole gain and the treatment is good value. But if the gains from the new treatment are less than those that are lost when the other treatments are reduced ot stopped, patients as a whole lose out and the treatment is bad value.

Diabetes increases the likelihood of patients experiencing a range of complications, ranging from heart disease to sight loss due to diabetic retinopathy. Treatments for type 2 diabetes help patients control their condition. If a patient has good control over their diabetes they are less likely to experience these complications. Avoiding these complications not only benefits the patient, but also means that the NHS does not have to treat these complications which frees up resources for other patients. These elements are taken into account when deciding whether a treatment is good value.

An additional element that has to be considered is that treatments for diabetes may increase or decrease a patient's weight by as much as a few kilograms. One of the main uncertainties is how large any patient benefits are from the direct impact weight changes have upon their day to day living. This is dependent upon how much a few kilograms gained or lost affects a patient's day to day living, the weight gains and losses associated with the various treatments for diabetes and how long these weight changes last for.

If weight changes of a few kilograms gained or lost have little or no impact upon a patient's day to day living there are few if any patient benefits from the flozins and sitagliptin over the more traditional treatments of pioglitazone, repaglinide and gliclazide. The traditional treatments may even provide more patient benefits. The flozins and sitagliptin cost around £400 more each year than the traditional treatments. As a consequence, the flozins represent very poor value for patients as a whole.

If a patient's day to day living is affected by whether a few kilograms are gained or lost this tends to increase the patient gains from the flozins. But compared to the traditional treatments these patient gains are typically still not large enough to justify the higher cost of the flozins and sitagliptin. The flozins still represent poor value for patients as a whole.

But if patients who would receive flozins would otherwise be treated with sitagliptin the additional cost of the flozins is only around £40 more each year. This means that fewer treatments elsewhere need to scaled back or discontinued to fund the adoption of the flozins, and that the flozins are good value for patients as a whole. The possible exception to this is dapagliflozin which is estimated to be not quite as effective as the other flozins. But if a patient's day to day living is affected by whether a few kilograms are gained or lost and the treatments' effects upon weight changes last a reasonably long time dapagliflozin also represents good value for patients as a whole.

Chapter 1. Background

The York and Humber Public Health Observatory (YHPHO) estimate that in 2015, around 3.5 million people in England have type 2 diabetes, with a prevalence of about 8%.[1] The prevalence has been increasing, partly due to demographic change, partly due to better detection, but mainly due to increased prevalence of overweight and obesity. Diabetes is costly to the National Health Service (NHS), with a recent study estimating that 10% of all NHS expenditure is on diabetes.[2]

The report, Prescribing for Diabetes, from the Health and Social Care Information Centre estimated that in 2013/14, 9.5% of prescribing costs were for diabetes, including drugs and blood glucose testing strips.[3]

There are two characteristics of type 2 diabetes: insulin resistance and a loss of insulin-producing capacity in the pancreas. Insulin resistance is the initial state, which the pancreas initially copes with by increased production of insulin from its beta cells. Over time, pancreatic insulin production falls. It is generally accepted that by the time T2DM is diagnosed, the pancreas has lost half its insulin-producing capacity.

Type 2 diabetes is regarded as a progressive disease. The UKPDS trial showed a deterioration in HbA1c of about 0.2% a year.[4] The UKPDS 49 paper reported that by 3 years, only 50% could maintain HbA1c under 7% on monotherapy and that this proportion fell to 25% after 9 years.[5]

However some people with early T2DM who manage to lose weight and increase physical activity, may then have enough beta cell capacity to remain well-controlled on diet alone or on diet plus monotherapy. They are probably a small minority, though a study in Trent region in 2003 found that 31% of people with type 2 diabetes were being managed on diet alone with over 80% achieving HbA1c of 7.5% or under.[6] Most patients do not lose sufficient weight and so their diabetes is expected to progress over time. They will require additional drug therapies, with about a third progressing to requiring insulin injections to try to control blood glucose levels. Progression may be slow. In a population-based study in Denmark, 79% of people with type 2 diabetes who started metformin, were still on metformin monotherapy 3 years later.[7]

Clinical Guideline 87

The NICE clinical guideline CG 87[8] was issued in May 2009, and is currently being updated. The recommendations in CG 87 included;

- Start drug treatment with metformin in patients who are overweight or obese, and whose control is inadequate with lifestyle measures (diet and physical activity) alone
- In patients who are not overweight, either metformin or a sulfonylurea should be considered
- When glycaemic control becomes unsatisfactory on metformin, start dual therapy by adding a sulfonylurea
- Consider using a DPP4 inhibitor (sitagliptin or vildagliptin then) instead of a sulfonylurea in dual therapy where hypoglycaemia would be a particular hazard
- Consider using pioglitazone instead of a sulfonylurea when hypoglycaemia would be a particular hazard
- Consider a DDP4 inhibitor or pioglitazone in triple therapy with metformin and a sulfonylurea when dual therapy was insufficient to achieve adequate control
- Pioglitazone might be preferred to a DPP4 inhibitor if there was marked insulin resistance
- If either a DPP4 inhibitor or pioglitazone would be suitable, consider patient preference.
- Addition of another drug, referred to as intensification of treatment, was when HbA1c was 7.5% or over (though with a recommendation that targets be adjusted for individual circumstances)
- The target for control was set at HbA1c 6.5%

We prefer to use the terms "dual therapy" and "triple therapy" to "second-line" and "third-line" because the latter terms could cover substitution as well as addition.

At the time when CG87 was produced, pioglitazone was still covered by patent. The patent has since expired and the price has dropped dramatically since generic forms entered the market. The DPP4 inhibitors were new, and the SGLT2 inhibitors had not been introduced. The only glucagon-like peptide agonist was twice daily exenatide.

Drugs for type 2 diabetes

We now have nine classes of glucose-lowering drugs for T2DM, though some contain only a single drug. Those which are used in monotherapy are;

- Metformin
- Sulfonylurea (SUs): usually 2nd or 3rd generation drugs - gliclazide, glimepiride and glipizide
- Pioglitazone
- Acarbose
- Meglitinides: nateglinide and repaglinide, though only the latter is licensed for monotherapy. These drugs act in the same way as the SUs, promoting release of insulin.

- The dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as the 'gliptins', not currently recommended by NICE for monotherapy (because of cost). There are now five available: sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin
- The sodium glucose co-transporter 2 (SGLT2) receptor inhibitors. In the UK dapagliflozin, empagliflozin and canagliflozin have been approved by NICE in combination therapy

There are two classes which are injectable treatments. Neither is commonly used in monotherapy. Because of both cost and because they need to be injected, they appear later in the treatment pathway;

- The glucagon like peptide-1 (GLP-1) analogues: exenatide, albiglutide and dulaglutide given once weekly, and liraglutide and lixisenatide given once daily. There is also a form of exenatide given twice daily. Exenatide, liraglutide and lixisenatide are being covered in the update of the NICE guideline on type 2 diabetes, but dulaglutide and albiglutide are not. Both dulaglutide and albiglutide are licensed in Europe for use in monotherapy, when metformin cannot be used, as well as for combination therapy.[9, 10]
- Insulins. In T2DM, insulin treatment starts with once daily basal insulin (NICE recommends NPH insulin as first choice) but if intensification is needed, short-acting insulins may be added at mealtimes, or twice daily biphasic insulin may be used.

There are now combinations of GLP-1 analogues with basal insulins such as insulin degludec combined with liraglutide (Xultophy, Nov Nordisk, Denmark) and insulin glargine and lixisenatide (Lixilan, Sanofi).

There are quite marked differences in costs of GLP-1 analogues, ranging from daily lixisenatide at around £690 to weekly dulaglutide at almost £1200. Patients may prefer to inject once a week. There may be differences in adverse effects. Longer-acting drugs increase heart rate more than shorter-acting ones though the importance of this is as yet uncertain.[11]

Despite the number of classes, there is still a need for drugs that that will lower glucose without causing hypoglycaemia or weight gain, and that can improve cardiovascular outcomes. The SUs, repaglinide and insulin cause varying degrees of weight gain, which may worsen insulin resistance. They can cause hypoglycaemia. The gliptins do not cause weight gain or hypoglycaemia, but have not been shown to improve cardiovascular outcomes..

The NICE guideline (CG87) on the management of T2DM is currently being revised. The first draft recommended that patients who cannot take or tolerate metformin should take repaglinide, a

meglitinide analogue. The meglitinide analogues are insulin secretagogues, shorter acting than the SUs.[12] They have not been widely used in the UK.
Pioglitazone is recognised as causing weight gain but does not cause hypoglycaemia. Metformin does not cause either weight gain or hypoglycaemia.

The diagram below (Figure 1) shows the flowchart proposed in the draft NICE guideline.

Algorithm for blood glucose lowering therapy in adults with type 2 diabetes

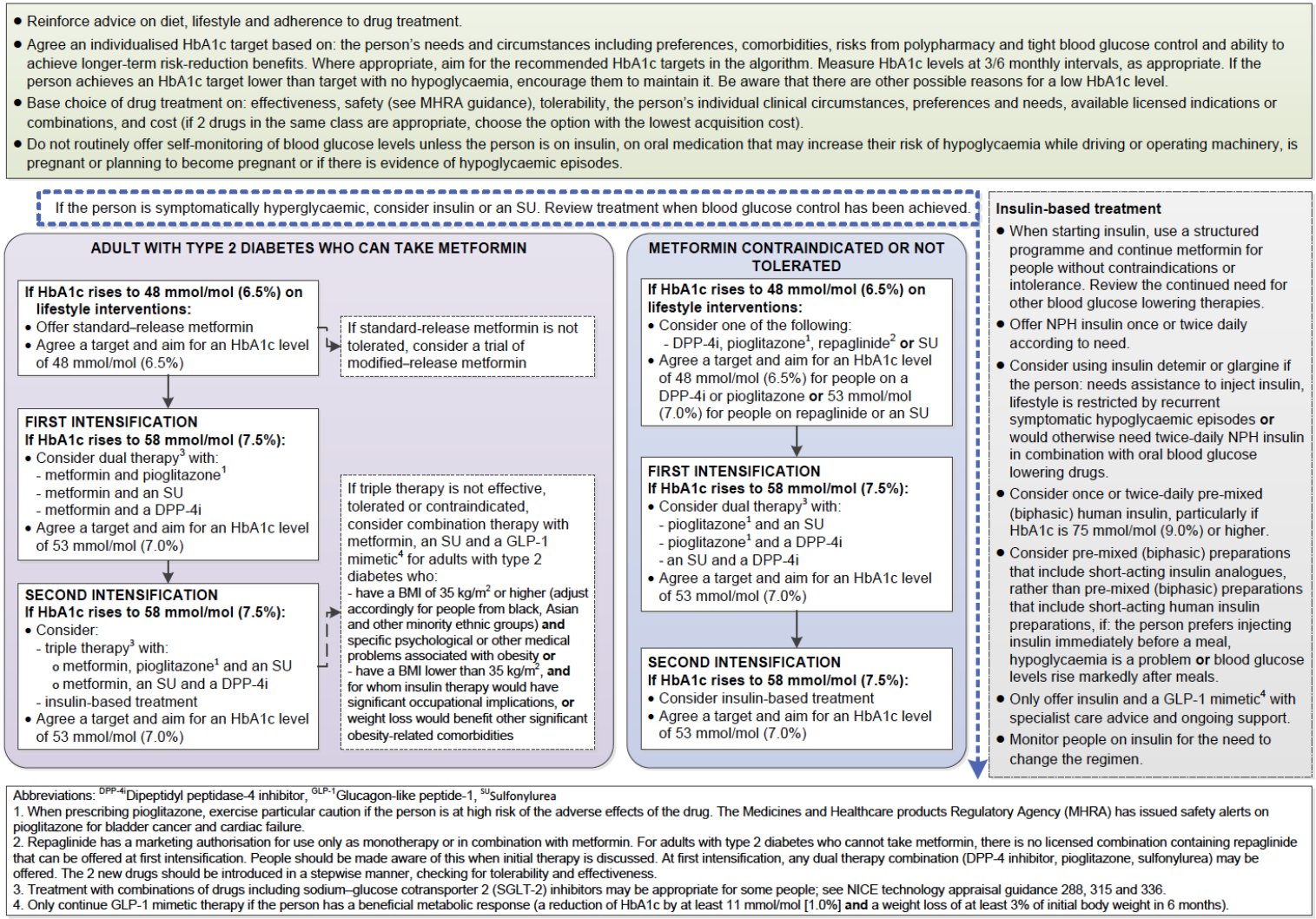

Figure 1 Flowchart proposed in the draft NICE guideline

The rational for choosing repaglinide was two-fold;

- a network meta-analysis showed repaglinide reduced HbA1c more than sulfonylureas, by 0.19%, and was non-significantly safer than SUs in terms of hypos. However, the draft NICE mentions a mixture of sulfonylureas, including tolbutamide, glibenclamide, glipizide, glimepiride and gliclazide. The largest number of trials comparing repaglinide with SUs featured glibenclamide. Gliclazide has been reported to cause fewer hypos than other SUs so a direct comparison of repaglinide with gliclazide might not have given the same results. Gliclazide is the SU preferred by clinicians in the UK.
- costing that assumed SMBG was required because of risk of hypoglycaemia on SUs and pioglitazone, but not for repaglinide, which is odd given that repaglinide causes hypos and pioglitazone does not. If this assumption is reversed, pioglitazone becomes the choice if metformin cannot be taken, though only just.

One drawback to using repaglinide in monotherapy in people who cannot take metformin, is that it is only licensed in dual therapy with metformin. So if repaglinide monotherapy was insufficient, dual therapy would mean starting two new drugs.

For the second round of consultation the position was changed as follows;
(a) metformin extended-release is recommended as an option for metformin-intolerant people;
(b) the other options for people who cannot take metformin were put on an equal footing with DPP4 inhibitors, pioglitazone, repaglinide and SUs all recommended as options.

Sulfonylureas

The sulfonylureas are insulin-secretagogues, which means that they work largely by stimulating insulin release by the beta cells in the pancreas. There is also some data to suggest that they have a peripheral action on muscle sensitivity to insulin, and this lies behind the practice, begun in the UKPDS trial, of continuing SU treatment even when therapy is escalated to insulin as a result of beta-cell failure. However, once the beta cell capacity falls, the SUs become less effective. There is some evidence that the duration of effectiveness is longer with gliclazide than glibenclamide.[13]

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The main adverse effects of the sulfonylureas are weight gain and hypoglycaemia. A population-based study from Tayside found an incidence of severe hypoglycaemia amongst people on sulphonylureas of 0.9 per 100 patient years.[14] This rate is similar to the 0.8% seen in the meta-analysis by Schopman and colleagues[15] Monami and colleagues in a good quality meta-analysis of 69 trials involving sulfonylureas, reported a cumulative incidence of at least one episode of severe hypoglycaemia of 1.2%, but this was based on 24 trials because the others did not have severe hypoglycaemia. There was some evidence that hypoglycaemia was less common with gliclazide than

with other SUs.[16] Schopman and colleagues reported that 0.1% of patients on gliclazide had severe hypoglycaemia and that 1.4% had PG under 3.1 mmol/l at some point in trials that ranged in duration from 24 to 104 weeks.[15] . Schernthaner and colleagues from the 27-week GUIDE trial, using modified release gliclazide, reported that 3.7% of patients had at least one PG < 3mmol/l, but that none need assistance. Compared to the glimepiride arm, there were about 50% fewer hypoglycaemic episodes, despite a reduction in HbA1c of 1.2% on gliclazide and 1.0% on glimepiride.[17]

The Schopman meta-analysis reported that overall, 0.8% of patients on sulfonylureas had a severe hypoglycaemic episode, but the proportions ranged from 0.1% for gliclazide to 2.1% for glipizide. In the ORIGIN trial, 75% of patients on standard treatment (25% of whom were on sulfonylureas) never had any hypoglycaemia.[18]

In the very large (11,140 patients) ADVANCE trial, gliclazide MR was used in two arms, intensive and standard. In the intensive arm, the aim was to achieve HbA1c of 6.5% or less.[19] This was achieved in 65% in the intensive arm and 29% in the standard arm. Severe hypoglycaemia event rates were 0.07 per 1000 patient years in the intensive arm and 0.04 per 1000 patient years in the standard arm. Minor hypoglycaemic events occurred at rates of 12 and 9 per 1000 patient years in intensive and standard arms respectively.

These rates of hypoglycaemia on sulfonylureas are much lower than the 7% reported for severe hypos by the UK Hypoglycaemia Study Group[20], but the patients in that study were recruited only from secondary care clinics.

In the Netherlands, the guideline for the management of type 2 diabetes advises that gliclazide is the sulfonylurea of choice, partly because of its safety in renal failure.[21, 22] A meta-analysis of sulfonylurea trials concluded that severe hypoglycaemia was rare with gliclazide, especially if the dose does not exceed 240mg daily. Non-severe hypoglycaemia was seen mainly in those on 320mg daily.[21]

Simpson and colleagues argued that since different sulfonylureas had different tissue selectivity and risk of hypoglycaemia, the cardiovascular risk might also vary.[23]They carried out a systematic review and network meta-analysis, and used glibenclamide as the reference risk. Compared to people taking glibenclamide, those on gliclazide had a relative risk for total mortality of 0.65 (95% Cr I 0.53-0.79). For cardiovascular mortality, the RR for gliclazide was 0.60 (95% Cr I 0.45-0.84), whereas other sulfonylureas showed no significant difference from glibenclamide.

Schramm and colleagues [24]used Danish record linkage data to compare the mortality and cardiovascular risks amongst patients on monotherapy with sulfonylureas and repaglinide, with those on metformin. The risks were higher on most sulfonylureas but not for gliclazide or repaglinide.

The risk of severe hypoglycaemia with sulfonylureas may have been over-estimated, but it remains a problem which can lead to hospital admission as well causing anxiety and interrupting usual activities.

SIGN recommends that sulfonylureas should be considered as first line in patients who cannot take metformin.[25] The 2015 ADA position statement expresses no preference amongst sulfonylureas, pioglitazone, flozins, and gliptins, in people who cannot take metformin.[26]

If sulfonylureas were the same price as the newer drugs such as the gliptins or the flozins, they would probably be superseded. But they are very cheap, and have been used for so long that all their adverse effects are known.
In this report, based on the evidence reported above, we use gliclazide as the sulfonylurea of choice. There are two forms of gliclazide, standard and modified release. The Diamicron Study Group reported these to be clinically equivalent in a 10 month study in 800 patients.[27] The MR form was given once a day and 3-120mg was equivalent to 80-320mg of the standard form taken twice daily. No severe hypoglycaemia occurred. Mild or moderate hypoglycaemia was seen in 5% of those on the MR form. Once daily administration may help adherence, but the MR form costs more - £62 a year at 60mg a day, £89 at 90mg. The standard form costs about £28 a year.

Pioglitazone

Pioglitazone, the only glitazone used in the UK, can cause oedema, which can precipitate congestive heart failure, and fractures. Congestive heart failure is a common cause of admission to hospital, and the second commonest first presentation of cardiovascular disease (after peripheral arterial disease).[28] A five-fold risk of macular oedema has also been reported.[29]
There is an increased risk of fractures amongst people taking pioglitazone. The fractures were originally reported as being atypical fractures of long bones [30] but Scottish data also show an increase in hip fractures.[31]

More recently there has been concern over bladder cancer. Pioglitazone use has now been discontinued in France.

However the evidence is inconsistent. A Canadian study using UK data [32] reported an increased risk of 1.83 (95% CI 1.10- 3.05). A French study reported a doubling of a very small risk of bladder

cancer.[33] The large Kaiser Permanente study from the USA reported an increase in risk with pioglitazone with RR of 1.18 but this was not statistically significant.[34] The PrOactive trial reported a RR of 2.83 (p = 0.04) but once cases of bladder cancer diagnosed in the first year were excluded there was no difference.[35] It was argued that cancers diagnosed with a year of starting the drug must have been there before. However Gale has argued that pioglitazone could be acting as a growth promoter in latent tumours.[36]

A very large study by Levin and colleagues mainly in the UK, Finland and British Columbia (one million people with type 2 diabetes, almost 6 million person years of observation) found no increased risk of bladder cancer, providing further reassurance.[37]

It should be noted that diabetes itself has been reported in a very large meta-analysis to increase the risk of bladder cancer with RR 1.35 (95% CI 1.17-1.56), though this applied only to those within 5 years of diagnosis.[38] Amongst those with duration over 5 years, RR was 1.08.
The EMA issued a statement in 2011 saying that there was a small increased risk of bladder cancer but that on balance pioglitazone could still be used as a second and third line treatment.[39] The MHRA concurred.[40]

Patients should be screened for haematuria before starting pioglitazone and then at least annually afterwards.

There are some cardiovascular benefits from pioglitazone (the reverse of what was seen with rosiglitazone) with a reported reduced risk of myocardial infarction, but there is clearly an increased risk of heart failure[30, 35], and regular monitoring with BNP seems advisable for the safest use of this drug.[41] Patients are advised of possible side-effects and advised to stop if oedema or shortness of breath develops. If there are concerns regarding heart failure, echocardiography is often carried out, to check that left ventricular function is satisfactory, before starting pioglitazone.

Despite its side effects, including progressive weight gain by as much as 5 kg, pioglitazone can be a valuable diabetes therapy, as it is an insulin sensitizer and allows reduction in insulin resistance, still known to be a major factor in the pathogenesis of type 2 diabetes and glucose intolerance. Early studies using genetic profiling showed that the Pro12Ala of the PPARG gene showed a population attributable risk of approximately 50% and taken together with clinical risk factors might define those most at risk of renal sodium retention and oedema. Unfortunately probably because of the fact that the PPAR gamma agonists also show greater metabolic efficacy in those with the Pro12Ala variant

this approach has not been developed in clinical practice, as those who would benefit most would have to be excluded.[42]

Many people with type 2 diabetes are considerably overweight and may develop non-alcoholic fatty liver disease (NAFLD). Pioglitazone has been reported to improve NAFLD[43] so if attempts at weight loss are unsuccessful and the NAFLD is progressing, pioglitazone may need to be considered for this group of patients. NAFLD is a spectrum of disease ranging from an increased fat content in the liver (steatosis) to inflammation (non-alcoholic steatohepatitis) and possibly on to cirrhosis. NAFLD is strongly associated with insulin resistance.

Despite its adverse effects, pioglitazone is still widely used, though its use may be declining, with new initiations falling in recent years. The Health and Social Care Information Centre Report gives figures for items prescribed in 2013/14[3] (see Table 1)

Table 1 Prescriptions 2013/14

Metformin	18,100,000
Sulfonylureas	8,400,000
Sitagliptin	2,020,100
Pioglitazone	1,408,600
Linagliptin	329,400
Vildagliptin	173,200
Repaglinide	83,800

The strongest argument for using pioglitazone is the very low cost, but the costs of adverse effects need to be considered.

The DPP4 inhibitors

The first two of these to reach the market, sitagliptin and vildagliptin, were appraised for CG87, and recommended for use in combination therapy.[8] There are now five DPP4 inhibitors with slightly different licensed indications. Others are coming including two that are taken only once a week, trelagliptin and omarigliptin, both now licensed in Japan.

The CG87 guidance is reproduced in Box 1

1.6.1 DPP-4 inhibitors (sitagliptin, vildagliptin)

1.6.1.1 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:

- the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or
- the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.

1.6.1.2 Consider adding a DPP-4 inhibitor (sitagliptin, vildagliptin) as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate (HbA1c ≥ 6.5%, or other higher level agreed with the individual) if:

- the person does not tolerate metformin, or metformin is contraindicated.

1.6.1.3 Consider adding sitagliptin[5] as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 7.5% or other higher level agreed with the individual) and insulin is unacceptable or inappropriate[6].

1.6.1.4 Only continue DPP-4 inhibitor therapy (sitagliptin, vildagliptin) if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA1c in 6 months).

A DPP-4 inhibitor (sitagliptin, vildagliptin) may be preferable to pioglitazone if:

- further weight gain would cause or exacerbate significant problems associated with a high body weight, or
- pioglitazone is contraindicated, or
- the person has previously had a poor response to, or did not tolerate, a thiazolidinedione.

The current draft of the updated guideline has at present omitted the stopping rule in 1.6.1.4.

Repaglinide

Repaglinide acts on the same receptor in the pancreas as the sulfonylureas (and another receptor) but is shorter-acting and was therefore thought to be particularly useful in controlling hyperglycaemia after meals. Like the SUs, its adverse effects include significant weight gain and hypoglycaemia.

The relevant recommendation in CG87[8], was "to consider offering a rapid-acting insulin secretagogue to a person with an erratic lifestyle". This presumably related to unpredictability of mealtimes, when there would be a case for using a shorter-acting meglitinide analogue instead of a sulfonylurea.

The cost of repaglinide treatment will depend on dosages used. It was designed to be taken to reduce post-prandial hyperglycaemia, which means it should be taken at meal-times. The NICE guideline costing assumes a total daily dose of 4mg. If that was comprised of 2 x 2mg tablets twice a day, the annual cost would be about £48. However that assumes that people take it at only two meals. If a third 2mg dose was added, the annual cost would be £72. But if the third dose was only 1mg (say to cover a small breakfast or lunch), the annual cost would be £92, because the 1mg tablets are almost double the price of the 2 mg ones. The variability in doses used in the repaglinide studies makes comparison with the sulphonylureas difficult.

The SGLT2 inhibitors

The Sodium Glucose Transporter 2 inhibitors (SGLT2 inhibitors), hereafter referred to as the flozins, have a unique mechanism of action. In the non-diabetic state glucose is allowed through the filter in the renal glomeruli but is fully reabsorbed in the renal tubules through sodium/glucose cotransporter mechanisms. Glycosuria (glucose in the urine) occurs when the renal threshold for glucose (blood glucose of approximately10 mmol/l) is exceeded. The main transport mechanism responsible for glucose reabsorption, SGLT2, is found in the proximal kidney tubule. This is encoded by the gene for the solute carrier family 5 sodium/glucose cotransporter (SLC5A2). Some people have a mutation in the SLC5A2 gene that causes a defective SGLT2 protein, resulting in glycosuria. Individuals who have this mutation do not have significant problems related to the glycosuria, such as urinary tract infections (UTIs), and they have a normal life expectancy with no increase in cardiovascular mortality or urogenital cancers. [44]This implies that blocking the transport mechanism should not cause problems.

The flozins block the SGLT2 system and so mimic the effect of the SLC5A2 mutation and reduce the reabsorption of renal filtered glucose back into the bloodstream, thereby lowering blood glucose levels. Due to their insulin-independent mode of action, they do this without weight gain or hypoglycaemia.[45]

For uncertain reasons, the SGLT2 inhibitors do not block all glucose reabsorption. Around 160-180mg of glucose is filtered into the urine each day, and the SGLT2 system reabsorbs 80-90% of that. The amount blocked appears to vary amongst the different drugs, with dapagliflozin 10mg blocking only about a third of reabsorption.[46, 47] Even very large doses of dapagliflozin (such as 100mg) do not block all glucose reabsorption in people with type 2 diabetes .[48]

There is also a SGLT1 transport mechanism, which is present both in the kidney and the gut. In the kidney, it is much less important than SGLT2. Inhibition of gut SGLT1 reduces absorption of glucose there, and it has been suggested that canagliflozin may have a dual action. This was reported first in healthy volunteers[49] but has since been reported in a study of people with type 2 diabetes.[50]

Because these drugs act through an insulin independent mechanism, they can be effective when other drugs that depend entirely (sulfonylureas and meglitinides) or in part (gliptins and GLP-1 analogues) on stimulating insulin release have lost effectiveness. In type 2 diabetes, the capacity of the pancreatic beta cells to produce insulin often falls over time.

In addition to improving glycaemic control, the SGLT2 inhibitors also reduce blood pressure. In a meta-analysis of 27 RCTs with 12,960 patients, Baker and colleagues reported a mean reduction in SBP of 4mm Hg.[51]

Marketing authorisations

The marketing authorisations for the three flozins licensed for use in monotherapy are similar;
"in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance".

NICE recommendations differ slightly for the three flozins as shown in Box 2

Box 2: NICE recommendations for SGLT2 inhibitors

Dapagliflozin has been approved by NICE as follows[52];

- in a dual therapy regimen in combination with metformin, only if it is used as described for dipeptidyl peptidase-4 (DPP-4) inhibitors in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87).
- Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is not recommended for treating type 2 diabetes, except as part of a clinical trial. This was because at the time of the dapagliflozin appraisal, there was insufficient evidence on its use in triple therapy.

Canagliflozin has been approved by NICE, as follows[53];

- in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if a sulfonylurea is contraindicated or not tolerated or the person is at significant risk of hypoglycaemia or its consequences
- Canagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with metformin and either a sulfonylurea or pioglitazone
- Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

Empagliflozin has been approved by NICE as follows[54];

1.1 Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if

- A sulphonylurea is contraindicated or not tolerated
- The person is at significant risk of hypoglycaemia or its consequences

1.2 Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:

- Metformin and a sulphonylurea
- Metformin and pioglitazone

1.3 Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes

Renal impairment

The dapagliflozin, canagliflozin and empagliflozin guidances differ also in use in moderate renal impairment. The guidance on dapagliflozin says that it should not be used in patients with GFRs below 60 ml/min, whereas the guidances on canagliflozin and empagliflozin say that if started before renal function declined to a eGFR of 60 ml/min, it may be continued till eGFR falls below 45 ml/min.

Age

Dapagliflozin is not recommended in people over 75 but there is no such restriction for canagliflozin or empagliflozin.

Pioglitazone

Dapagliflozin is not licensed for use in combination with pioglitazone. Both canagliflozin and empagliflozin are.

Dosages

There are two doses of canagliflozin and empagliflozin. Canagliflozin comes as 100mg and 300mg. The licence states that the 300mg dose may be used in those who tolerate the 100mg dose – so ruling out canagliflozin 300mg as a starting dose. Similarly, with empagliflozin, the 25mg dose is licenced for those who can tolerate the 10mg starting dose.

Newer SGLT2 inhibitors include luseogliflozin (Taisho and Novartis), ipragliflozin (Astella Pharma), tofogliflozin (Sanofi and Takeda) and remogliflozin (BHV Pharma) but these are not included in the NICE scope. Some are still in pre-licensing trials.

The therapeutic pathway

Where should SGLT2 inhibitors fit into the therapeutic pathway? Factors to be considered include:

- Effect on glycaemic control as reflected in HbA1c reductions
- Effect on weight, compared to other drugs, some of which cause marked weight gain
- Effect on cardiovascular risk, including on blood pressure and lipid levels, and ideally as reflected in longer-term cardiovascular outcomes.
- Adverse effects, particularly increased genital and urinary infections
- Duration of diabetes. In long-standing T2DM, the efficacy of the flozins will not be affected by a fall in endogenous insulin production
- Interactions with other drugs, especially in patients on treatment for co-morbidities
- Ease of use, by oral administration rather than injection
- Cost

Figure 2 shows the annual costs of the drugs for T2DM (drug costs only)

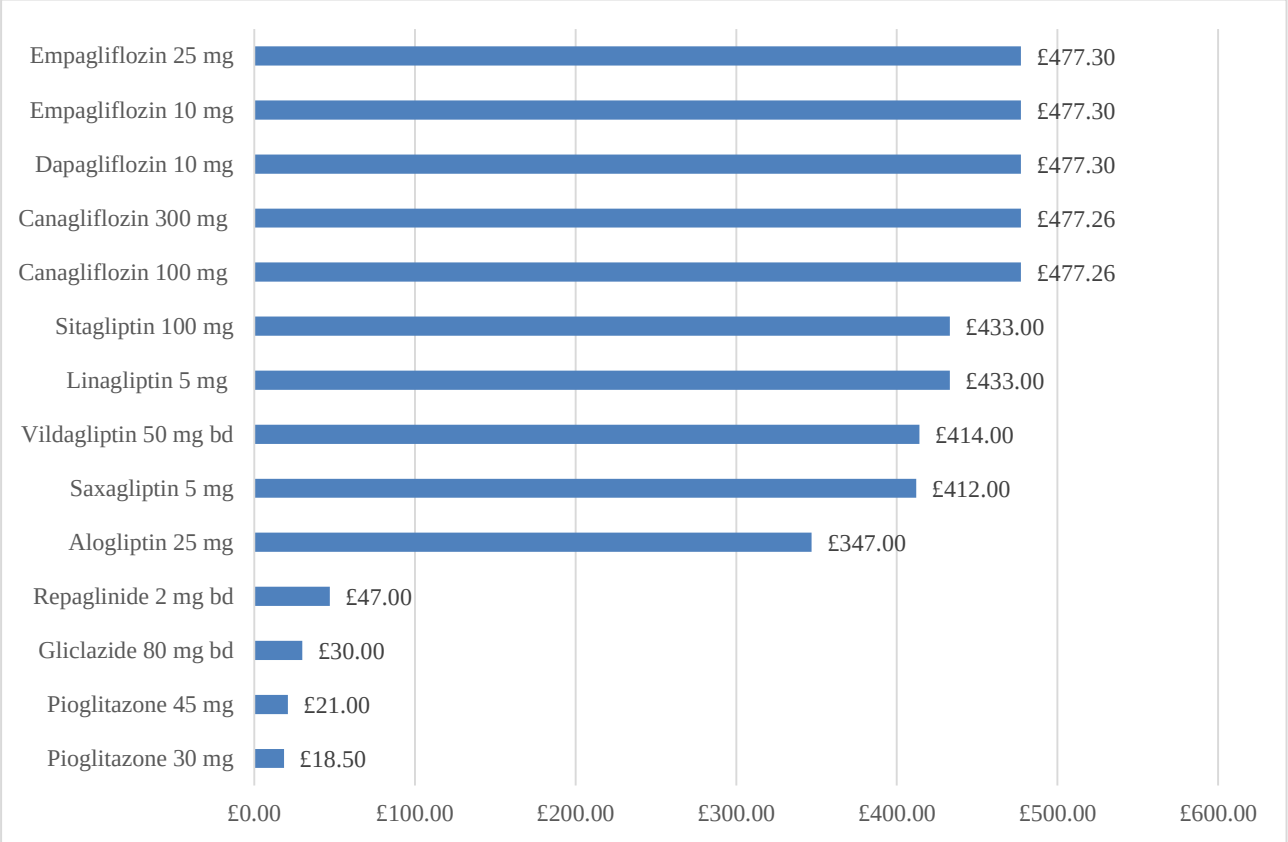

Figure 2 Costs of different pharmacological interventions for diabetes
Source: Drug Tariff[55]; Manufacturer submission/ERG report of Canagliflozin

Decision Problem

The objective of the appraisal as stated by NICE is;

"To appraise the clinical and cost effectiveness of canagliflozin, dapagliflozin and empagliflozin monotherapy within their licensed indications for treating type 2 diabetes."

In PICO (Population, Intervention, Comparator, Outcomes) terms;

- The population is people with type 2 diabetes, not currently on glucose-lowering drugs, but requiring a glucose-lowering agent, but who cannot take metformin
- The interventions are the SGLT2 inhibitors, dapagliflozin, canagliflozin and empagliflozin
- The comparators listed in the NICE scope are repaglinide, sulfonylureas, pioglitazone and the DPP-4 inhibitors, hereafter referred to as the gliptins

- The outcomes would ideally be the rates of complications of diabetes, but most trials of new diabetes drugs are short term, and rely on modelling changes in HbA1c, blood pressure, weight and lipids to predict longer term outcomes.

As noted above, both the NICE guideline CG87 and the current draft update recommend starting with diet and lifestyle, adding metformin if lifestyle change is insufficient. However 5-15% of people with type 2 diabetes cannot take metformin, either because they cannot tolerate it, or because of contraindications to use. The intolerance is usually because of gastrointestinal side-effects such as diarrhoea, especially with higher doses. Faecal incontinence can occur. Bailey and Turner[56] reported that 5% of people could not tolerate any dose of metformin, and Garber[57] also reported that 5% had to stop. Of those who could take it, over half could manage the maximum dose (2250mg/day). De Fronzo[58] reported that with gradual dose escalation, 85% could take 2250mg per day. The adverse effects are reduced by using slow-release metformin: diarrhoea from 18% to 8%; any GI adverse effects from 26% to 12 %.[59] So the slow-release form should be tried before abandoning metformin. Scarpello et al reported that use of bile acid sequestrants could improve tolerance to metformin but many patients find these drugs impalatable.[60, 61]

The main contraindication to metformin use is chronic renal impairment, and NICE recommends that metformin should not be used once eGFR falls below 30ml/minute, and used with caution if eGFR is in the range <45ml/min to >30ml/minute.

The guidance on contra-indications may be over-cautious, and are largely with lactic acidosis in mind. Emslie-Smith and colleagues[62] using population-based data in Tayside found 621 episodes of contra-indications, but in only10% of patients was metformin stopped. Overall, 25% of people on metformin had contra-indications but adverse effects were rare. The fear of lactic acidosis with metformin use may be a carry-over from problems with phenformin, the other biguanide, which increases lactate levels – metformin does not. Phenformin was withdrawn from use in the UK many years ago because of the lactic acidosis risk. The Cochrane review of metformin and lactic acidosis concluded that there was no increase in lactic acidosis with metformin.[63]

For who cannot tolerate metformin or in whom it is contra-indicated, the usual next drug has been a sulphonylurea such as gliclazide. CG87 recommended that a sulfonylurea may be considered as first line monotherapy if the person is not overweight; or if

- metformin is not tolerated or is contraindicated, or
- a rapid therapeutic response is required because of hyperglycaemic symptoms

CG87 mentioned the meglitinide analogues only briefly;

- a rapid acting insulin secretagogue may be considered for a person with an erratic lifestyle

It also listed acarbose as being considered if a person is unable to use other oral glucose lowering agents.

Issues

The patients involved will be those who cannot take metformin. One issue is that trials of flozins and other drugs as monotherapy have not been restricted to patients that have not been able to tolerate metformin. A literature search found few studies comparing people who got diarrhoea on metformin with those who did not. A study from Japan[64] identified several factors that increased the incidence of diarrhoea (often transient, in first few days): female gender, initial dose of 750mg, age under 65, and BMI over 25.

Given the lack of data, it is necessary to assume that the effectiveness of other drugs, and the effect on long-term complications, is no different in those who get gastro-intestinal adverse effects with metformin, than from those who can tolerate it. However some renal function restrictions also apply to other drugs such as the flozins.

Some previous appraisals of diabetes drugs have often found very little differences in lifetime QALY gains and sometime in lifetime costs. For example, Table 38 of the ERG report on empagliflozin in combination therapy noted a difference in lifetime cost of £40 and in QALYs of 0.030 – which means 11 days. Another QALY difference noted was 0.003 – 1.1 days. There are two problems with such differences. Firstly, they result in very unstable ICERs. Secondly and more importantly, such differences are effectively meaningless over a lifetime. It would be useful if NICE could decide what the smallest meaningful difference in QALYs is. A QALY difference of 0.1 would equate to 36 days. If we are modelling over an average 20 years of expected life (most modelling is done over a 40 year time span), those 36 days represent 0.005% of the lifespan. Any difference of 0.1 or fewer QALYs could be regarded as no difference. Perhaps 0.1 QALY is too small and 0.2 or 0.3 would be better, over a mean expected lifespan of 20 years. The meaningful difference should be expressed as a proportion of expected life expectancy.

Similarly small cost differences should be discarded, especially as many costs will change over the modelling timescale, including drug prices. Current methods assume that drug prices remain constant for the duration.

Targets

We note that the consultation draft for the NICE Type 2 diabetes guideline update suggests that an HbA1c of 7.5% should be the switching point for intensification (as in CG 87) aiming at a target of 7.0% (Section 1.3.4). In section 1.5, Recommendation 38, the target of 6.5% is suggested for most adults managed on the combination of diet and a single drug not associated with hypoglycaemia. However the draft notes the need for individualised setting of targets.
These individual targets may take the following factors into account.[65]

- the duration of diabetes. Patients who have not developed complications such as retinopathy after 20 years duration are unlikely to do so, and have less to gain from tight control
- age and life expectancy, and hence time to develop complications. Intensification may be unnecessary and possibly harmful in people over 75 years of age with no symptoms of diabetes
- the risk of severe hypoglycaemia
- co-morbidities
- patient preferences

Glycaemic targets are based mainly on reducing the risk of microvascular disease. With a greater number of younger people being diagnosed with type 2 diabetes, glycaemic control becomes increasingly important to reduce the potential microvascular disease burden. There is less evidence that tight control using existing treatments reduces macrovascular disease or overall mortality[66] though this may be because trials are not long enough. In the UKPDS, there was no difference in macrovascular outcomes at study end[67] but with the longer term follow-up, a significant difference emerged[68] despite a considerable narrowing of the difference in glycaemic control. However neither the ACCORD trial[69] nor the ADVANCE trial[70] showed that intensive control (HbA1c 6.4% and 6.3% respectively) reduced cardiovascular outcomes compared to standard therapy (HbA1cs 7.5% and 7.0%). A meta-analysis by Boussageon and colleagues (BMJ 2011/343/d4169. Effect of intensive glucose lowering) showed no reduction in all-cause mortality or cardiovascular death in trials of intensive versus standard regimens.

Targets also need to take account of potential benefits and harms. Vijan and colleagues[71] used data from the UKPDS to model likely benefits of improving glycaemin control at different ages and by different means (metformin, insulin), taking into account the burden of treatment. For older people the benefits of intensifying treatmen could be outweighed by even minor adverse effects and other inconvenience. A reduction of 1% in HbA1c in a 45-year old might gain 0.8 QALYs (10 months) but the same reduction in someone aged 75 might gain 0.06 QALYs (22 days). If that was achieved using insulin, the adverse effects on quality of life from insulin treatment could mean that the net effect was a QALY loss.

Chapter 2 Clinical effectiveness.

Methods

Inclusion criteria

Types of studies

We included randomised controlled trials (RCTs) with a minimum duration of 24 weeks. Observational studies were included to assess safety data.

Types of participants

We included trials in people with Type 2 diabetes on diet and exercise therapy only or in people on monotherapy with a glucose-lowering agent after a washout period. The target group was patients with type 2 diabetes unable to take metformin, but this distinction was not made in the trials.

A search was carried out for studies comparing people who can and cannot tolerate metformin, looking for any differences in factors that might affect the modelling, such as weight, blood pressure, cholesterol. Nothing significant was found.

Types of interventions

Only trials of monotherapy were included.

To be included, trials had to investigate canagliflozin (100 mg or 300 mg), dapagliflozin (10 mg) or empagliflozin (10 mg or 25 mg). Eligible comparators were repaglinide, gliclazide as representative of the sulfonylureas, pioglitazone, DPP-4 inhibitors (the gliptins), or placebo.

The three flozins were also compared with each other. As there were no head to head trials of the flozins, data from a network meta-analysis was required.

Types of outcomes

Studies were eligible if they investigated at least one of the following outcomes:

- mortality
- complications of diabetes, including cardiovascular, renal and eye
- HbA1c/glycaemic control
- body mass index
- frequency and severity of hypoglycaemia

- changes in cardiovascular risk factors
- adverse effects of treatment, including urinary tract infections, genital infections and malignancies
- health-related quality of life

Search strategy

Searches were run in Ovid Medline, Embase and Web of Science from the inception of the databases until February 2015. Thereafter weekly auto-alerts were run in PubMed in process and Embase until September 2015 to check for newly emerging studies. The searches were not restricted by language or publication type. The full search strategy is shown in Appendix 1.

Selection of studies

Two reviewers independently checked titles and abstracts of the search results against the inclusion criteria. Studies were retrieved in full if they appeared to fulfil the inclusion criteria or when eligibility could not be determined from the search results alone.

Assessment of study quality

The quality of the RCTs was assessed using the Cochrane risk of bias tool, which included the following items (rated as adequate, unclear, not reported, or inadequate):

- Method of randomisation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data (>20% drop-out regarded as inadequate)
- Intention-to-treat analysis
- Selective reporting
- Similarity at baseline
- Other (e.g. power analysis)

Overall quality was expressed in terms of proportion of items rated as ‘adequate’.

Quality was assessed by one reviewer and checked by a second reviewer.

Data extraction

Data were extracted using a pre-designed data extraction table, with one reviewer extracting and another reviewer checking the data.

Results were expressed as means and standard deviations. Standard errors and confidence intervals were converted to standard deviations using the equations provided in the Cochrane handbook. Results for lipids were expressed as mmol/L. Cholesterol values expressed in mg/dL were converted to mmol/L by dividing by 38.67 and lipid values expressed in mg/dL were converted to mmol/L by dividing by 88.57.

Data summary

Data were summarised using text and tables.

The following subgroup analyses were considered:

- BMI <25, 25-29, 30 and over
- baseline HbA1c

Results

Search results

Seven studies were included in the final analysis. We will usually refer to them by first author and year. They were;

Canagliflozin

- CANTATA-M 2013[72]
- Inagaki 2014[73]

Dapagliflozin

- Ferrannini 2010 (with Bailey and colleagues 2014)[74, 75]
- Ji 2014[76]
- Kaku 2014[77]

Empagliflozin

- Lewin 2015[78]
- Roden 2013/4[79, 80]

A list of excluded studies, and reasons for exclusion, is in Appendix 2

Characteristics of included studies

A summary of study characteristics is shown in Table 2.

Table 2 Summary study characteristics

Study	Intervention	n	Age (years)	Diabetes duration (years)	HbA1c (%)	BMI (kg/m^2)
CANAGLIFLOZIN						
CANTATA-M (Stenlöf 2013)[72]	canagliflozin 100 mg/day	195	55.1 SD10.8	4.5 SD4.4	8.1 SD1.0	31.3 SD6.6
Quality 5/9 criteria adequate	canagliflozin 300 mg/day	197	55.3 SD10.2	4.3 SD4.7	8.0 SD1.0	31.7 SD6.0
	Placebo	192	55.7 SD10.9	4.2 SD4.1	8.0 SD1.0	31.8 SD6.2
	100 mg/day HbA1c >10%	47	49.7 SD11.1	4.6 SD4.6	10.6 SD0.9	30.4 SD7.1
	300 mg/day HbA1c >10%	44	48.8 SD10.8	5.2 SD4.8	10.6 SD0.6	30.5 SD5.5
Inagaki 2014[73]	canagliflozin 100 mg/day	90	58.4 SD10.4	4.7 SD4.6	8.0 SD0.7	25.6 SD4.2
Quality 8/9 criteria adequate	placebo	93	58.2 SD11.0	5.6 SD5.8	8.0 SD0.7	25.9 SD4.4
DAPAGLIFLOZIN						
Ferrannini 2010 / Bailey 2014[74, 75]	dapagliflozin 10 mg/day am	70	50.6 SD10.0	0.45 (0.1, 3.4) (median, IQR)	8.0 SD0.9	33.6 SD5.4
Quality 8/9 adequate	dapagliflozin 10 mg/day pm	76	50.7 SD9.7	0.40 (0.1, 2.45)	8.0 SD1.1	33.3 SD5.6
	placebo	75	52.7 SD10.3	0.5 (0.1, 3.4)	7.8 SD0.9	32.3 SD5.5
	dapagliflozin 10 mg/day HbA1c >10%	39	47.9 SD12.1	1.4 (0.2, 3.5)	10.7 SD0.9	31.1 SD5.9
Ji 2014[76]	dapagliflozin 10 mg/day	133	51.2 SD9.9	1.7 SD2.8	8.3 SD1.0	25.8 SD3.4
Quality 9/9 adequate	placebo	132	49.9 SD10.9	1.3 SD2.0	8.4 SD1.0	25.9 SD3.6
Kaku 2014[77]	dapagliflozin 10 mg/day	88	57.5 SD9.3	4.9 SD4.5	7.5 SD0.6	26.1 SD4.5
Quality 6/9 adequate	placebo	87	60.4 SD9.7	5.3 SD6.2	7.5 SD0.6	25.2 SD4.4

Study	Intervention	n	Age (years)	Diabetes duration (years)	HbA1c (%)	BMI (kg/m^2)
EMPAGLIFLOZIN						
Lewin 2015[78]	empagliflozin 10 mg/day	132	53.9 SD10.5	32.6% ≤1 yr, 45.5% >1 to 5 yrs, 11.4% >5 to 10 yrs, 10.6% >10 yrs	8.1 SD1.0	31.5 SD5.7
Quality 6/9 adequate	empagliflozin 25 mg/day	133	56.0 SD9.3	36.1% ≤1 yr, 36.1% >1 to 5 yrs, 18.8% >5 to 10 yrs, 9.0% >10 yrs	8.0 SD1.0	31.2 SD5.7
	linagliptin 5 mg/day	133	53.8 SD11.5	37.6% ≤1 yr, 42.9% >1 to 5 yrs, 16.5% >5 to 10 yrs, 3.0% >10 yrs	8.1 SD0.9	31.9 SD5.9
Roden 2013/4[79, 80]	empagliflozin 10 mg/day	224	56.2 SD11.6	39% ≤1 year, 41% 1 to 5 yrs, 13% 5 to 10 yrs, 7% >10 yrs	7.9 SD0.9	28.3 SD5.5
Quality 9/9 adequate	empagliflozin 25 mg/day	224	53.8 SD11.6	41% ≤1 yr, 37% 1 to 5 yrs, 17% 5 to 10 yrs, 6% >10 years	7.9 SD0.9	28.2 SD5.5
	sitagliptin 100 mg/day	223	55.1 SD9.9	42% ≤1 yr, 39% 1 to 5 yrs, 14% 5 to 10 yrs, 5% >10 yrs	7.9 SD0.8	28.2 SD5.2
	placebo	228	54.9 SD10.9	32% ≤1 yr, 46% 1 to 5 yrs, 15% 5 to 10 yrs, 8% >10 yrs	7.9 SD0.8	28.7 SD6.2
	empagliflozin 25 mg/day HbA1c >10%	87	50.2 SD11.3	52% ≤1 yr, 25% 1 to 5 yrs, 14% 5 to 10 yrs, 8% >10 yrs	11.5 SD1.4	28.2 SD5.5

Details can be found in Appendix 3.

Study design. The studies were all double blind multicentre trials and only the two empagliflozin trials had active comparators (Roden 2013/4 and Lewin 2015). Four studies were carried out in centres around the world (CANTATA-M 2013, Ferrannini 2010, Lewin 2015, Roden 2013/4), while three (Inagaki 2014, Ji 2014, Kaku 2014) were in Asian populations. Primary endpoints were generally reported at 24 or 26 weeks, but four trials had extensions, following participants up to 52 weeks (CANTATA-M 2013, Lewin 2015) or 76 to 78 weeks (Ferrannini 2010, Roden 2013/4). However the CANTATA-M study (2013) did not report results for the placebo group for the extension period, so results were not considered here. All studies were sponsored by industry.

Participants. The studies included between 183 and 986 participants, with 70 to 228 participants in the main comparison groups. Three studies included small exploratory groups of patients (n=39 to 87) with HbA1c >10% - however, these were not randomised groups (it being unethical not to treat such high levels) and no relevant comparison group existed. Between 34.1 and 58.7% of participants in the main comparison groups were women and mean age was between 50 and 60 years. In most studies, the entry HbA1c of patients was restricted to between 7% and 10 or 10.5%. Most participants had duration of diabetes of less than five years. Mean baseline HbA1c was between 7.5 and 8.4% in the main comparison groups and between 10.6 and 11.5% in the high HbA1c groups. BMI was between 25 and 34 kg/m^2. Four studies had ethnically mixed populations (CANTATA-M 2013, Ferrannini 2010, Lewin 2015, Rodens 2013/4), while three studies included only Asian participants (Japanese in the Inagaki and Kaku studies, mainly Chinese in Ji 2014).

Interventions. Two studies examined canagliflozin. The CANTATA-M (2013) study compared 100 or 300 mg/day with placebo. After the main intervention period of 26 weeks, placebo was replaced with 100 mg/day of sitagliptin (double blind) for another 26 weeks. Inagaki 2014 compared 100 mg/day of canagliflozin with placebo. They also included a 200 mg/day group, but this is not considered here because it is not a marketed dose.

Three studies examined dapagliflozin. Ferrannini 2010 compared 10 mg/day of dapagliflozin given in the morning with the same amount given in the evening and with placebo. The trial also included groups receiving 2.5 or 5 mg/day of dapagliflozin, but these were not included in the current analysis as they are not recommended doses. After the main intervention period of 24 weeks, participants in the placebo group were switched to low dose metformin (500 mg / day, double blind). Both Ji 2014 and Kaku compared 10 mg/day of dapagliflozin given in the morning with placebo. Both also included a 5 mg/day group which is not considered here.

Two trials studied empagliflozin. Lewin 2015 compared 10 or 25 mg/day of empagliflozin with 5 mg/day of linagliptin. The trial also included groups receiving a fixed combination of empagliflozin and linagliptin (10 or 25 mg/day of empagliflozin and 5 mg/day of linagliptin), but these were not considered here. Roden 2013/4 compared 10 or 25 mg/day of empagliflozin with 100 mg/day of sitagliptin and with placebo.

Some studies included run-in periods for wash-out of previous medication (if required) and to establish a diet / exercise regime.

Rescue therapy was provided as outlined in the detailed data tables (Appendix 3).

Outcomes. The primary outcome in all trials was change in HbA1c from baseline to the end of the main intervention period. Most studies also reported on body weight, blood lipids and blood pressure, as well as on safety parameters including hypoglycaemia. Outcomes with respect to complications of diabetes were not reported, and neither was health-related quality of life.

Three trials defined hypoglycaemia as plasma glucose levels of ≤3.9 mmol/L with or without symptoms (CANTATA-M 2013, Lewin 2015, Roden 2013/4). Inagaki 2014 distinguished between symptomatic (typical hypoglycaemic symptoms irrespective of blood glucose levels) and asymptomatic (blood glucose ≤3.9 mmol/L without symptoms) hypoglycaemia. In Ji 2014 and Ferrannini 2010, hypoglycaemia was defined as plasma glucose levels of ≤3.5 mmol/L. Only three trials defined major hypoglycaemia (CANTATA-M 2013, Ferrannini 2014, Ji 2014). All three trials defined major hypoglycaemia as requiring external assistance and two specified associated blood glucose levels of <3.0 mmol/L (Ferrannini 2014, Ji 2014). Kaku and colleagues 2014 did not define hypoglycaemia.

Note that the 3.9 mmol/l cut-off is above the lower end of the normal range for plasma glucose (3.5mmol/l). It is the threshold for action to avoid hypoglycaemia in people on drugs that may cause it.

Quality of included studies

Details of study quality can be found in Appendix 4.

Two studies fulfilled all the quality criteria (Ji 2014 and Roden 2013/4), two fulfilled eight of the nine quality criteria (Inagaki 2014 and Ferrannini 2010), one only fulfilled six of nine criteria (Kaku 2014) and two only fulfilled five (CANTATA-M 2013, Lewin 2015).

Two studies did not report on the method of randomisation and three did not report on allocation concealment. All studies were double blind, but in two studies it was not clearly reported whether outcome assessors were also blinded to study treatment. Rates of discontinuation were reported by all studies and were between 7 and 20%. In most studies, rates of discontinuation were lower than 20% and balanced between groups. In Inagaki 2014, only 7% discontinued in the canagliflozin group, while 20% discontinued in the placebo group. Only one study did not clearly carry out an intention-to-treat analysis and studies gave no evidence of selective reporting, except that in two studies some results were only shown in graphs and numeric values were not provided. Baseline characteristics were similar for the main comparison groups in all studies and all studies reported on a power analysis.

Outcomes

A summary of results is shown in Table 3

Table 3 Summary of results of trials

	Time	ΔHbA1c (%)	Δ weight (kg)	ΔSBP (mmHg)	ΔTC (mmol/L)	ΔLDL (mmol/L)	ΔHDL (mmol/L)
CANAGLIFLOZIN							
CANTATA-M (Stenlöf 2013)							
canagliflozin 100 mg/day	26 weeks	-0.77 SD0.7	-2.5 SD2.4	-3.3 SD11.1	NR	0 SD0.67	+0.11 SD0.27
canagliflozin 300 mg/day	26 weeks	-1.03 SD0.7	-3.4 SD2.4	-5.0 SD11.2	NR	+0.12 SD0.67	+0.11 SD0.27
placebo	26 weeks	+0.14 SD0.7	-0.5 SD2.4	+0.4 SD11.0	NR	-0.07 SD0.65	+0.04 SD0.26
Inagaki 2014							
canagliflozin 100 mg/day	24 weeks	-0.74 SD0.66	-2.6 SD2.3	-7.9 SD10.3	NR	+0.15 SD0.51	+0.07 SD0.18
placebo	24 weeks	+0.29 SD0.68	-0.5 SD2.3	-2.7 SD10.1	NR	-0.01 SD0.50	-0.03 SD0.18
DAPAGLIFLOZIN							
Ferrannini 2010 / Bailey 2014							
dapagliflozin 10 mg/day am	24 weeks	-0.89 SD0.92	-3.20 SD4.18	-3.6 SD15.9	NR	NR	NR
dapagliflozin 10 mg/day pm	24 weeks	-0.79 SD0.87	-3.10 SD3.49	-2.3 SD12.2	NR	NR	NR
placebo	24 weeks	-0.23 SD0.87	-2.20 SD3.46	-0.9 SD15.6	NR	NR	NR
dapagliflozin 10 mg/day am	102 weeks	-0.61 SD0.70	-3.94 SD3.52	+3.9 SD14.7	NR	NR	NR
placebo / metformin	102 weeks	-0.17 SD0.67	-1.34 SD3.34	+2.1 SD18.6	NR	NR	NR
Ji 2014							
dapagliflozin 10 mg/day	24 weeks	-1.11 SD0.76	-2.25 SD2.60	-2.3 SD11.7	+0.06 SD0.41	+0.19 SD0.72	+0.30 SD0.44
placebo	24 weeks	-0.29 SD0.79	-0.27 SD2.64	+0.8 SD12.8	-0.04 SD0.40	-0.03 SD0.67	+0.11 SD0.41
Kaku 2014							
dapagliflozin 10 mg/day	24 weeks	-0.45 SD0.57	-2.22 SD2.44	-3.2 SD11.2	+0.01 SD0.34	-0.03 SD0.57	+0.16 SD0.38
placebo	24 weeks	-0.06 SD0.57	-0.84 SD2.47	-0.5 SD11.4	+0.02 SD0.33	+0.12 SD0.59	+0.07 SD0.40
EMPAGLIFLOZIN							
Lewin 2015							
empagliflozin 10 mg/day	24 weeks	-0.83 SD0.56	-2.3 SD4.0	NR	+0.2 SD1.2	+0.1 SD1.2	+0.1 SE0.0
empagliflozin 25 mg/day	24 weeks	-0.95 SD0.57	-2.2 SD4.0	NR	+0.2 SD1.2	0 SD1.2	+0.1 SE0.0
linagliptin 5 mg/day	24 weeks	-0.67 SD0.57	-0.8 SD4.0	NR	-0.1 SD1.2	-0.1 SD1.2	0 SE0.0
empagliflozin 10 mg/day	52 weeks	-0.85 SD0.65	-2.3 SD4.3	-2.2 SD10.5	NR	NR	NR
empagliflozin 25 mg/day	52 weeks	-1.01 SD0.66	-2.4 SD4.3	-2.1 SD10.5	NR	NR	NR

	Time	ΔHbA1c (%)	Δ weight (kg)	ΔSBP (mmHg)	ΔTC (mmol/L)	ΔLDL (mmol/L)	ΔHDL (mmol/L)
linagliptin 5 mg/day	52 weeks	-0.51 SD0.66	-0.3 SD4.3	-0.4 SD10.5	NR	NR	NR
Roden 2013/4							
empagliflozin 10 mg/day	24 weeks	-0.66 SD0.76	-2.3 SD2.6	-2.9 SD12.2	+0.07 SD0.75	+0.06 SD0.6	+0.11 SD0.15
empagliflozin 25 mg/day	24 weeks	-0.78 SD0.80	-2.5 SD2.6	-3.7 SD12.2	+0.15 SD0.75	+0.11 SD0.6	+0.13 SD0.15
sitagliptin 100 mg/day	24 weeks	-0.66 SD0.76	+0.18 SD2.6	+0.5 SD12.2	+0.08 SD0.75	+0.03 SD0.6	+0.02 SD0.15
placebo	24 weeks	+0.08 SD0.81	-0.33 SD2.58	-0.3 SD12.3	+0.05 SD0.75	+0.04 SD0.6	+0.04 SD0.15

HbA1c

Canagliflozin.

Canagliflozin at 100 mg/day reduced HbA1c by between 0.74% (Inagaki) and 0.77% (CANTATA-M) from baseline, which amounted to between 0.91 and 1.03% more than with placebo (P< 0.001 for both). Between 31.5% and 44.6% reached HbA1c <7%. With 300 mg/day, HbA1c was reduced by 1.03%, which was 1.17% more than with placebo (p<0.001). In this group, 62.4% reached HbA1c <7%. In both studies, reductions in HbA1c were significantly greater in participants with higher HbA1c values.

Dapagliflozin.

Dapagliflozin at 10 mg/day reduced HbA1c by between 0.45% (Kaku) and 1.11% (Ji: p<0.0001) from baseline, which amounted to between 0.39 and 0.82% more than with placebo. Between 48.8 and 51.4% of participants reached HbA1c <7% compared to between 20.5 and 32.0% in the placebo group. There was no significant difference in HbA1c results depending on whether dapagliflozin was given in the morning or in the evening (Ferrannini 2010). Reductions in HbA1c were greater in the exploratory group with HbA1c >10% (Ferrannini 2010) as well as in higher HbA1c subgroups of the main study cohorts (Ferrannini 2010, Ji 2014, Kaku 2014). In Ji 2014, results were similar for the exclusively Chinese cohort. In Ferrannini 2010, at 102 weeks, HbA1c reductions were still significantly greater with 10 mg/day dapagliflozin than with low dose metformin (-0.61% compared to baseline and -0.44% compared to placebo).

Empagliflozin.

Empagliflozin at 10 mg/day reduced HbA1c by between 0.66 (Roden) and 0.83% (Lewin) from baseline, which amounted to 0.16% more than with linagliptin, no difference to sitagliptin, and 0.58% more than with placebo. Empagliflozin at 25 mg/day reduced HbA1c by between 0.78 (Roden) and 0.95% (Lewin) from baseline, which amounted to between 0.28% more than with linagliptin, 0.12% more than with sitagliptin, and 0.86% more than with placebo (<0/0001 for comparisons with placebo). Between 35.3 and 38.8% of participants reached HbA1c <7% with 10 mg/day of empagliflozin, 41.5 to 43.6% with 25 mg/day of empagliflozin, 37.5% with sitaglipitin, 32.3% with linagliptin, and 12.0% with placebo. Reductions in HbA1c were greater in the exploratory group with HbA1c >10% (Roden 2013/4) as well as in higher HbA1c subgroups of the main study cohorts (Roden 2013/4, Lewin 2015). In Lewin 2015, at 52 weeks, HbA1c was reduced by 1.01% from baseline, which amounted to 0.5% more than with placebo.

Weight

Canagliflozin.

Canagliflozin at 100 mg/day reduced weight by between 2.5 and 2.6 kg from baseline, which amounted to between 3.0 and 3.1 kg more than with placebo ($p < 0.001$ for both). With 300 mg/day, weight was reduced by 3.4 kg which was 3.9 kg more than with placebo.

Dapagliflozin.

Dapagliflozin at 10 mg/day reduced weight by between 2.2 and 3.2 kg from baseline, which amounted to between 0.9 and 2.0 kg more than with placebo. In the study by Ji and colleagues (2014), results were similar for the exclusively Chinese cohort. In Ferrannini 2010, at 102 weeks, weight reductions were still significantly greater with 10 mg/day dapagliflozin than with low dose metformin (-3.9 kg compared to baseline and -2.6 kg compared to placebo).

Empagliflozin.

Empagliflozin at 10 or 25 mg/day reduced weight by between 2.2 and 2.5 kg from baseline, which amounted to 1.4 to 1.5 kg more than with linagliptin, 2.5. to 2.7 kg more than with sitagliptin, and 2.0 and 2.2 kg more than with placebo. In Lewin 2015, weight was reduced by 2.3 and 2.4 kg with 10 and 25 mg/day of empagliflozin after 52 weeks, which was 2.0 and 2.1 kg more than with linagliptin.

The weight loss on the SGLT2 inhibitors is less than might be expected from the glucose loss in the urine. Rajeev and colleagues[81] have reviewed possible explanations, such as a compensatory increase in food intake, but the mechanism is uncertain. Ferrannini and colleagues[82] reported that patients in an empagliflozin trial lost only 38% of the weight loss predicted from the calories lost via glycosuria, and suggested that this was due to an increase in food intake.

Lipids

Canagliflozin.

Canagliflozin at 100 mg/day increased LDL-cholesterol levels by between 0 and 0.15 mmol/L from baseline, which amounted to between 0.07 and 0.16 mmol/L more than with placebo. The corresponding HDL-cholesterol levels were increases of between 0.07 and 0.11 mmol/L from baseline and 0.07 to 0.1 mmol/L difference from placebo ($p<0.01$). With 300 mg/day, LDL-cholesterol was increased by 0.12 mmol/L which was 0.19 mmol/L more than with placebo, and HDL-cholesterol was

increased by 0.11 mmol/L which was 0.07 mmol/L different from placebo. The two studies did not report total cholesterol levels.

Dapagliflozin.

Ferrannini 2010 did not report on lipid levels. In the other studies, total cholesterol changed by +0.01 to +0.06 mmol/L from baseline in the 10 mg/day dapagliflozin groups, the difference from placebo was between -0.01 and +0.1 mmol/L. LDL-cholesterol changed by between +0.19 and -0.03 mmol/L from baseline (difference to placebo between +2.2 and -0.15 mmol/L). HDL-cholesterol changed by between +0.16 and +0.3 mmol/L from baseline (difference to placebo between +0.19 and +0.09 mmol/L).

Empagliflozin.

Total cholesterol changed by +0.07 to +0.2 mmol/L from baseline in the 10 or 25 mg/day empagliflozin groups, the difference from control was between +0.02 and +0.3 mmol/L. LDL-cholesterol changed by between +0.06 and +0.11 mmol/L from baseline (difference to control +0.02 mmol/L). HDL-cholesterol changed by between +0.10 and +0.13 mmol/L from baseline (difference to control between +0.07 and 0.1 mmol/L).

Systolic blood pressure

Canagliflozin.

Canagliflozin at 100 mg/day reduced systolic blood pressure by between 3.3 and 7.9 mmHg from baseline, which amounted to between 3.7 and 5.2 mmHg more than with placebo ($p<0.001$). With 300 mg/day, systolic blood pressure was reduced by 0.5 mmHg which was 0.9 mmHg more than with placebo. None of these differences were significant.

Dapagliflozin.

Dapagliflozin at 10 mg/day reduced systolic blood pressure by between 2.3 and 3.6 mmHg from baseline, which amounted to between 1.4 and 3.1 mmHg more than with placebo. In Ji 2014, results were similar for the exclusively Chinese cohort. In Ferrannini 2010, at 102 weeks, systolic blood pressure was increased by 3.9 mmHg from baseline, which was 1.8 mmHg more than with placebo. None of these values were significant.

Empagliflozin.

Empagliflozin at 10 or 25 mg/day reduced systolic blood pressure by between 2.1 and 3.7 mmHg from baseline, which amounted to between 1.7 and 3.4 mmHg more than in the control group. None of these differences were significant.

Hypoglycaemia

The definition of hypoglycaemia varied amongst trials with most using 4.0 mmol/l as the threshold, which seems a little high, when the lower limit of normal is 3.5 mmol/l (Amiel S. Diabetic Hypoglycemia 2013/5/issue 3). The threshold of 4.0 mmol/l is used as an indicator of the need for corrective action, and is also relevant for driving.

Canagliflozin.

Rates of hypoglycaemia were not substantially different between canagliflozin and placebo groups. The CANTATA-M study (2013) defined hypoglycaemia as PG of under 4.0mmol/l. They reported rates of hypoglycaemia of 3.6% in the 100 mg/day canagliflozin group, 3.0% in the 300 mg/day group and 2.6% in the placebo group. There were no cases of major hypoglycaemia.
In Inagaki 2014, there were two cases of symptomatic (2.2%) and four cases of asymptomatic (4.4%) hypoglycaemia (PG under 4.0mmol/l) in the 100 mg/day canagliflozin group and one case of asymptomatic (1.1%) and two cases of symptomatic (2.2%) hypoglycaemia in the placebo group.

Dapagliflozin.

Rates of hypoglycaemia were not substantially different between dapagliflozin and placebo groups. Over 24 weeks, not more than two cases of hypoglycaemia occurred in any of the comparison groups. There were no cases of major hypoglycaemia.

Empagliflozin.

In Roden 2013/4, there was one case of hypoglycaemia (defined as below 4.0 mmol/l or requiring assistance) in each of the comparison groups over 24 weeks (none of them was symptomatic), and two cases in each group at 76 weeks or more (only one of these in 10 mg/day empagliflozin group was symptomatic). In Lewin 2015, there was one case of hypoglycaemia (also defined as under 4.0 mmol/l) in the linagliptin group and the 25 mg/day empagliflozin group and four cases in the 10 mg/day empagliflozin group. None of these required assistance.

Given the infrequency of reported hypoglycaemia, the similarities of the frequencies of hypoglycaemia in active and placebo arms, and the cut-off level used, the AG considers that it would be reasonable to assume that the flozins do not cause hypoglycaemia.

Table 4 and Table 5 summarise the occurrence of UTIs and GTIs, respectively, in the studies considered for this review.

Table 4 Summary of Urinary Tract Infections

Inagaki 2014		**Canagliflozin 100mg**	**Canagliflozin 200mg**	**Placebo**		
	24 weeks	2/90 (2.2%)	1/89 (1.1%)	1/93 (1.1%)		
	24 weeks (Men)	0/59 (0.0%)	0/73 (0.0%)	1/60 (1.7%)		
	24 weeks (Women)	2/31 (6.5%)	1/16 (6.3%)	0/33 (0.0%)		
Stenlöf 2013		**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Placebo**	**Canagliflozin 100mg (high HbA1c)**	**Canagliflozin 300mg (high HbA1c)**
	26 weeks	12/195 (6.2%)	13/197 (6.6%)	4/192 (2.1%)	6/47 (12.8%)	2/44 (4.5%)
2014	26 weeks (Men)	2/195 (2.5%)	5/197 (5.6%)	0/192 (0.0%)		
	26 weeks (Women)	10/195 (8.8%)	8/197 (7.4%)	4/192 (3.8%)		
	52 weeks	18/195 (9.2%)	18/197 (9.1%)	5/192 (2.6%)		
	52 weeks (Men)	5/195 (6.2%)	8/197 (9.0%)	0/192 (0.0%)		
	52 weeks	13/195 (11.4%)	10/197 (9.3%)	5/192		

	(Women)			(4.8%)		
Kaku 2014		**Dapagliflozin 10mg**		**Placebo**		
	24 weeks	2/88 (2.3%)		1/87 (1.1%)		
Ji 2014		**Dapagliflozin 10mg**		**Placebo**		
	24 weeks	6/133 (4.5%)		1/132 (0.8%)		
	24 weeks (Chinese)	4/110 (3.6%)		0/110 (0.0%)		
Ferrannini 2010/Bailey 2015		**Dapagliflozin 10mg (AM)**		**Placebo**	**Dapagliflozin 10mg (PM)**	**Dapagliflozin 10mg (high HbA1c)**
	24 weeks	9/70 (12.9%)		1/75 (1.3%)	2/76 (2.6%)	7/39 (17.9%)
	102 weeks	11/70 (15.7%)		1/75 (1.3%)		
	102 weeks (men)	2/34 (5.9%)		0/31 (0.0%)		
	102 weeks (women)	9/36 (25.0%)		1/44 (2.3%)		
Roden 2013/4		**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Placebo**	**Sitagliptin 100mg**	**Empagliflozin 25mg (open-label)**

	24 weeks	7/224 (3.1%)	9/223 (4.0%)	0/229 (0.0%)	2/223 (0.9%)	1/87 (1.1%)
	24 weeks (Men)	4/142 (2.8%)	2/144 (1.4%)	0/124 (0.0%)	1/141 (0.7%)	1/64 (1.6%)
	24 weeks (Women)	3/82 (3.7%)	7/79 (8.9%)	0/105 (0.0%)	1/82 (1.2%)	0/23 (0.0%)
	≥ 76 weeks	13/224 (5.8%)	14/24 (6.3%)	4/228 (1.8%)	2/223 (0.9%)	

Table 5 Summary of Genital Tract Infections

Inagaki 2014		**Canagliflozin 100mg**	**Canagliflozin 200mg**	**Placebo**		
	24 weeks	2/90 (2.2%)	1/89 (1.1%)	1/93 (1.1%)		
	24 weeks (Men)	0/59 (0.0%)	0/73 (0.0%)	1/60 (1.7%)		
	24 weeks (Women)	2/31 (6.5%)	1/16 (6.3%)	0/33 (0.0%)		
Stenlöf 2013		**Canagliflozin 100mg**	**Canagliflozin 300mg**	**Placebo**	**Canagliflozin 100mg (high HbA1c)**	**Canagliflozin 300mg (high HbA1c)**
2014	26 weeks	12/195 (6.2%)	13/197 (6.6%)	4/192 (2.1%)	6/47 (12.8%)	2/44 (4.5%)
	26 weeks (Men)	2/195 (2.5%)	5/197 (5.6%)	0/192 (0.0%)		
	26 weeks (Women)	10/195 (8.8%)	8/197 (7.4%)	4/192 (3.8%)		
	52 weeks	18/195 (9.2%)	18/197 (9.1%)	5/192 (2.6%)		
	52 weeks (Men)	5/195 (6.2%)	8/197 (9.0%)	0/192 (0.0%)		
	52 weeks (Women)	13/195 (11.4%)	10/197 (9.3%)	5/192 (4.8%)		
Kaku 2014		**Dapagliflozin 10mg**		**Placebo**		
	24 weeks	2/88 (2.3%)		1/87 (1.1%)		
Ji 2014		**Dapagliflozin 10mg**		**Placebo**		

	24 weeks	6/133 (4.5%)		1/132 (0.8%)		
	24 weeks (Chinese)	4/110 (3.6%)		0/110 (0.0%)		
Ferrannini 2010/Bailey 2015		**Dapagliflozin 10mg (AM)**		**Placebo**	**Dapagliflozin 10mg (PM)**	**Dapagliflozin 10mg (high HbA1c)**
	24 weeks	9/70 (12.9%)		1/75 (1.3%)	2/76 (2.6%)	7/39 (17.9%)
	102 weeks	11/70 (15.7%)		1/75 (1.3%)		
	102 weeks (men)	2/34 (5.9%)		0/31 (0.0%)		
	102 weeks (women)	9/36 (25.0%)		1/44 (2.3%)		
Roden 2013/4		**Empagliflozin 10mg**	**Empagliflozin 25mg**	**Placebo**	**Sitagliptin 100mg**	**Empagliflozin 25mg (open-label)**
	24 weeks	7/224 (3.1%)	9/223 (4.0%)	0/229 (0.0%)	2/223 (0.9%)	1/87 (1.1%)
	24 weeks (Men)	4/142 (2.8%)	2/144 (1.4%)	0/124 (0.0%)	1/141 (0.7%)	1/64 (1.6%)
	24 weeks (Women)	3/82 (3.7%)	7/79 (8.9%)	0/105 (0.0%)	1/82 (1.2%)	0/23 (0.0%)
	≥ 76 weeks	13/224 (5.8%)	14/24 (6.3%)	4/228 (1.8%)	2/223 (0.9%)	
Lewin 2015		**Empagliflozin 10mg**	**Empagliflozin 25mg**		**Linagliptin 5mg**	
	52 weeks	7/135 (5.2%)	6/135 (4.4%)		4/135 (3.0%)	
	52weeks (men)	2/77 (3.1%)	1/64 (1.3%)		1/75 (1.3%)	
	52weeks	5/58 (7.1%)	5/71 (8.8%)		3/60 (5.0%)	

	(women)					

Adverse events

In this section, we include data from trials and other studies in combination therapy as well as monotherapy.

Urogenital Tract Infections

Although most urinary tract infections (UTIs) are mild and easily resolved with appropriate antibiotic treatment, more severe infections can be devastating, resulting in bacteraemia, sepsis and death. Because of the frequency with which they occur, UTIs also impose a substantial economic burden on healthcare systems.[83]

Symptoms of UTI include dysuria (a burning feeling when urinating); frequency of urination; urgency (a feeling of an intense urge to urinate); pain or pressure in the back or lower abdomen; nausea and/or vomiting; cloudy, dark, bloody, or strange-smelling urine; feeling tired or shaky; fever or chills.

The presence of glucose in the urine (glycosuria) creates a suitable environment for the growth and proliferation of bacteria. Glycosuria also promotes increased adherence of bacteria to uroepithelial cells, in particular *E. coli*.[84] By blocking renal glucose reabsorption, SGLT2 inhibitors cause glycosuria, and increase the risk of UTI in patients.[84] (2).

Glycosuria in patients with T2DM predisposes these patients to develop genital tract infections (GTIs), in particular, genital mycotic infections i.e. vulvovaginal candidiasis in women and candida balanitis in men, as it provides a favourable growth environment for otherwise commensal genital microorganisms. Candida albicans is the most common cause, but Candida glabrata is also an important cause in women with T2DM.[85]

Symptoms of genital candidiasis can include itching; burning; genital discharge; pain during sexual intercourse; soreness; redness in the genital area; rash.

Both UTIs and GTIs are more common in females.[86]

Canagliflozin

In the Inagaki study of Japanese patients with T2DM[73], urogenital tract infections were infrequent, mild, managed with standard treatments and did not recur in any of the patients. The low incidence

may be at least partly because patients with a history of such infections were excluded from the trial. The incidence of UTIs was similar across all groups.[73] GTIs were more frequent in the canagliflozin groups compared to placebo, and mostly occurred in women.

In the Stenlöf study (CANTATA-M study) of predominantly white people[72, 87] there were small increases in UTIs with canagliflozin 100mg (7.2% at 24 weeks, 8.2% at 52 weeks) and 300mg (5.1% and 7.1%) compared with placebo (4.2% and 6.3%), All UTIs were mild to moderate in severity and no patients discontinued treatment due to a UTI.

Lavalle-González et al examined the efficacy and safety of canagliflozin 100mg and canagliflozin 300mg versus placebo and sitagliptin, for 26 weeks, in patients with T2DM who were being treated with background metformin; interestingly, the incidence of UTIs was only higher in the canagliflozin 100mg group.[88] The incidence of genital mycotic infections was higher in females and males with canagliflozin compared with placebo, but all were mild to moderate in severity, and responded to standard antifungal treatment. Once again, the incidence was higher in females compared to males as expected[88]; furthermore, the incidence of genital mycotic infections was higher in patients with high HbA1c.[88] No patients discontinued treatment due to a GTI.

In a separate 52-week open-label study by Inagaki of canagliflozin alone or as add-on to other oral antihyperglycaemic drugs in Japanese patients with diabetes, UTI was present in 2/127 (1.6%) with canagliflozin 100mg and 5/253 (2.0%) with canagliflozin 200mg, and none were severe (9). GTIs mostly occurred in females; most of the events were mild in severity and the patients recovered after antifungal therapy.[89]

Leiter et al. also compared canagliflozin 100mg and canagliflozin 300mg with glimepiride over 104 weeks in patients with T2DM inadequately controlled with metformin, and found the incidence of UTIs to be higher in the canagliflozin groups.[90]

Interestingly, Neal et al. looked at canagliflozin 100mg and canagliflozin 300mg when used together with insulin treatment over a 52 week time period and found no increase in the incidence of UTIs.[91]

Further, in a double-blind, Phase 3 clinical study, patients aged > 55 years to < 80 years inadequately controlled with their current treatment regimen (n = 714) were randomized to receive either canagliflozin 100mg or canagliflozin 300mg or placebo. Over 2 years, the incidence of GTIs was higher with canagliflozin 100mg (23.9%) or canagliflozin 300mg (18.7%) 300mg compared with placebo (4.3%) in women and men (5.6 % and 10.9 % versus 1.4 %, respectively). The largest number

of events occurred within 6 months of treatment initiation and declined with time. Most GTIs were mild to moderate in intensity and responded to standard treatment.[92]

In a pooled analysis by Nicolle et al.[93] the association between UTIs and canagliflozin treatment based on data from patients with T2DM enrolled in Phase 3 clinical studies, and on data from individual Phase 3 clinical studies in special patient populations, showed that the incidence of UTIs tended to be higher with canagliflozin 100mg and canagliflozin 300mg compared with placebo, but with no dose-dependence.

Finally, a recent report based on pooled data from patients with T2DM enrolled in Phase 3 clinical studies supports the notion of higher incidences of genital mycotic infections with canagliflozin compared to control patients with T2DM; GTIs being generally mild to moderate in intensity and responding to standard treatments.[94]

In summary, canagliflozin treatment (≥ 24 weeks) is associated with a higher incidence of urogenital tract infections, but there is no evidence of a dose-dependent response. UTIs were mild to moderate in severity and were amenable to standard treatment with no recurrence. This was also true in patients on pre-existing diabetic medication i.e. metformin. GTIs were also higher in females, and in older patients (> 55 years but < 80 years) – the risk of GTIs with canagliflozin use is increased mostly early after treatment initiation i.e. within first 6 months. GTIs were also mild to moderate in severity and were amenable to standard treatment.

Dapagliflozin

Dapagliflozin has been shown to have a dose-dependent effect on glycosuria in patients with T2DM[46], and treatment with dapagliflozin 10 mg as add-on to metformin showed that increased glycosuria with dapagliflozin was maintained for up to 102 weeks.[95] However, there is no demonstrable dose relationship between glycosuria and UTIs.[96]

In the Kaku monotherapy study in Japanese patients[77], after 24 weeks, 2 patients each in the dapagliflozin 10mg and placebo groups experienced at least one event suggestive of UTIs, but they were mild to moderate in severity.[77] Two patients in the dapagliflozin 10mg group and one patient in the placebo group experienced one or more GTI events, and GTIs were mild to moderate in severity.[77]

In a separate 52-week open-label Phase 3 study by Kaku consisting of a single treatment arm with no comparator, dapagliflozin (initiated at 5mg/day and titrated to 10mg/day as required) was administered as monotherapy (n = 249) or combination therapy (n = 479) with other

antihyperglycaemic agents (sulfonylurea, glinides, metformin, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, or glucagon-like peptide-1 receptor agonists) in Japanese patients with T2DM with inadequate glycaemic control.[97] (19). Urogenital infections were rare, mild to moderate in intensity, and rates were similar in the monotherapy and combination therapy groups.[97]

In the study by Ji et al in predominantly Chinese patients, urogenital tract infections were few, with higher incidence in the dapagliflozin group (5.3%) compared with placebo (3.0%). All reported events were predominantly of mild or moderate intensity.[76] One patient had urethritis of moderate intensity, which resolved with antibiotic treatment; the patient continued with the study.

In the 24-week study by Ferrannini et al, there was an increased incidence of urogenital tract infections with dapagliflozin treatment compared with placebo.[74] The incidence of urogenital tract infections in the exploratory evening dose cohort was similar to the morning dose cohort. Urogenital tract infections resolved with standard treatment, and rarely led to discontinuation.[74]

In the 102-week Bailey study[95], which is essentially a continuance of the 24-week Ferrannini study[74], low-dose metformin 500mg/day was added to the placebo group.[95] Once again, the incidence of urogenital tract infections with dapagliflozin treatment was higher compared with the placebo + low-dose metformin group.[95] Urogenital tract infections occurred during the first 6 months of dapagliflozin therapy, were more common in women, and most were single episodes of mild or moderate severity (16). All urogenital tract infections responded to standard management.[98] One patient on dapagliflozin discontinued the study because of UTI.

In triple therapy, dapagliflozin as add-on to metformin plus sulfonylurea, in a 24-week, trial was associated with a higher incidence of urogenital tract infections than in the placebo group.[99]

Rosenstock et al in a 24-week trial against saxagliptin reported that urogenital infections were more frequent in the dapagliflozin/metformin arm than either saxagliptin/metformin or saxagliptin/dapagliflozin/metformin groups.[100]

In a recent report by Ptaszynska et al.[101], the association between urogenital tract infections and dapagliflozin treatment based on pooled analyses from 12 placebo-controlled studies of Phase 2b or Phase 3 clinical studies in T2DM patients receiving comparator or dapagliflozin as monotherapy, add-on to antidiabetic therapy, or as initial combination with metformin showed that urogenital tract infections occurred more often with dapagliflozin treatment compared with placebo, but were mild or moderate in severity. Pyelonephritis was rare and balanced among treatments.

In summary, dapagliflozin monotherapies and combination therapies (≥ 24 weeks) are associated with a higher incidence of urogenital tract infections, but there is no evidence of a dose-dependent response. Urogenital infections were generally mild to moderate in severity, tended to occur during the first 6 months of dapagliflozin therapy, were more common in women, and were amenable to standard treatment. Urogenital infection rates were similar between monotherapy and combination therapy groups in all studies with the exception of combination therapies involving saxagliptin.[100]

Empagliflozin

Roden et al.[80, 102] found that after 24 weeks, UTIs were mild to moderate in intensity (only 1 patient in the empagliflozin 25mg group discontinued the study), and more common in women but similar in all arms. After 76 weeks, the frequency of UTIs was again similar in all groups. However, the frequency of GTIs was higher in the empagliflozin groups (3.1% and 4.0%) than the placebo (0%) and sitagliptin (0.9%) groups. GTIs were once again more common in women. GTI events were of moderate intensity in 3 patients in the empagliflozin 25mg group (1 patient discontinued the study); all other events were mild.

Barnett et al in the EMPA-REG RENAL study of empagliflozin versus placebo in patients with renal impairment found that both UTIs and GTIs were more frequent in T2DM patients with Stage 3 CKD and Stage 4 CKD, but not Stage 2 CKD.[103]

In the Lewin trial[78], after 52 weeks, urogenital infections were more common in women, and empagliflozin treatment was almost always associated with a higher incidence of urogenital infections compared with the placebo group. The exceptions were empagliflozin 25mg versus placebo for UTI and empagliflozin 10mg/linagliptin 5mg versus placebo for GTI. One patient (receiving empagliflozin 25mg) had a UTI of severe intensity, but did not lead to discontinuation of the study drug, and 1 patient (receiving empagliflozin 10mg) had chronic pyelonephritis that was mild in intensity and was not considered to be related to the study drug.[78] There were no severe GTI events, but two patients (1 on empagliflozin 25mg/linagliptin 5mg and one on empagliflozin 10mg) discontinued the study because of GTIs.

DeFronzo et al evaluated combinations of empagliflozin/linagliptin (empagliflozin 10mg/linagliptin 5mg and empagliflozin 25mg/linagliptin 5mg) as second-line therapy in subjects with T2DM inadequately controlled on metformin.[104] They found that after 52 weeks, the incidence of UTIs was similar across the empagliflozin 25mg, empagliflozin 10mg and linagliptin 5mg groups. In contrast to UTIs, the frequency of GTIs was higher in the empagliflozin 25mg and empagliflozin 10mg

compared with the linagliptin 5mg group; interestingly, the 2 combinations of empagliflozin/linagliptin therapies had a lower frequency of urogenital infections compared to these 3 groups.

Similar findings were reported from the Rosenstock placebo-controlled trial in obese (BMI ≥ 30kg/m^2 and ≤ 45kg/m^2) inadequately controlled (HbA1c ≥ 7.5 to ≤ 10%) T2DM patients where empagliflozin was added on to multiple daily injections of insulin for 52 weeks i.e. similar rates of UTIs and higher rates of GTIs in the empagliflozin groups compare with the placebo group.[105] However, in the EMPA-REG BASAL study, which enrolled T2DM patients with BMI ≤ 45 kg/m^2, inadequately controlled (HbA1c > 7% to ≤ 10%), despite treatment with basal glargine or detemir insulin (≥ 20IU/day) or NPH insulin (≥ 14IU/day), with or without metformin and/or sulfonylurea use, Rosenstock et al observed that both UTIs as well as GTIs were more frequent in the empagliflozin groups compare with the placebo group.[106]

Häring et al. studied the effect of adding either empagliflozin 10 mg or empagliflozin 25mg or placebo for 24 weeks in T2DM patients inadequately controlled (HbA1c ≥ 7% to ≤ 10%) on metformin and sulfonylurea [EMPA-REG METSU][107]or on metformin alone [EMPA-REG MET].[108] In both studies, the incidence of UTIs was slightly higher and the incidence of GTIs higher in the empagliflozin groups compared with the placebo groups, respectively. 71.2% of patients of the EMPA-REG METSU continued in a double-blind extension for ≥ 52 weeks, named the EMPA-REG EXTEND METSU study[109], and 72.7% of patients of the EMPA-REG MET study continued in a double-blind extension study for ≥ 52 weeks, named the EMPA-REG EXTEND MET study.[110] Both these studies demonstrated that UTIs were not more frequent in the empagliflozin groups compared with the placebo, but GTIs were reported in more patients on empagliflozin therapies than placebo[109, 110] Similar findings were found in the 104-week randomised, active-controlled, double-blind, parallel-group, Phase 3 trial, comparing empagliflozin and glimepiride as add-on therapy to metformin treatment in patients with T2DM, the EMPA-REG H2H-SU study.[111]

The EMPA-REG PIOGLITAZONE compared empagliflozin as add-on therapy to pioglitazone (≥ 30mg/day) with or without metformin (≥ 1500mg/day), at unchanged doses for ≥ 12 weeks, in patients with T2DM.[112] Afterwards, 61.2% of patients who completed 24 weeks of treatment continued in a double-blind extension trial for ≥ 52 weeks (total duration ≥ 76 weeks), the EMPA-REG EXTEND™ PIO study.[113] Both these studies found that UTIs were not more frequent in the empagliflozin groups compared with the placebo arms. However, GTIs were reported in more patients on empagliflozin therapies than placebo.[112, 113]

In summary, empagliflozin monotherapies and combination therapies (≥ 24 weeks) are associated with a higher incidence of GTIs but not UTIs, as almost all studies reported similar rates of UTI across all treatment and placebo groups. Urogenital infections were more common in women, generally mild to moderate in severity and amenable to standard treatment.

Some trials show little difference in UTI results between the SGTL2 inhibitor and placebo arms. A possible explanation is that the placebo group had glycosuria, due to poor diabetes control, leading to an increased risk of UTI. We note that in a trial of dapagliflozin against an active comparator, glipizide, the difference in UTI rates was greater than in most of the trials against placebo.[114]

Frequencies of UTIs.
The trials of different drugs reported different rates of UTIs, but a recent meta-analysis of 19 trials found no significant differences in risk amongst the three drugs. [115]

When do UTIs occur?
Several trials report cumulative incidence of UTIs. Kaku reports 2.3% at 24 weeks and 3.6% by 52 weeks. So 1.3% of UTIs occur in months 7 to 12. Ferrannini reports 5.7% at 24 weeks and 8.6% at 102 weeks. So 2.9% occur from week 24 to week 102. Roden reports 6.7% at week 24 and 9.4% by week 76. So 2.7% occurred from week 24 to week 76.
Patients on SGLT2 inhibitors who have more than one UTI will be switched to another drug. For modelling purposes, we will assume that;

- 60% of flozin-induced UTIs will occur in the first 6 months
- All flozin-induced UTIs will occur in the first two years
- Two UTIs will trigger a change of therapy.

Diabetic ketoacidosis (DKA)

DKA is a serious complication of diabetes, seen predominantly but not exclusively in type 1 diabetes. It is life-threatening. It requires admission to hospital for intensive treatment with intravenous infusion and insulin. It is therefore costly to health care.

In recent months, cases of DKA have been reported associated with treatment with SGLT2 inhibitors. The European Medicines Agency (EMA) has announced a review of the risk of DKA amongst people treated with these drugs.[116] It notes that 101 cases of DKA had been reported worldwide in patients treated with SGLT2 inhibitors, which based on an estimated 500,000 patients-years of use, would be a risk of one in 5000 patient years. The EMA also notes that in some cases the level of blood glucose

was much lower than is usually seen in DKA ("euglycaemic DKA"), and expressed concern that this might lead to delays in diagnosis.

In the USA, the Food and Drug Administration has also announced a review and has issued a safety announcement.[117] The FDA had received notifications of DKA in patients treated with SGLT2 inhibitors.

The manufacturers of canagliflozin, Janssen, have reported that in their series of trials, the incidence of DKA was very low – 0.5 per 1,000 patients years on canagliflozin 100mg daily, 0.8 on canagliflozin 300mg daily, and 0.2 per 1,000 years on placebo.[118] The other manufacturers have yet to publish data, but enquiries by Rosenstock and Ferrannini for a commentary in Diabetes Care elicited rates from the manufacturer for dapagliflozin and empagliflozin of under 0.1%, though no details are given of time period.[119] Rosenstock and Ferrannini suggest that some of the cases reported in the USA may have been in patients with type 1 diabetes.

With greater use of the SGLT2 inhibitors, rare adverse events can be expected. Acute pancreatitis has been reported shortly after canagliflozin was started[120] but cause and effect is not proven. A case of severe hypercalcaemia has been reported[121] possibly linked to the osmotic diuresis and ingestion of calcium-containing indigestion tablets.

Late reporting of adverse events is not unusual. The FDA have also recently issued a safety alert on the gliptins, the DPP4 inhibitors, after reports of severe joint pain.[122]

What is becoming clearer as evidence accumulates, is that the SGLT2 inhibitors have actions beyond the kidney, for example on the pancreas, with an increase in plasma glucagon levels, and effects on blood lipids.[123]

Cardiovascular safety

All three of the SGLT2 inhibitors reviewed in this report are in large, long-term cardiovascular studies, mandated by the FDA to satisfy the post-marketing requirements in the USA. The results of these (CANVAS[124] for canagliflozin and DECLARE[125] for dapagliflozin are awaited but there have been early reports of reductions in cardiovascular events.[126]

Bone health

The FDA has issued a warning on decreases in bone density and an increased risk of fractures in people taking canagliflozin, possibly through effects on phosphate metabolism involving parathyroid

hormone, fibroblast growth factor 23 and vitamin D.[127] Fractures have also been reported amongst people taking dapagliflozin. Kohan and colleagues[128] randomised 252 people with moderate renal impairment (94% in the range 30 to 59 ml/min) to placebo or dapagliflozin. HbA1c fell by 0.44% on dapagliflozin 10mg daily and by 0.32% on placebo, but there was good weight loss on dapagliflozin (reduction by 1.89 kg) and a useful reduction in SBP (6.8 mmHg). However 8 of 85 (9.4%) people on dapagliflozin 10mg suffered fractures, compared to none on placebo.

Kwon[129] reviewed bone safety and canagliflozin for the FDA, using data from the canagliflozin phase 3 programme, for 6177 patients on the drug and 3262 on other treatments. The proportions suffering fractures were 2.1% and 1.6% for canagliflozin and others respectively, with most of the difference being in low trauma fractures (1.6% and 1.2%), with the main difference being in the upper limb (0.7% versus 0.3%). The incidence per 1000 patient years was 18.1 for canagliflozin regimens and 14.2 for other regimens. So the risk of fracture is small but increased by around 30% in people taking canagliflozin.

The mechanism by which canagliflozin increases fracture risk is uncertain.[130] An important issue is that the fracture rate is not increased in the first year of treatment, but appears later. So any increase in fracture risk may not be detected in short trials (Taylor 2015). (The FDA warning however states that fractures can occur as early as 12 weeks after starting canagliflozin.)

The EMPA-REG outcome study

The results of this trial were published on 17th September 2015.[131] The trial recruited 7020 patients at high risk of cardiovascular disease. High risk included having a history of myocardial infarction (MI) or stroke, coronary artery stenosis of 50% or more, previous coronary revascularisation, and peripheral vascular disease. The trial scores quite well with the Cochrane risk of bias score (Appendix 5) with the deficiencies probably due to failure to provide details rather than design or execution flaws.

Patients were randomised to placebo, and empagliflozin 10mg or 25mg. Patients were recruited from 590 sites in 42 countries, an average of 12 per site. 72% were white, 21% Asian and 5% Black including African-Americans. The Asians were from 10 countries with a mix of South and East Asian centres, ranging from India to Japan and Korea. There were no centres in China except Hong Kong, but there were centres in Taiwan and Singapore. Numbers are not given by country. There were 12 UK centres, and 41% of all recruits were from Europe, including Russia. The mean HbA1c at baseline was just under 8.1%. In 57% of patients, duration of diabetes was over 10 years. At baseline 74% were on metformin, 48% on insulin, 43% of sulfonylureas and 11% on DPP-4 inhibitors. About 30% were on monotherapy and 48% on dual therapy, implying that 26% were on more complex regiments

with three drugs or more. Discontinuation from trial medication occurred in 29% of the placebo group and 23% of the empagliflozin group, with 13% and 11.5% being due to adverse events (which did not include need for rescue therapy).

After 12 weeks, other glucose-lowering drugs could be adjusted or added. Targets were not specified centrally but left to local guidelines. Changes were made in 31.5% of the placebo group and 19.5% of the empagliflozin group. The changes in the empagliflozin group included the introduction of insulin (5.8%), a DPP4 inhibitor (5.6%), a sulfonylurea (3.8%), metformin (3.7%), a TZD (1.2%) or a GLP-1 analogue (1.4%). This means that we cannot use the drift upwards of HbA1c of 0.1% per year in the empagliflozin group as a guide to progression of diabetes. Despite the addition of other glucose-lowering drugs, the mean HbA1cs at week 206 were 7.81% in the empagliflozin group and 8.16% in the placebo group, a difference of 0.35%.

Being a high risk group, at baseline 95% were on anti-hypertensive medications (81% on angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs); 65% on beta-blockers; 33% on calcium channel blockers). 77% were on statins, 9% on fibrates and 4% on ezetimibe. 43% were on diuretics, unspecified, but loop diuretics are not recommended for use with canagliflozin and dapagliflozin.

According to the supplementary information (Table S12), cardiovascular medications introduced after baseline included, in the empagliflozin arms, ACEIs or ARBs in 23.6%, which does not seem compatible with the 81% on these drugs at baseline. Perhaps there were changes of drug or dosages. Similarly Table S12 reports statins being introduced in 22% of the empagliflozin group, which implies that at study end, 99% were on statins, with 14% also on fibrates.

A range of subgroups was specified in the protocol.[132] The results were analysed by staff from Boehringer Ingelheim who co-funded it with Eli Lilly. The two empagliflozin groups were pooled for the analysis, because event rates were almost identical (CVD deaths 3.8% with 10mg and 3.5% with 25mg). When the main outcomes were assessed for the 10mg and 25mg empagliflozin groups separately, the differences were not significantly different from the placebo group.

The primary outcome was a composite of death from a cardiovascular cause, non-fatal MI and non-fatal stroke. The primary outcome occurred in 10.5% of people on empagliflozin and in 12.1% of those on placebo, giving hazard ratio 0.86 (95% CI 0.74-0.99). Table **6** shows some of the outcomes.

Table 6 Results of EMPA-REG-OUTCOMES trial

	Placebo	Empagliflozin
Number of patients	2333	4687
All-cause mortality	8.3%	5.7%
Cardiovascular mortality	5.9%	3.7%
Non-cardiovascular mortality	2.4%	2.0%
Primary composite outcome	12.1%	10.5%
MI		
non-fatal	5.2%	4.5%
fatal	0.2%	0.3%
silent	1.2%	1.6%
Stroke	3.0%	3.5%
fatal	0.4%	0.3%
non-fatal	2.6%	3.2%
Hospital admission – heart failure	4.1%	2.7%
Hospital admission - unstable angina	2.8%	2.8%
UTIs	18.1%	18.0%
GTIs	1.8%	6.4%
DKA	1 event	4 events

The DKA rate in the empagliflozin was double that in the placebo group but the excess risk was only about 1 in 1500 per year, and numbers were very small.

The proportion of fatal to non-fatal MIs looks odd – 5 deaths out of 126 MIs. Similarly of 69 strokes, only 9 were fatal. This raises the question of where the 137 cardiovascular deaths come from.

Supplementary table S5 reports 11 deaths from acute MI in the placebo group and 15 in the pooled empagliflozin group, but these figures do not match those in table 1 in the main paper. The figures for fatal stroke also differ between main text and supplement 11 versus 9 for placebo, 16 versus 14 for empagliflozin.

Supplementary table S5 gives cardiovascular deaths reproduced in Table **7**.

Table 7 Cardiovascular deaths in the EMPA-REG Outcome trial.

Cause	placebo	Empagliflozin	Difference in %
Sudden death	1.6%	1.1%	0.5%
Heart failure	0.8%	0.2%	0.6%
Acute MI	0.5%	0.3%	0.2%
stroke	0.5%	0.3%	0.2%
Cardiogenic shock	0.1%	0.1%	0
Other cardiovascular deaths	2.4%	1.6%	0.8%

Total mortality was 8.3% in the placebo group and 5.7% in the pooled empagliflozin, a difference of 2.6%.

The ill-defined "other cardiovascular deaths" comprise 41% and 44% of all cardiovascular deaths for placebo and empagliflozin respectively, and they account for 29% and 28% of all deaths respectively. Three causes account for 83% of the observed difference in mortality: sudden death, heart failure and "other cardiovascular deaths".

The totals of proportions having the individual events in the composite primary outcomes exceeds the primary outcome proportion, presumably because some patients had more than one event.
The Kaplan-Meier curves diverge after about 2 months, with curious accelerations in the placebo group curves after 42 months.

How were these cardiovascular benefits achieved?
HbA1c was 0.57% lower in the empagliflozin group than the placebo arm at week 12 but steadily narrowed thereafter to 0.35% at week 206. Given the weak relationship between glycaemic control and cardiovascular disease[66] this difference seems unlikely to have caused the difference.

SBP fell by about 5.5mmH in the empagliflozin group and by about 2 mmHg in the placebo group by week 16 but the difference between the empagliflozin and placebo groups narrowed thereafter to about 2mmHg. There was no difference in BP lowering between doses. Diastolic BP fell by about 2.5 mmHg in all three arms. By 206 weeks, there was no difference between diastolic BP between empagliflozin and placebo groups.

For some complications of diabetes, blood pressure control is as important as glycaemic control, as was shown by the UKPDS study, where "tight" blood pressure control (with a mean BP of 144/82, it was not really tight) reduced overall mortality by 32% (RR 0.68; 95% CI 0.49-0.94).[133]

Weight was reduced by 2kg in the empagliflozin group and by 1.2kg in the placebo group.
Changes in lipids were small. On empagliflozin 25 mg, LDL-c rose (placebo-adjusted) from baseline 2.2 mmol/L to about 2.3 by 12 months, stayed there till about 136 weeks then fell to about 2.21 mmol/l, just below the placebo level. On empagliflozin 25mg, HDL-C rose by about 0.05 mmol/L then fell slightly. The placebo level rose by about 0.01mmol/L. (Figures derived from graph – data not provided in text.) The baseline TC:HDL ratio was 3.5, perhaps because so many were on statins and other lipid-lowering drugs. These lipid changes seem insufficient to explain the mortality results.

However the combination of factors may have more effect than the individual ones, and the reduction in blood pressure, though small, is similar to that seen in the Heart Outcomes Prevention Evaluation (HOPE) trial[134] where a reduction of 2-4mmHg in blood pressure from ramipril (an ACEI) was thought by the HOPE authors to be sufficient to explain about a quarter of the observed 25% reduction in cardiovascular events, in another high risk group with vascular disease and/or diabetes.

Discontinuation rates from study drugs due to adverse events are reported as 19.4% for placebo and 17.3% for empagliflozin in the paper but as 13.0% and 11.5% in appendix H.
Subgroup analysis for the primary composite outcome shows;

- Statistically significant benefit in Asians (a mixed group, with about 44% from north-east Asia) but not in whites, though death from cardiovascular causes is significantly reduced in whites. This implies that whites gained less for non-fatal MI and stroke. The Asian group is rather heterogenous and no details are given of risks in East Asians versus South Asians. There are differences in the balance of insulin deficiency and insulin resistance.
- Statistically significant benefit in those with baseline HbA1c under 8.5% but not in those above that
- Statistically significant benefit in those with BMI < 30 but not in those above that level
- Statistically significant benefit in those on insulin but not in those on non-insulin regimens. 51% in both groups were on insulin.
- Greater benefit in those aged over 65

In a number of subgroups, reductions in cardiovascular death were statistically significant when reductions in the primary outcome were not. To recall, the primary outcome was cardiovascular death, non-fatal MI and non-fatal stroke. Of 282 primary outcome events in the placebo group, 49% were

cardiovascular deaths. Of 490 primary outcome events in the empagliflozin groups, 35% were cardiovascular deaths. So a greater proportion of events in the empagliflozin group was of non-fatal events. The fact that in some subgroups, cardiovascular death rates are significantly different when the composite primary outcome is not, is explained by a lack of any statistically significant differences in non-fatal MI and non-fatal stroke.
Non-fatal MI was diagnosed on the basis of symptoms plus one or more of;

- Troponin or creatine kinase-MB
- ECG changes
- Imaging of new non-viable or non-motile myocardium

This study has attracted world-wide interest. It contrasts with the equivalent studies with the DPP4 inhibitors, which did not show any reduction in cardiovascular outcomes. They were;

- SAVOR for saxagliptin (The Saxagliptin assessment Of Vascular Outcomes Recorded in patients with diabetes mellitus).[135]
- EXAMINE for alogliptin (Examination of cardiovascular outcomes with alogliptin versus standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome.[136]
- TECOS for sitagliptin (Trial Evaluating Cardiovascular Outcomes with Sitagliptin.[137]

There was no difference in cardiovascular outcomes in SAVOR except that more patients on saxagliptin than on placebo (3.5% versus 2.8%: HR 1.27 95% CI 1.07-1.51) were admitted to hospital with heart failure.

The findings in EXAMINE were similar – no difference in endpoints – except an increase in heart failure in a subgroup analysis of patients with no heart failure at baseline (2.2% on alogliptin, 1.3% on placebo; HR 1.76 95% CI 1.07-2.90).

TECOS results were again similar – no differences in a composite primary endpoint of CV death, non-fatal MI and non-fatal stroke, nor in other endpoints including hospital admission for heart failure, and death from any cause.

These results were seen as providing reassurance, in the wake of the rosiglitazone story with an increase in cardiovascular events.[138] They could also be seen as disappointing in that they did not reduce the most important complication of diabetes, the excess of cardiovascular disease. However as has been pointed out by Hirshberg and Katz.[139], these trials ran for only a few years and showed only small changes in HbA1c (reductions of 0.27 to 0.36% compared to placebo) so reducing the chance of showing reductions in cardiovascular events.

The subgroup analyses in EMPA-REG Outcome are interesting. Younger, lighter, better controlled patients did better, as did the Asian group. There could be overlapping features here in that the East Asians tend to be lighter. There was no evidence of overall mortality reduction in white people but some reduction in CVD mortality, which suggests that there were more non-cardiovascular deaths in white people on empagliflozin. Further details will no doubt be released but with such a very large study, further analysis is bound to take time.

The differences observed do not seem sufficient to justify the very optimistic media coverage, such as reports that "Lilly's Jardiance diabetes pill could be a $6 billion-a-year blockbuster".[140]

It is worth noting that the Empa Outcome trial involved patients at high cardiovascular risk who had had diabetes for many years and who were on complex regimens for their diabetes. The results are not applicable to people starting monotherapy with empagliflozin.

Chapter 3. Network meta-analysis of SGLT2 inhibitors and comparators in monotherapy

One question is whether all the three flozins in this appraisal should be regarded as equally potent. In addition to the SGLT2 transport system in the kidney, there is also a related transport system in the gut, SGLT1. Most SGLT2 inhibitors appear to be highly-selective, with no significant effect on SGLT1, but one of the class, canagliflozin, does affect SGLT1, and it has been suggested by Polidori and colleagues[49] that canagliflozin may reduce blood glucose by a dual action in both gut and kidney. However that suggestion followed a very short-term study of canagliflozin in healthy individuals, and the gut effect was seen only with higher doses such as 300mg, and not with the 100mg dose.

A study by Stein and colleagues from Janssen Research and Development[50] looked at the SGLT1 effect in people with type 2 diabetes and found that canagliflozin 300 mg, but not 150 mg, reduced post-prandial plasma glucose, by about 0.5 mmol/l (from graph) for about two hours after administration, since it depends on an intestinal drug action not a systemic one. Hence this reduction would only occur after the single daily dose.

If the SGLT1 effect is clinically significant in people with type 2 diabetes, then one might expect canagliflozin 300 mg to be more potent in reducing HbA1c levels than SGLT2 inhibitors without the SGTL1 effect.

The CANTATA-M study 2013[72] did not report weight SDs for the two doses of canagliflozin so this study could not be included in weight comparison. The weight data for canagliflozin 100 mg comes from Inagaki 2014[73] where the 100 mg and 200 mg doses of canagliflozin were used. We excluded the 200 mg dose since this is not a standard dose.

For assessing the relative merits of the SGLT2 inhibitors in monotherapy, the first comparison is amongst the usual starting doses: canagliflozin 100mg, dapagliflozin 10mg and empagliflozin 10mg. By including empagliflozin 25mg and canagliflozin 300mg, we can assess the effect of increasing the doses. However a caveat is necessary. The empagliflozin 25mg and canagliflozin 300mg are used in people who can tolerate the starting dose, but have an insufficient HbA1c response. Such patients may not respond as well to SGLT2 inhibition as the average patient, and the effect of increasing the doses may be less than seen in the trials.

The aim of our NMA was not only to compare canagliflozin, empagliflozin and dapagliflozin, but also to assess their effects relative to active comparators.

Methods

Selection of trials

We applied the following selection criteria;

- Trials of 24 -26 weeks, starting with placebo as the common comparator
- Trials only of selected drugs. For example, we did not include all sulfonylureas but focused on gliclazide which should be the sulfonylurea for comparison in trials of newer agents.[22] We did not include all DPP4 inhibitors, originally intending to focus on sitagliptin.
- Baseline HbA1c of 7.5% or more, based on the NICE guideline for treatment intensification. There are some RCTs in patients with lower baseline HbA1cs, but they have less scope for lowering HbA1c
- Drop-out rates of no more than 20%

However, the first of these criteria had to be relaxed in order to include gliclazide since we found no trials of gliclazide against placebo. We had to indirectly link gliclazide with placebo via linagliptin and pioglitazone. All the other drugs included had trials against placebo. Unfortunately, we found no satisfactory trials of repaglinide for inclusion.

We searched the lists of trials used for the NICE guideline group on type 2 diabetes, but carried out additional searches specifically for gliclazide trials, since the guideline group pooled trials of sulfonylureas.

The evidence on repaglinide

The annex to the NICE guideline CG87 lists 7 studies on repaglinide but only three gave 24 week data.

Abbatecola et al report a randomised trial comparing repaglinide and glibenclamide.[141] The main outcome measure was cognitive function, with the hypothesis being the tighter control of post-prandial plasma glucose would reduce cognitive decline, in patients aged 60-78, mean age 74. (Note that according to the BNF, repaglinide is "not recommended" in people over 75.)
The baseline HbA1c in patients in this trial was quite low – 7.25%. So it is an exclusion for our purposes. The final HbA1c is not given in the text, but from the graph is about 6.6% with no difference between the drugs.

In the Jovanovic 2000 trial, patients were randomised to placebo, and repaglinide 1mg or 4mg daily. Under 30% of patients were drug naïve, and 10% had been on two glucose lowering drugs.[142]
Baseline HbA1c was 8.6% in the placebo group and rose to 10% at 24 weeks. In those who had been

on previous combination treatment, HbA1c rose by 1.8% on placebo, and fell by inconsequential 0.07% and 0.05% on repaglinide 1mg and 4mg. Drop-out rates were very high – 60% in the placebo group of which half had to start rescue treatment, and 23% and 31% in the repaglinide groups. Given that 70% had been on prior drug therapy, the high proportion in the placebo group requiring rescue treatment is not surprising, but it devalues any conclusions drawn from this study.

The third 24 week study used by NICE was by Saleem et al from Lahore.[143] This compared the effects on HbA1c of repaglinide and glibenclamide. It says that 50 patients were "randomly selected" for each group but gives no details of how this was done, or on allocation concealment. Blinding was not feasible because of different dosing frequencies – one or twice daily for glibenclamide, pre-prandially up to three times a day for repaglinide. No patients are reported to have dropped out. The recruitment period in this study (March 2006 to March 2007) overlaps with that for another paper by the same group (Shah et al 2011)[144] which reports only plasma glucose, in 200 patients. The changes in FPG and 2-hour PG are almost identical in the two studies. The Shah paper has no HbA1c data. Saleem et al 2011 report a reduction by 24 weeks in HbA1c of 0.6% on repaglinide and 0.4% on glibenclamide. The final repaglinide dose was 4.27mg daily, and the final glibenclamide dose was 8.8mg (identical to the Shah et al article). The Shah article states that dosages were reported as being adjusted based on glucose levels, so it is not clear why the final glucose levels are so different, with a reduction in FPG in the repaglinide group which is almost double that in the glibenclamide group. No details of source of funding are given. We think that the patients in the Saleem study may be a subset of those in the Shah study.

We also note the trial by Jibran and colleagues.[145] This paper is very similar to the Saleem et al 2011[143] paper, but has no authors in common. The numbers of patients are the same, and values for baseline age, weight and BMI have identical means and SDs. The result tables are identical in means and SDs. Much of the text is the same. The patients are said to have been recruited in different time periods.

Glibenclamide is a first generation sulphonylurea and was not included in our NMA, so the Saleem/Jibran and Abbatecola trials are not included.

The NICE guideline group also considered evidence on repaglinide at 12 months, from four trials. These included the Abbatecola and Saleem trials mentiond above, and two better quality ones by Derosa et al[146] and Marbury et al.[147]The Derosa trial compared repaglinide with glimepiride, in patients with mean HbA1c of 8.0%, and showed a reduction of 1.2% at 12 months. We use the effect sizes from this study in our modelling, for changes in HbA1c, SBP and weight. However we prefer gliclazide to glimepiride, so the Derosa trial is not included in our NMA. The Marbury trial recruited

both patients who had never had any glucose lowering drugs (13%) and those who had previously been treated with sulfonylureas and other drugs (87%). The reduction in HbA1c was much greater in the pharmacotherapy-naive group – 1.3% at 12 months, similar to the Derosa results. In previously treated patients, the HbA1c actually rose by 0.3%. Mean baseline HbA1c was quite high at 8.7% so the results may be less applicable to patients treated according to the NICE guidelines with close monitoring and prompt intensification when HbA1c exceeded 7.5%. The sulfonylurea comparator was glibenclamide, so the trial is not used in our NMA.

The network diagram is shown in Figure 3. The included trials are listed in Table **8**.

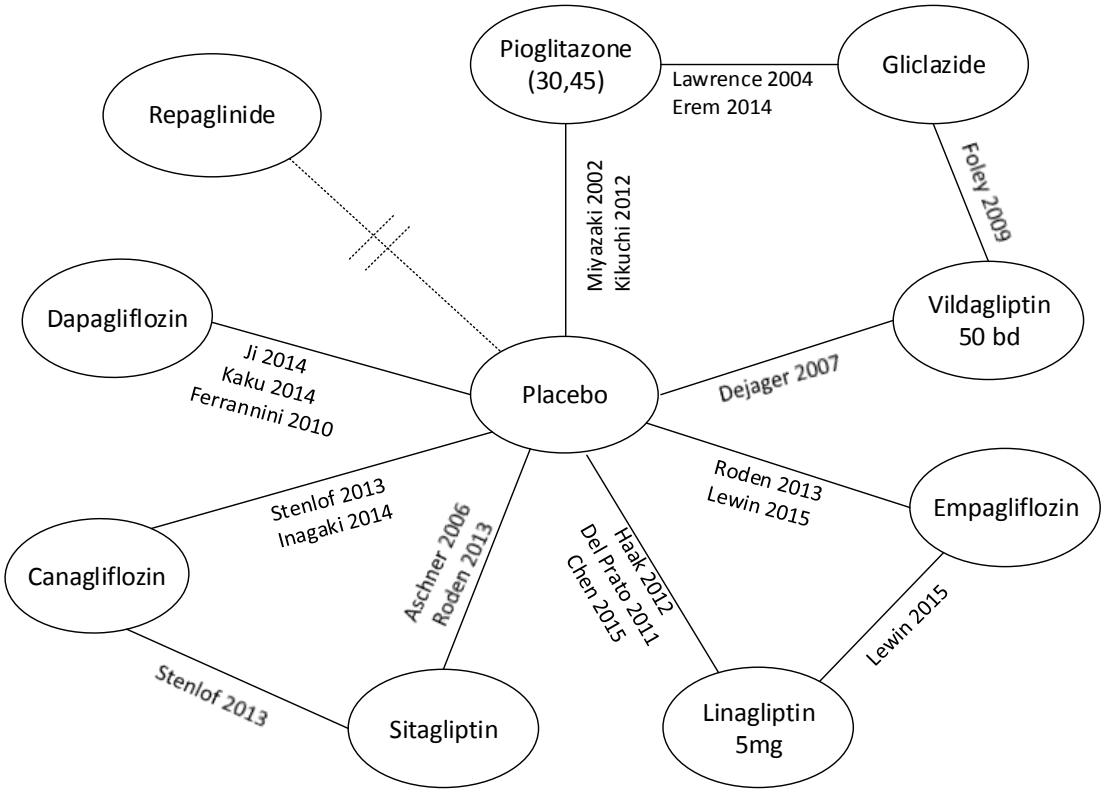

Figure 3 Network meta-analysis diagram

Table 8 Trials included in the NMA

Trial	Drug	Comparator	Notes
Inclusions			
Aschner 2006[148]	Sitagliptin 100mg	Placebo	
Chen 2015[149]	Linagliptin	Placebo	
Dejager 2007[150]	Vildagliptin	Placebo	
Del Prato 2011[151]	Linagliptin	Placebo	
Erem 2014[152]	Pioglitazone	Gliclazide	
Ferranini 2010[74]	Dapagliflozin	Placebo	
Foley 2009[153]	Gliclazide	Vildagliptin	
Haak 2012[154]	Linagliptin	Placebo	
Inagaki 2014[73]	Canagliflozin 100	Placebo	
Ji 2014[76]	Dapagliflozin	Placebo	
Kaku 2014[77]	Dapagliflozin	Placebo	
Kikuchi 2012[155]	Pioglitazone	Placebo	
Lawrence 2004[156]	Pioglitazone	gliclazide	
Lewin 2015[78]	Empagliflozin	Placebo	Linagliptin
Miyazaki 2002[157]	Pioglitazone	Placebo	
Roden 2013[80]	Empagliflozin	Placebo	Sitagliptin
Stenlof 2013[72]	Canagliflozin 100 and 300mg	Placebo	Sitagliptin in extension

Summary measures

The primary measures of treatment effect were the mean differences (MD) in change from baseline for glycated haemoglobin, weight gain, and systolic blood pressure. A negative value indicates improvement in the outcome. In the case of missing values for standard deviation of change from baseline values, the standard deviation was imputed as described in detail in the Cochrane Handbook.[158] In brief, we assumed a correlation of r=0.5 between baseline and follow-up to estimate standard deviation for change from baseline

Data synthesis and model implementation

We used a Bayesian network meta-analysis (NMA) method to analyse all the data, preserving randomized treatment effects within trials and accounting for correlation between comparisons with three-arms or four-arms using the freely available software, WinBUGS 1.4.3. The statistical heterogeneity in treatment effect estimates was estimated using between study variance (i.e. square root of the standard deviation of underlying effects across trials) with 95% CrI.[159] To estimate inconsistency in the networks of evidence, we calculated the difference between indirect and direct estimates whenever indirect estimates could be constructed with a single common comparator.[159] Inconsistency was defined as disagreement between direct and indirect evidence with a 95% CrI

excluding 0 for MD.[160] The model convergence was assessed using trace plots and the Brooks-Gelman-Rubin statistic.[161] The analysis was undertaken using two Markov chains, which was ran simultaneously. The model was found to be converging adequately after 20,000 samples for both chains. We ran the model further using 70,000 samples and the results presented in the paper are based on these samples as we discarded the first 20,000 samples.

We used both the fixed and random effect models. The Bayesian Deviation Information Criterion (DIC) was used to compare the two models to see which was appropriate to compare treatment effects. The DIC measures the fit of the model while penalizing it for the number of effective parameters. The model with the lowest DIC value was considered as the most appropriate NMA model. Based on DIC values obtained from the two models and also because of small number of studies available for the NMA, a fixed effect model was chosen. Due to small number of studies, it would have been difficult to estimate between studies variance if a random effect model was implemented.

All results are reported as posterior medians of mean differences with corresponding 95% credible intervals (CrIs). Credible intervals are the Bayesian equivalent of classic confidence intervals. A 95% credible interval can be interpreted as there being a 95% probability that the parameter takes a value in the specified range. Drugs were not ranked, but were considered in terms of effect sizes and uncertainties.

Results

Glycated haemoglobin (haemoglobin A1c)

Networks of eligible comparisons for the glycated haemoglobin (HbA1c) are shown in Figure 4 showing predominantly pairwise comparisons of drugs with placebo. There were eleven comparisons (ten drugs plus placebo).

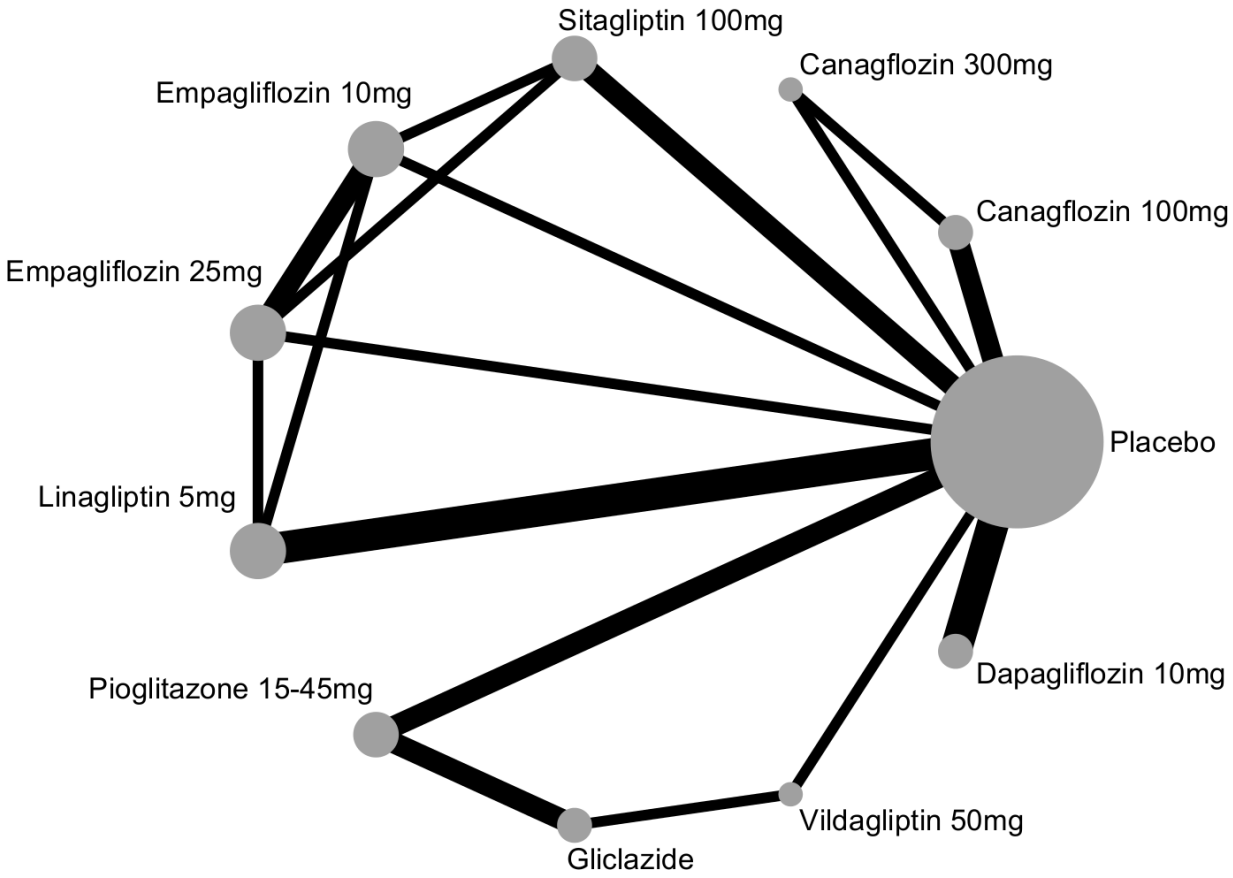

Figure 4 Network plot – glycated haemoglobin (HbA1c)

Figure 5 and Table 9 displays a caterpillar plot of the mean difference (MD) and 95% credible intervals (CrI) for all comparisons for mean change in HbA1c (at 24 weeks) from baseline. All SGLT-2 inhibitors were all significantly more effective than placebo in reducing mean change in HbA1c from baseline, with the reduction ranging from -1.19% to -0.59%. Canagliflozin 300mg, pioglitazone and canagliflozin 100mg were significantly more effective in reducing mean change in HbA1c from baseline than linagliptin 5mg, dapagliflozin 10mg and vildagliptin 50mg. The reductions in HbA1c from baseline were similar for linagliptin 5mg and dapagliflozin 10mg. The between study variance was small suggesting no heterogeneity, but the credible intervals were wide which reflects the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for HbA1c.

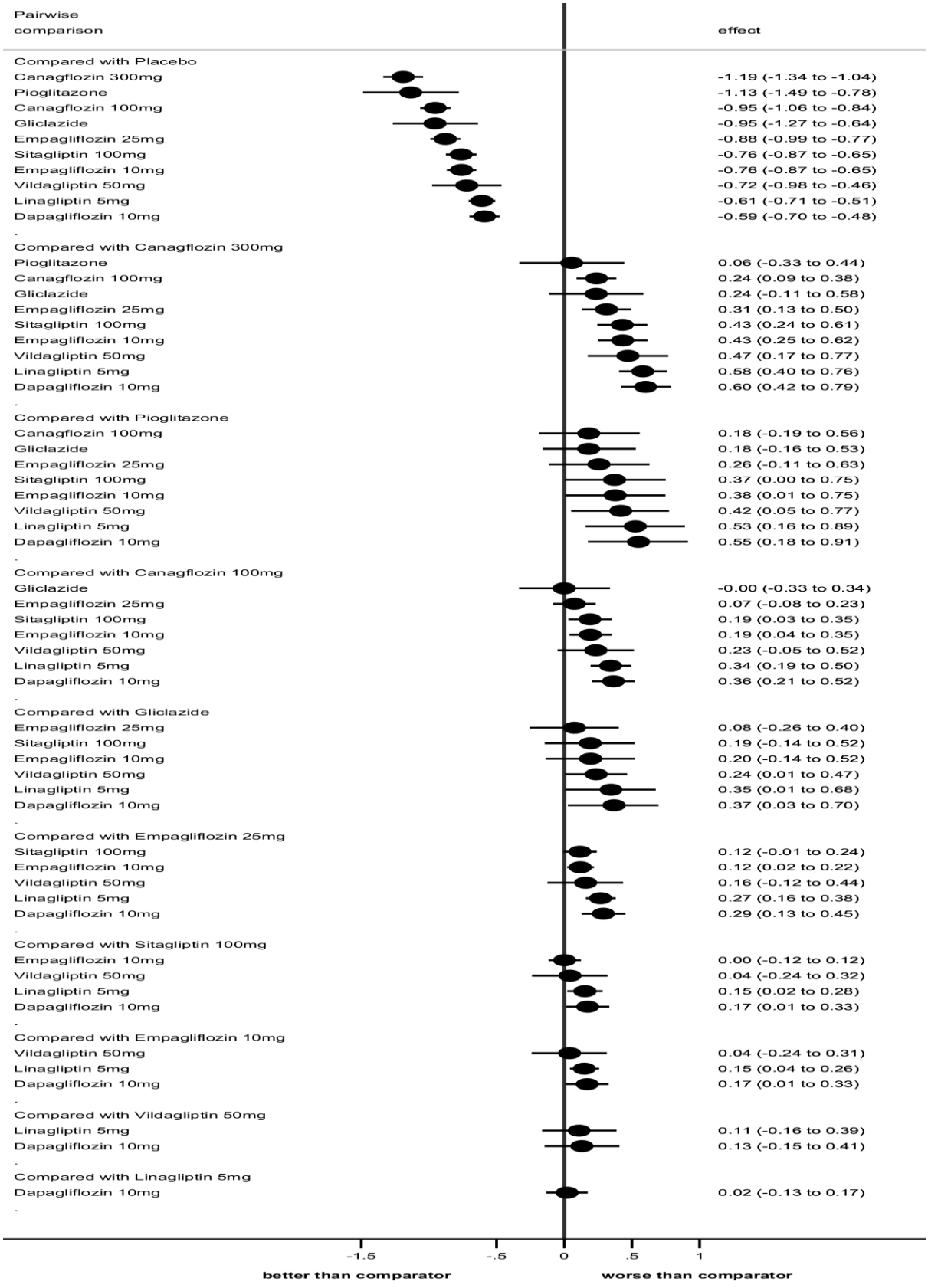

Figure 5 Pairwise comparisons of all drugs for glycated haemoglobin (HbA1c)

Table 9 Pairwise comparisons of all drugs for glycated haemoglobin (HbA1c)

Pairwise comparison	Mean difference (95% Credible Intervals)
Compared with Placebo	
Canagliflozin 300mg	-1.19 (-1.34 to -1.04)
Pioglitazone	-1.13 (-1.49 to -0.78)
Canagliflozin 100mg	-0.95 (-1.06 to -0.84)
Gliclazide	-0.95 (-1.27 to -0.64)
Empagliflozin 25mg	-0.88 (-0.99 to -0.77)
Sitagliptin 100mg	-0.76 (-0.87 to -0.65)
Empagliflozin 10mg	-0.76 (-0.87 to -0.65)
Vildagliptin 50mg	-0.72 (-0.98 to -0.46)
Linagliptin 5mg	-0.61 (-0.71 to -0.51)
Dapagliflozin 10mg	-0.59 (-0.70 to -0.48)
Compared with Canagliflozin 300mg	
Pioglitazone	0.06 (-0.33 to 0.44)
Canagliflozin 100mg	0.24 (0.09 to 0.38)
Gliclazide	0.24 (-0.11 to 0.58)
Empagliflozin 25mg	0.31 (0.13 to 0.50)
Sitagliptin 100mg	0.43 (0.24 to 0.61)
Empagliflozin 10mg	0.43 (0.25 to 0.62)
Vildagliptin 50mg	0.47 (0.17 to 0.77)
Linagliptin 5mg	0.58 (0.40 to 0.76)
Dapagliflozin 10mg	0.60 (0.42 to 0.79)
Compared with Pioglitazone	
Canagliflozin 100mg	0.18 (-0.19 to 0.56)
Gliclazide	0.18 (-0.16 to 0.53)
Empagliflozin 25mg	0.26 (-0.11 to 0.63)
Sitagliptin 100mg	0.37 (0.00 to 0.75)
Empagliflozin 10mg	0.38 (0.01 to 0.75)
Vildagliptin 50mg	0.42 (0.05 to 0.77)
Linagliptin 5mg	0.53 (0.16 to 0.89)
Dapagliflozin 10mg	0.55 (0.18 to 0.91)
Compared with Canagliflozin 100mg	
Gliclazide	-0.00 (-0.33 to 0.34)
Empagliflozin 25mg	0.07 (-0.08 to 0.23)
Sitagliptin 100mg	0.19 (0.03 to 0.35)
Empagliflozin 10mg	0.19 (0.04 to 0.35)
Vildagliptin 50mg	0.23 (-0.05 to 0.52)
Linagliptin 5mg	0.34 (0.19 to 0.50)
Dapagliflozin 10mg	0.36 (0.21 to 0.52)
Compared with Gliclazide	
Empagliflozin 25mg	0.08 (-0.26 to 0.40)
Sitagliptin 100mg	0.19 (-0.14 to 0.52)
Empagliflozin 10mg	0.20 (-0.14 to 0.52)
Vildagliptin 50mg	0.24 (0.01 to 0.47)

Pairwise comparison	**Mean difference (95% Credible Intervals)**
Linagliptin 5mg	0.35 (0.01 to 0.68)
Dapagliflozin 10mg	0.37 (0.03 to 0.70)
Compared with Empagliflozin 25mg	
Sitagliptin 100mg	0.12 (-0.01 to 0.24)
Empagliflozin 10mg	0.12 (0.02 to 0.22)
Vildagliptin 50mg	0.16 (-0.12 to 0.44)
Linagliptin 5mg	0.27 (0.16 to 0.38)
Dapagliflozin 10mg	0.29 (0.13 to 0.45)
Compared with Sitagliptin 100mg	
Empagliflozin 10mg	0.00 (-0.12 to 0.12)
Vildagliptin 50mg	0.04 (-0.24 to 0.32)
Linagliptin 5mg	0.15 (0.02 to 0.28)
Dapagliflozin 10mg	0.17 (0.01 to 0.33)
Compared with Empagliflozin 10mg	
Vildagliptin 50mg	0.04 (-0.24 to 0.31)
Linagliptin 5mg	0.15 (0.04 to 0.26)
Dapagliflozin 10mg	0.17 (0.01 to 0.33)
Compared with Vildagliptin 50mg	
Linagliptin 5mg	0.11 (-0.16 to 0.39)
Dapagliflozin 10mg	0.13 (-0.15 to 0.41)
Compared with Linagliptin 5mg	
Dapagliflozin 10mg	0.02 (-0.13 to 0.17)

Weight gain

Networks of eligible comparisons for the weight gain are shown in Figure 6**,** showing predominantly pairwise comparisons of drugs with placebo. There were eleven comparisons (ten active drugs plus placebo).

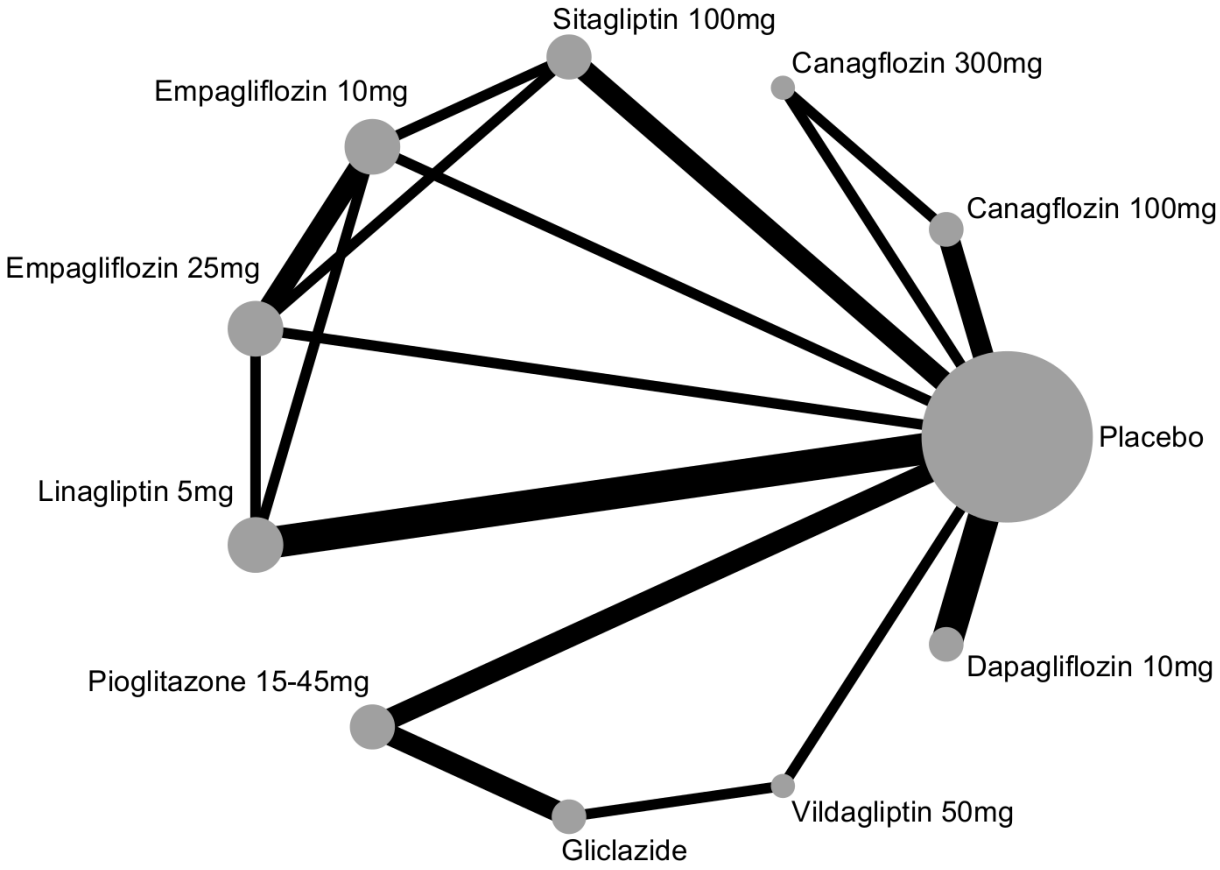

Figure 6 Network plot – weight gain

Figure 7 and Table 10 displays a caterpillar plot of the mean difference (MD) and 95% credible intervals (CrI) for all comparisons for mean change in weight gain from baseline. Sitagliptin 100mg, vildagliptin 50mg, gliclazide and pioglitazone were associated with significant weight gain compared with placebo, with the weight gain ranging from 0.74kg to as much as 3.79kg. Compared with placebo, canagliflozin 300mg, canagliflozin 100mg, empagliflozin 25mg, empagliflozin 10mg and dapagliflozin 10mg were associated with significant weight loss, ranging from -2.91kg to -1.58kg. Compared with all other drugs in the network, canagliflozin 300mg was associated with significant weight reduction. The between study variance was small suggesting no heterogeneity, but the credible intervals were wide which reflects the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for weight gain.

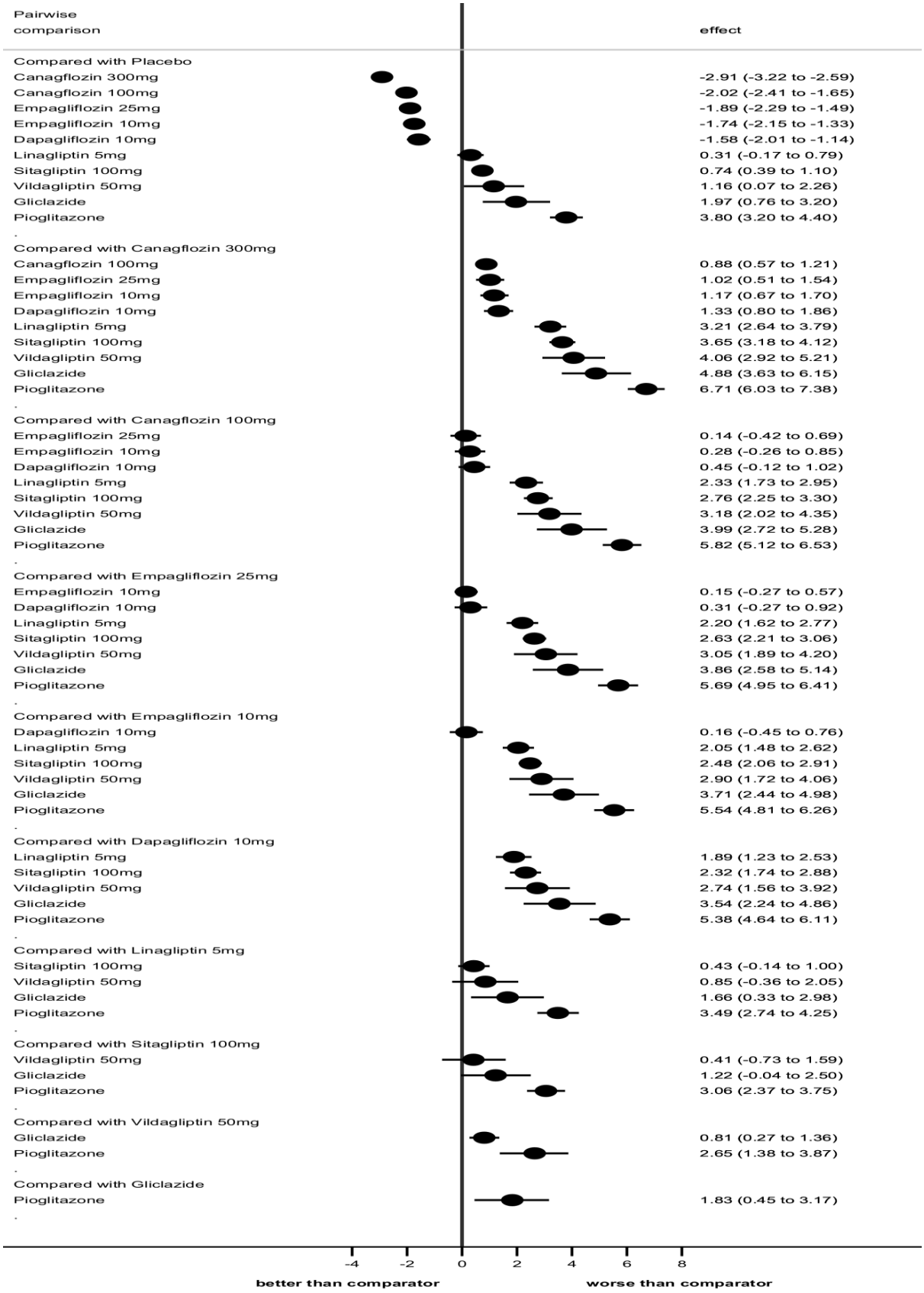

Figure 7 Pairwise comparisons for weight gain

Table 10 Pairwise comparisons of all different flozins for weight gain

Pairwise comparison	Mean difference (95% Credible Intervals)
Compared with Placebo	
Canagliflozin 300mg	-2.91 (-3.22 to -2.59)
Canagliflozin 100mg	-2.02 (-2.41 to -1.65)
Empagliflozin 25mg	-1.89 (-2.29 to -1.49)
Empagliflozin 10mg	-1.74 (-2.15 to -1.33)
Dapagliflozin 10mg	-1.58 (-2.01 to -1.14)
Linagliptin 5mg	0.31 (-0.17 to 0.79)
Sitagliptin 100mg	0.74 (0.39 to 1.10)
Vildagliptin 50mg	1.16 (0.07 to 2.26)
Gliclazide	1.97 (0.76 to 3.20)
Pioglitazone	3.80 (3.20 to 4.40)
Compared with Canagliflozin 300mg	
Canagliflozin 100mg	0.88 (0.57 to 1.21)
Empagliflozin 25mg	1.02 (0.51 to 1.54)
Empagliflozin 10mg	1.17 (0.67 to 1.70)
Dapagliflozin 10mg	1.33 (0.80 to 1.86)
Linagliptin 5mg	3.21 (2.64 to 3.79)
Sitagliptin 100mg	3.65 (3.18 to 4.12)
Vildagliptin 50mg	4.06 (2.92 to 5.21)
Gliclazide	4.88 (3.63 to 6.15)
Pioglitazone	6.71 (6.03 to 7.38)
Compared with Canagliflozin 100mg	
Empagliflozin 25mg	0.14 (-0.42 to 0.69)
Empagliflozin 10mg	0.28 (-0.26 to 0.85)
Dapagliflozin 10mg	0.45 (-0.12 to 1.02)
Linagliptin 5mg	2.33 (1.73 to 2.95)
Sitagliptin 100mg	2.76 (2.25 to 3.30)
Vildagliptin 50mg	3.18 (2.02 to 4.35)
Gliclazide	3.99 (2.72 to 5.28)
Pioglitazone	5.82 (5.12 to 6.53)
Compared with Empagliflozin 25mg	
Empagliflozin 10mg	0.15 (-0.27 to 0.57)
Dapagliflozin 10mg	0.31 (-0.27 to 0.92)
Linagliptin 5mg	2.20 (1.62 to 2.77)
Sitagliptin 100mg	2.63 (2.21 to 3.06)
Vildagliptin 50mg	3.05 (1.89 to 4.20)
Gliclazide	3.86 (2.58 to 5.14)
Pioglitazone	5.69 (4.95 to 6.41)
Compared with Empagliflozin 10mg	
Dapagliflozin 10mg	0.16 (-0.45 to 0.76)
Linagliptin 5mg	2.05 (1.48 to 2.62)
Sitagliptin 100mg	2.48 (2.06 to 2.91)
Vildagliptin 50mg	2.90 (1.72 to 4.06)

Pairwise comparison	**Mean difference (95% Credible Intervals)**
Gliclazide	3.71 (2.44 to 4.98)
Pioglitazone	5.54 (4.81 to 6.26)
Compared with Dapagliflozin 10mg	
Linagliptin 5mg	1.89 (1.23 to 2.53)
Sitagliptin 100mg	2.32 (1.74 to 2.88)
Vildagliptin 50mg	2.74 (1.56 to 3.92)
Gliclazide	3.54 (2.24 to 4.86)
Pioglitazone	5.38 (4.64 to 6.11)
Compared with Linagliptin 5mg	
Sitagliptin 100mg	0.43 (-0.14 to 1.00)
Vildagliptin 50mg	0.85 (-0.36 to 2.05)
Gliclazide	1.66 (0.33 to 2.98)
Pioglitazone	3.49 (2.74 to 4.25)
Compared with Sitagliptin 100mg	
Vildagliptin 50mg	0.41 (-0.73 to 1.59)
Gliclazide	1.22 (-0.04 to 2.50)
Pioglitazone	3.06 (2.37 to 3.75)
Compared with Vildagliptin 50mg	
Gliclazide	0.81 (0.27 to 1.36)
Pioglitazone	2.65 (1.38 to 3.87)
Compared with Gliclazide	
Pioglitazone	1.83 (0.45 to 3.17)

Systolic blood pressure

Networks of eligible comparisons for the systolic blood pressure are shown in Figure 8, showing predominantly pairwise comparisons of drugs with placebo. There were seven comparisons.

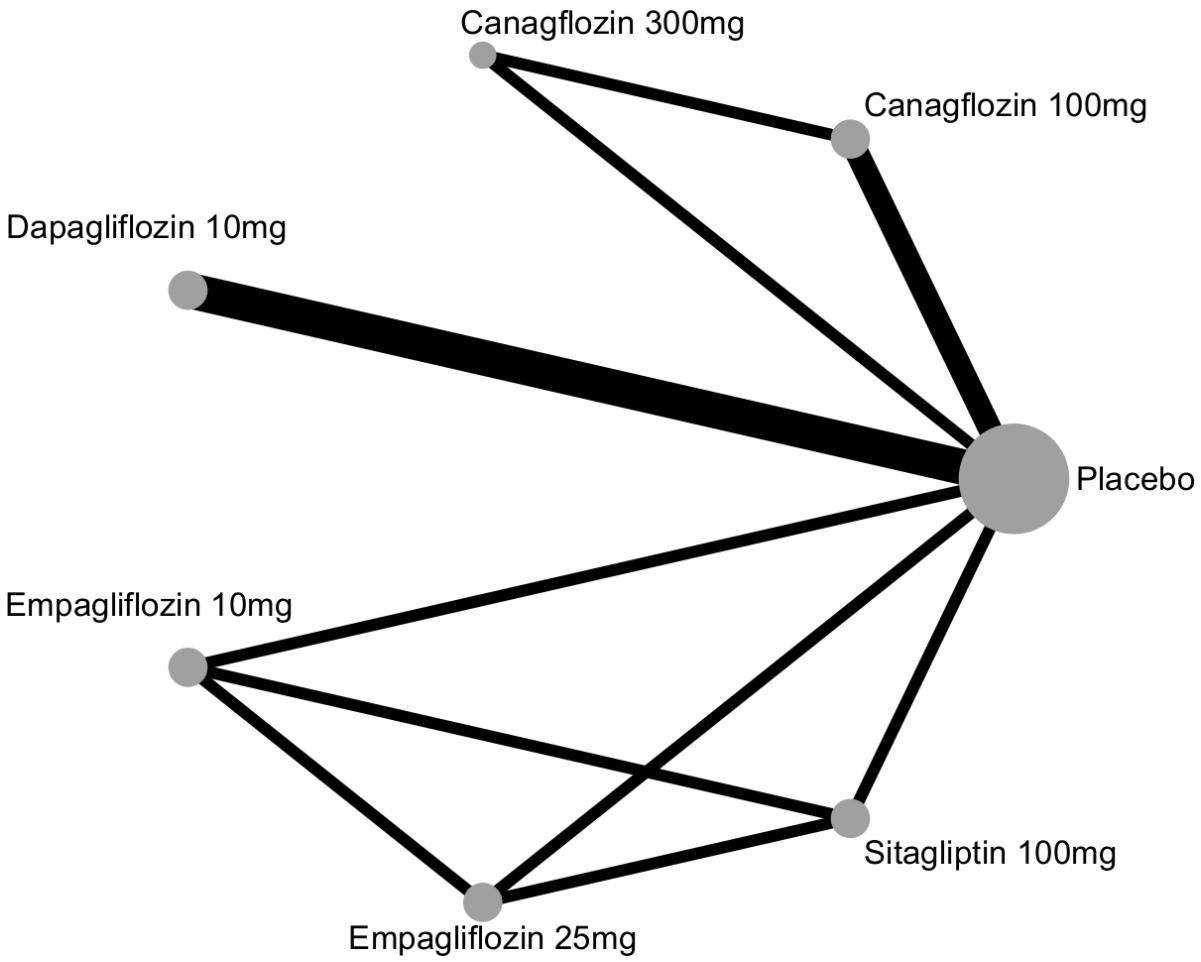

Figure 8 Network plot – systolic blood pressure

Figure 9 and Table 11 displays a caterpillar plot of the mean difference (MD) and 95% credible intervals (CrI) for all comparisons for mean change in systolic blood pressure from baseline. Canagliflozin 100mg, empagliflozin 25mg, dapagliflozin 10mg and empagliflozin 10mg were significantly effective in reducing mean change in systolic blood pressure from baseline compared to placebo and sitagliptin 100mg. Canagliflozin 100mg gave the largest reduction in mean change in systolic blood pressure from baseline compared with placebo (-4.22 mmHG). The between study variance was small suggesting no heterogeneity, but the credible intervals were wide which reflects the small number of studies available for pairwise comparisons. Analyses based on direct versus indirect comparisons showed no evidence of inconsistency between direct and indirect evidence in the network for systolic blood pressure.

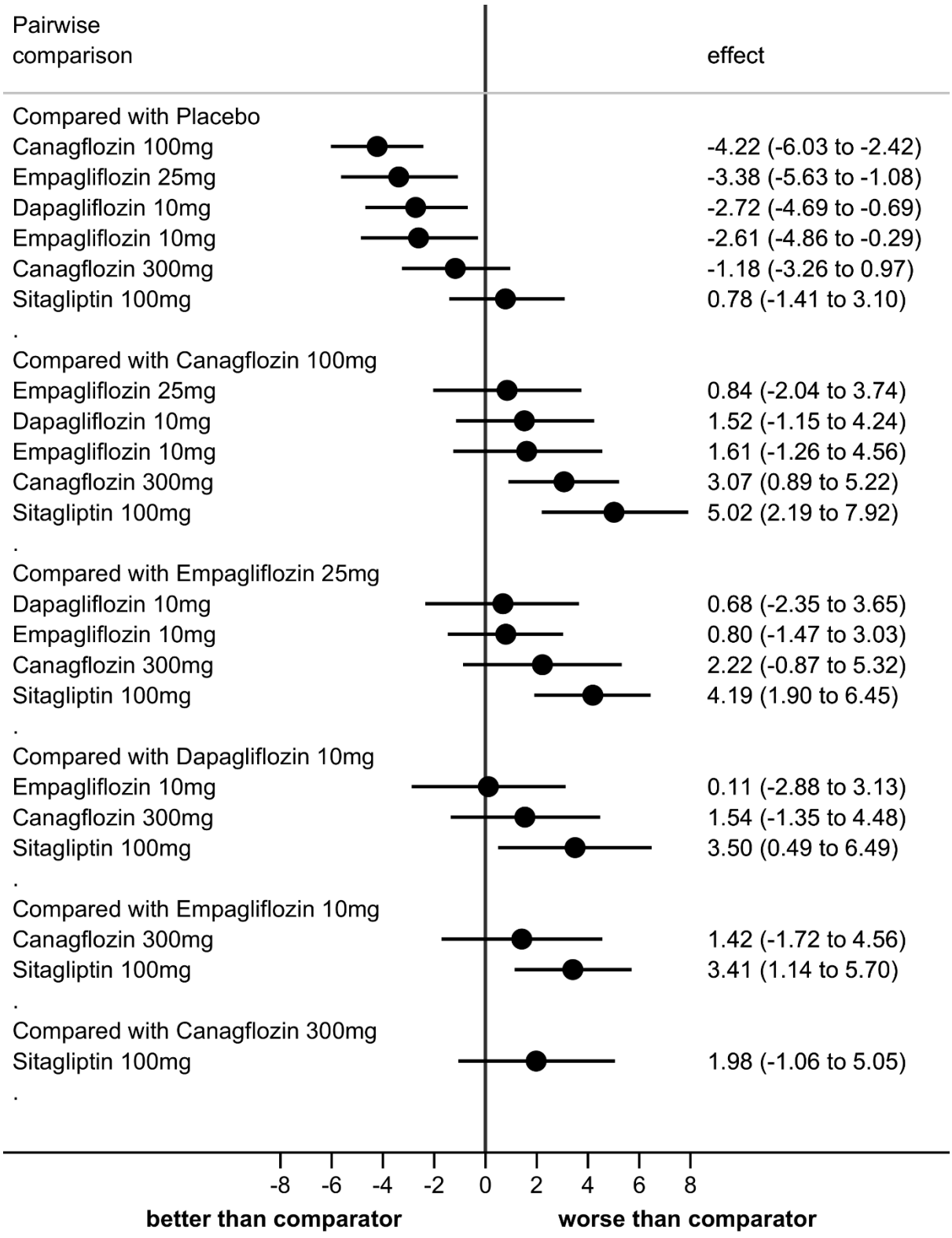

Figure 9 Pairwise comparisons for systolic blood pressure

Table 11 Pairwise comparisons for systolic blood pressure

Pairwise comparison	Mean difference (95% Credible Intervals)
Compared with Placebo	
Canagflozin 100mg	-4.22 (-6.03 to -2.42)
Empagliflozin 25mg	-3.38 (-5.63 to -1.08)
Dapagliflozin 10mg	-2.72 (-4.69 to -0.69)
Empagliflozin 10mg	-2.61 (-4.86 to -0.29)
Canagflozin 300mg	-1.18 (-3.26 to 0.97)
Sitagliptin 100mg	0.78 (-1.41 to 3.10)
Compared with Canagflozin 100mg	
Empagliflozin 25mg	0.84 (-2.04 to 3.74)
Dapagliflozin 10mg	1.52 (-1.15 to 4.24)
Empagliflozin 10mg	1.61 (-1.26 to 4.56)
Canagflozin 300mg	3.07 (0.89 to 5.22)
Sitagliptin 100mg	5.02 (2.19 to 7.92)
Compared with Empagliflozin 25mg	
Dapagliflozin 10mg	0.68 (-2.35 to 3.65)
Empagliflozin 10mg	0.80 (-1.47 to 3.03)
Canagflozin 300mg	2.22 (-0.87 to 5.32)
Sitagliptin 100mg	4.19 (1.90 to 6.45)
Compared with Dapagliflozin 10mg	
Empagliflozin 10mg	0.11 (-2.88 to 3.13)
Canagflozin 300mg	1.54 (-1.35 to 4.48)
Sitagliptin 100mg	3.50 (0.49 to 6.49)
Compared with Empagliflozin 10mg	
Canagflozin 300mg	1.42 (-1.72 to 4.56)
Sitagliptin 100mg	3.41 (1.14 to 5.70)
Compared with Canagflozin 300mg	
Sitagliptin 100mg	1.98 (-1.06 to 5.05)

One question was whether canagliflozin is more potent than other SGLT-2 inhibitors, due to its dual effect on SGLT-2 and SGLT-1 receptors. In monotherapy, both doses of canagliflozin lowered HbA1c slightly more than both doses of empagliflozin, which does not have a significant effect on SGLT-1 receptors. Nor does canagliflozin 100mg. This suggests that the SGLT-1 effect does not explain all the differences in HbA1c results. It may explain some of the difference between the two doses of canagliflozin, or it may not be clinically significant.

However, irrespective of the mechanism, one finding is that canagliflozin 300mg does have a greater effect on HbA1c than dapagliflozin and empagliflozin. Indeed, the 100mg dose also has a clinically significantly greater reduction in HbA1c than dapagliflozin 10mg (but see caveats to follow).

Table 12 compares the effects and adverse effects of the two doses of canagliflozin, with effects taken from our NMA and AEs from the published studies. Effects are compared to placebo. However, we do not know whether the reduction seen with canagliflozin 300mg in the trials would be as great in patients who responded insufficiently to the 100mg dose.

Table 12 Effects of canagliflozin dosages

	Canagliflozin 100	Canagliflozin 300mg	difference
HbA1c reduction	0.95%	1.19%	0.26%
Weight reduction	2.02kg	2.91kg	0.89kg
SBP reduction	4.2mmHg	1.2 mmHg	3 mmHg
UTIs by 12 months	8.2%	7.1%	No sig diff
GTIs by 12 months	9.2%	9.1%	
Volume depletion AEs	1.5%	2.0%	
Diuresis AEs	4.6%	7.6%	
Reported hypos by 12 months	5.1%	3.6%	Placebo rate 2.6%

If in patients in whom an SGLT2 inhibitor is considered the appropriate choice, it is considered worth trying canagliflozin 300 mg if the 100mg dose does not have enough effect, it would be logical to also try canagliflozin 300mg if dapagliflozin or empagliflozin are insufficiently effective. The licence implies that they would have to switch to canagliflozin 100mg first, if only briefly. However the same caveat would apply – the HbA1c reduction seen with canagliflozin 300mg might be less amongst patients who have not responded sufficiently to starting doses.

Table 13 shows that the differences in effects of the two empagliflozin doses are slight, using figures from the Roden and Lewin trials.[78-80]

Table 13 Effects of empagliflozin dosages

	Empagliflozin 10mg		Empagliflozin 25mg	difference
HbA1c reduction	0.66 and 0.83		0.78 and 0.95	0.12
Weight reduction	2.2 and 2.3		2.4 and 2.5	0.2kg
SBP reduction	2.1mm HG		3.7	1.6
UTIs by 12 months	16.3%		10.4%	5.9% in favour of 25mg
GTIs by 12 months	5.2%		4.4%	0.8%

Again, a caveat is required. Those who do not respond to empagliflozin 10mg may not achieve as great a reduction in HbA1c after increasing to 25mg daily, as in the table above. The differences are in any case, mostly not clinically meaningful.

In the NMA reported here, dapagliflozin reduced HbA1c significantly less than canagliflozin 100mg, but it should be noted that the Kaku 2014 trial[77] of dapagliflozin recruited patients with mean baseline HbA1c of 7.5%**,** whereas most trials had baseline HbA1c of around 8%.To summarise, the placebo adjusted HbA1c reductions in the trials at 24-26 weeks were, for the starting dosages;

Canagliflozin 100mg

CANTATA[72] 0.91%

Inagaki[73] 1.03%

Dapagliflozin 10mg

Ferrannini[74, 75] 0.66%

Ji[76] 0.82%

Kaku[77] 0.39%

Empagliflozin

Roden[79, 80] 10mg 0.74%

Hence the Kaku trial, while qualifying for our NMA based on the baseline HbA1c of 7.5%, will be reducing the mean effect of dapagliflozin.
When interpreting weight changes, the baseline BMIs need to be considered. The trials in China and Japan recruited people with BMIs in the 25-26 range, whereas the European trials had mean BMIs ranging from 28 to almost 34. The pattern of type 2 diabetes differs in East Asians, with lower BMI and a more insulin-secretory defect.[162] This does not apply to South Asians (Indian subcontinent) in whom insulin-resistance is more important.

Another factor to be considered in interpretation is that in the dapagliflozin trials, HbA1c fell in the placebo groups, by 0.29% and 0.23% in the Ji and Ferrannini trials. In the Ferranni trial, weight fell significantly, by 2.2kg. In the placebo groups in the canagliflozin trials, HbA1c rose by 0.29% (Inagaki) and 0.14% (Stenlof CANTATA-M). Ferranini and colleagues[74] (and the AstraZeneca submission, which talks of a "motivated placebo group" on page 58) suggested that the reduction in HbA1c in the placebo group might have been due to improved adherence to lifestyle advice in that group, but since the placebo tablets matched the dapagliflozin ones, this seems unlikely.

Problems with evidence and effect sizes for modelling.

This review has encountered a number of problems.

Many trials provided data on only some of the variables which are used in the UKPDS Outcomes model. For example, SBP changes were often not reported. This applied more to older trials of comparators than to the more recent trials of the SGLT2 inhibitors.

Some trials provided no data with which to calculate TC:HDL ratio. However a more important problem is that when TC levels were reported, they were often high, giving quite high TC:HDL-C ratios. It is likely that greater use of statins renders such data obsolete. For our modelling, we will assume that all GPs and diabetologists follow NICE guidance and are using atorvastatin 20mg for primary prevention in all people with type 2 diabetes. This will produce a TC:HDL ratio of about 3.0.

Another problem is with effect sizes after intensifications. For example, there are reviews of the effects on HbA1c and weight of sulfonylureas when added to monotherapy, but the bulk of evidence is addition to metformin monotherapy. The weight gain after adding gliclazide to a SGLT2 inhibitor may be different – it may only restore weight to the baseline before weight loss on the flozin. And the weight gain after adding gliclazide to pioglitazone may be less because pioglitazone itself causes weight gain.

In passing, it is worth noting that the weight gains in trials may be greater than in routine primary care. De Fine Olivarius and colleagues[163] reported that 330 patients did not gain weight after starting sulfonylureas. They make the point that most patients with type 2 diabetes are treated in primary care and are seldom recruited to trials. And that trials may therefore not be generalizable to all patients.

As regards reductions in adding sulfonylurea to monotherapy, some reviews report that adding a sulfonylurea to metformin results in a reduction in HbA1c of around 1%. However the size of the reduction will depend on the HbA1c level on metformin alone. Genuth quotes a reduction of 1% from a baseline of 8.3%.[164] This may be a bigger reduction than would be seen in people who have just crept over the NICE switching threshold of 7.5%.

In the same review, Genuth reports that pioglitazone added to metformin reduces HbA1c by 1.0%, and a DPP4 inhibitor does so by 0.7%.

Hirst et al produced a good quality systematic review and meta-analysis in which they examined reductions in HbA1c after starting sulfonylureas in dual therapy.[165] Sulfonylureas (glibenclamide, glipizide and glimepiride) reduced HbA1c by 0.95% on average but with considerable heterogeneity – reductions ranged from 0.47% to1.3%. They found little variation in HbA1c reductions by baseline HbA1c but most of those baselines were well above 8%, ranging from 7.5% to 9.5%. The only trial with baseline HbA1c under 8.4%, had starting HbA1c of 7.5%, and that was the trial by Feinglos and colleagues[166] which showed a reduction of only 0.47%. This trial is closest to what we would expect in care as recommended by the NICE guideline, and with baseline HbA1c of 7.5%, the reduction in HbA1c of 0.47% would be sufficient to improve HbA1c to around 7.0% and would be seen as a reasonable result.

One problem with the review by Hirst et al was that most trials were short term. A very useful observational study by Cook and colleagues[167] used data on 2,220 patients from the UK General Practice Research Database (GPRD) to study glycaemic control over time after a sulfonylurea was added to metformin, because of poor glycaemic control, with median HbA1c 8.8%. There was a prompt reduction to median of 7.3% after six months of sulfonylurea, but thereafter, HbA1c started rising again, by 0.32% between months 6 and 12. Half the patients had HbA1c of 8.0% or over by one year of starting sulfonylureas.

Cook and colleagues also noted that intensification of treatment was often delayed till HbA1c is over 9%. However their data were from 1998 to 2004 and may no longer apply. Neverthless the large drops often reported after sulfonylureas are started may be because of very poor control, and we should not expect such large reductions in HbA1c in carefully monitored patients who have only recently gone above the NICE switching threshold of 7.5%.

In a trial comparing dapagliflozin with glipizide as add-ons to metformin, and with baseline HbA1c of about 7.7%, the reductions in HbA1c by week 52 were 0.50% on dapagliflozin and 0.48% on glipizide.[168]

The durability issue with sulfonylureas has been reported by several studies, of which the best known may be the ADOPT trial[169] in which time to monotherapy failure was longer with rosiglitazone and metformin than with glibenclamide, with 34% of the glibenclamide patients needing additional treatment by 5 years compared to only 15% of those on rosiglitazone.

Del Prato and colleagues[168] looked at duration of effect of dapagliflozin and glipizide in dual therapy when added to metformin. HbA1c fell more rapidly, and further on glipizide, but then rose again more quickly. So at about 12 weeks, the falls were (from graph) about 0.8% on glipizide and 0.5% on

dapagliflozin, but by 52 weeks the curves had met at reductions of about 0.5%, though about 20% of patients were absent by that time point. After 52 weeks, HbA1c rose on both drugs, but more on glipizide, with a gap of 0.30% by 208 months. However the numbers by that time-point were low – 20% of the dapagliflozin group and 18% of the glipizide group. The reductions were due to patients starting rescue therapy after HbA1c rose. Rescue was mandatory once HbA1c reached 8.0% or more, and was at the investigators discretion between 7.0 and 8.0%. So similar proportions in each group had to move to rescue therapy, implying no difference in durability.

There is a 2015 abstract by Bacon et al[170] from Janssen comparing time until insulin is started between canagliflozin and dapagliflozin, when used in dual or triple therapy. It also used the ECHO-T2DM model. In triple therapy, the authors report insulin being started on average at 5.1 years with canagliflozin (starting with 100mg daily and increasing as required to 300 mg) compared to 3.3 years with dapagliflozin. Insulin was started when HbA1c exceeded 7.5%.

For the effects of adding sitagliptin we have two useful trials with HbA1c baseline 7.7 and 7.8% which reported reductions in HbA1c of 0.67% and 0.79% (Scott 2007, Nauck 2007) giving a mean of 0.73%.

A recent report from CADTH (Appendix of CADTH report)[171] concludes that pioglitazone added to monotherapy reduces HbA1c by 0.78%. It also gives the reduction with DPP4 inhibitors as a mean of 0.7% .

At intensification to triple therapy, one option would be to introduce a long-acting GLP-1 analogue. NICE has so far only approved exenatide LA for this purpose, but there are now other drugs in this group, including dulaglutide and albiglutide.

In the DURATION 1 trial[172], Drucker and colleagues compared exenatide LA with the short-acting twice daily form. Patients were on a mixture of baseline treatments with only 38% on dual therapy. However reductions in HbA1c were reported to be similar across baseline treatment groups. On exenatide LA, HbA1c fell by 1.9% from a baseline of 8.3%, with 60% of patients getting HbA1c under 6.5%. The advantages of using a GLP-1 analogue, compared to insulin, are the once weekly injection, weight loss (in DURATION 1 weight fell by 3.7kg on exenatide LA), a low risk of hypoglycaemia (there were no severe hypos in DURATION 1 and minor hypos were seen only in patients on sulfonylurea), and some reduction in SBP (4.7mmHg). Another advantage of adding a GLP-1 analogue to treatment with an SGLT2 inhibitor is that the latter increases plasma glucagon levels which would be suppressed by the former, though if triple therapy includes a sulfonylurea such as gliclazide, glucagon secretion may already be suppressed.[173]

Chapter 4. Clinical effectiveness aspects of the submissions from the manufacturers.

Three submissions were received, from;

- Janssen for canagliflozin
- AstraZeneca for dapagliflozin
- Boehringer Ingelheim for empagliflozin

The submissions had three main sections;

- A review of the evidence on clinical effectiveness and safety
- A network meta-analysis comparing SGLT2 inhibitors with comparators
- Cost-effectiveness analysis

Clinical effectiveness

As regards clinical effectiveness, the evidence provided by the manufacturers was very similar to that presented earlier in this report. The same trials were presented. The submissions were good quality and we have very few comments.

The Janssen submission included 52-week results from an extension to the CANTATA-M study[87], which we omitted because there was no comparison group. In brief, the 52-week data showed that the reductions in HbA1c were largely maintained (reductions on 100mg 0.91% at 26 weeks and 0.81% at 52 weeks; reductions on 300mg 1.16% at 26 weeks and 1.11% at 52 weeks). However a little more weight was lost by 52 weeks.

The Boehringer submission included data from a 76 week extension study which had been published in abstract form only.[79] Almost 40% of patients dropped out leading to extensive use of last observation carried forwards, which is not a reliable method because people do not drop out at random. It is likely that those who stayed in were doing better than those who dropped out.

The Boehringer submission make a useful point about adherence to therapy. This would apply not just to diabetes medications. People with diabetes tend to have co-morbidities such as hypertension and osteoarthritis (due to excess weight) and so may be on other medications for other conditions. Donnan and colleagues reported that the more medications were prescribed and the more complex the regiment, the poorer the compliance.[174]. Lilly now market a combination tablet with empagliflozin and linagliptin.

One omission from the AstraZeneca submission was any mention of cancer risk. The FDA were concerned about imbalance of breast, prostate and bladder cancer even though in none of these cases was the risk statistically significantly raised.[175] In the trials, there were 9 cases of bladder cancer amongst 5501 subjects in the dapagliflozin group versus one amongst 3516 in the placebo arms. Some of these cancers appeared too soon after the patients started dapagliflozin for credible causality and all but one of the patients had had microscopic haematuria, suggestive of bladder pathology, before starting the drug or within six months of doing so.[176] One hypothesis is that an increased UTI rate in patients on dapagliflozin leads to increased testing or urine and hence of detection of bladder tumours, but 7 of the 10 patients diagnosed with bladder cancer had not had UTIs.[176]

Breast cancer was observed in 9 patients (0.04% of female patients) in the dapagliflozin arms but in none of the placebo groups. However two cases were diagnosed within 6 weeks of starting dapagliflozin so were certainly not due to the drug.

There were 10 cases of prostate cancer in the dapagliflozin arms (0.34%) versus 3 in the placebo arms (0.16%).

Some cancers, albeit less common ones, were less common (though 95% CIs overlapped with no difference) in the dapagliflozin groups, and overall there was no difference in rates for all cancers.
It is difficult to explain the differences in bladder and breast cancer, but it seems unlikely that dapagliflozin is the cause.

Network meta-analyses

There were marked differences amongst the NMAs. For example, the AstraZeneca one included 7 trials of sulfonylureas, with five involving glibenclamide. The Janssen one included 9 trials of sulfonylureas, with 5 trials comparing glibenclamide with other sulfonylureas and two of glibenclamide against pioglitazone. Only one trial was in both NMAs.
The Boehringer NMA included 22 trials involving sulfonylureas: glibenclamide 7, glimepiride 6, gliclazide 6, glipizide 3 and tolbutamide one.
Of the 7 sulfonylurea trials in the AstraZeneca NMA, 4 were also in the Boehringer NMA. Of the 9 sulfonylurea trials in the Janssen NMA three were also in the Boehringer NMA. Only one trial was in all three of the manufacturers' NMAs.

AstraZeneca

The Astrazeneca NMA starts with a major assumption with which the Assessment Group disagrees, which is that the classes of drugs (sulfonylureas, thiazolidinediones, DPP4 inhibitors and SLT2

inhibitors) can be grouped. In the case of the thiazolidinediones (TZDs), this does not matter because all the trials cited include pioglitazone. However our view is that the sulfonylureas have different effects, and that gliclazide is the sulfonylurea of choice, as explained in chapter 1.

We also disagree with the assumption by AstraZeneca that when monotherapy fails, NPH insulin would be started. This seems strange when there is such a range of oral medications that can be tried. We note that a recommendation to introduce insulin as second drug was one option in the consensus statement by a group on behalf of the American Diabetes Association and the European Association for the Study of Diabetes in 2006.[177] However this consensus was strongly critised by a larger group of experts as being based more on opinion that evidence.[178]

One problem with the AstraZeneca NMA is the data reported in the forest plot (Figure 4.6) for the pooled sulfonylureas, which include glibenclamide, glimepride, glipizide and one gliclazide trial. The net effect size in HbA1c lowering is 0.12% which is unusually low. Two trials provide 85% of the weight in this meta-analysis, Rosenstock 2013[179] and Shihara 2011.[180] In the forest plot the Shihara trial, glimepiride is shown as reducing HbA1c by 0.10%, and in the Rosenstock trial glipizide is shown as increasing HbA1c by 0.03%. These results are not credible.

In the Rosenstock trial[179], about half the patients left the trial before conclusion, with 21.5% of the glipizide group doing so because they needed additional "rescue" treatment because of hyperglycaemia. About half the recruits had been on glucose-lowering drugs before entry, and had a 4-week washout period. However the primary analysis included the rescued patients and this is reflected in the one of the analyses, which reported a 0.09% reduction in HbA1c. (It is not clear where the rise of 0.03% in the AstraZeneca forest plot comes from.) The baseline HbA1c in the glipizide group was 7.45%, and 33% had baseline HbA1c of 7.0% or less. So a large reduction in HbA1c would not be expected. However if the rescue group is removed, those completing the trial had mean reduction in HbA1c of 0.31% (from text) or about 0.5% (from graph).

The Shihara 2011 trial[180] compared glimepiride and pioglitazone monotherapy in drug-naïve Japanese patients. Basline HbA1c was 7.8% in the glimepiride group and it fell to 6.8% by 6 months (from graph – reduction of 6.9% in text at 3 months). It is not clear where the 0.1% figure used in the AstraZeneca meta-analysis comes from, though we note that the HbA1c difference between glimepiride and pioglitazone at 3 months as 0.1%.

One other sulfonylurea trial in the forest plot is shown as having a very small reduction in HbA1c. This is Erem 2014[152], which was used in the Assessment Group NMA. The AstraZeneca forest plot reports a reduction in HbA1c of 0.14% compared to placebo. There was no placebo group in Erem

2014 which compared gliclazide with pioglitazone and metformin. The HbA1c was reduced from 8.26% at baseline in the gliclazide group to 6.92% at 6 months, so a more credible reduction against placebo might have been to use the 1.34% before and after figure.

Given that these Rosenstock and Shihara trials dominate the meta-analysis, the sulfonylurea section of it is not credible. It contains 8 trials but the others are smaller and carry less weight. Apart from the Erem trial, their HbA1c results in the other five are as expected from sulfonylureas, showing reductions ranging from 0.6% to 1.8%.

However, these problems may just affect the forest plot. In appendix 8.9, the reduction attributed to glipizide in the Rosenstock trial is 0.23%, still smaller than usual but more credible. The reduction stated in this table for glimepiride in the Shihara trial is 1.0%. In addition, the caterpillar figure 8.9 in the appendices looks reasonable and is followed by a reported difference for sulfonylureas versus placebo of 0.80% in Table 8.21.

Table 4.4 in the AstraZeneca NMA gives a reduction in HbA1c of 0.99% with sulfonylureas, compared to placebo. In the modelling a figure of -0.95% is used, which corresponds with both of the submitted AstraZeneca models and table 5.3 of their submission. So the forest plot figures are a minor mishap which does not affect the AZ modelling.

Review of statistical methods

Model type: The MS estimated both fixed- and random-effects meta-analyses for the continuous and count based outcome measures. It used the Deviance Information Criterion (DIC) to assess model fit, with at least a 3 point change signifying an improved model. Also, the MS compared the posterior distribution of between study standard deviations with the prior distributions to assess whether it was updated by the available evidence (i.e. the additional information had had an effect). Random-effects models were fitted first, as they were considered *a priori* as the appropriate model. Fixed–effects models were only selected if they significantly improved model fit as demonstrated by DIC and changes to the posterior distribution of between study standard deviations. Clinical and statistical heterogeneity were assessed through an evaluation of sources and the I^2 statistic for pairwise comparisons respectively. Heterogeneity was examined through a sensitivity analysis using meta-regression to adjust for the effects of baseline HbA_{1c}. Consistency was also assessed through a comparison of the direct and indirect evidence using pairwise meta-analyses of the active treatments versus placebo for the outcome of HbA_{1c} only. The overall modelling strategy used in the MS seemed appropriate.

Distributions & Priors: The MS undertook Bayesian Markov Chain Monte Carlo (MCMC) network meta-analyses for continuous and count based outcome measures. It specifies that vague priors were used for unknown parameters, however no details were provided as to the distributions or link functions used in the models. Vague priors are usually specified, however there are occasions when other priors should be assessed to establish the possible effects on the posterior estimates (e.g. binomial model with a logit link function or a rate model with log link function (where a uniform prior is used for the standard deviation) or where data are sparse and the model fails to converge (where vague gamma priors are used for precision)). No sensitivity analyses assessing the effects of different distributions, link functions or priors were presented. As the treatments considered in the network meta-analyses were assessed by class, this may be less of a concern. The MS reports that MCMC models were run using 3 chains starting from different values of the unknown parameters, used a burn in of ≥20,000 iterations, an update of ≥100,000 iterations and a parameter thin of 10. Convergence was assessed using history plots of the chains for the relevant parameters (overlapping histories indicating convergence) and a Monte Carlo error for each parameter (error of ≤5% of posterior standard deviation indicating convergence). No assessment is reported regarding the influence of autocorrelation. The approach taken in the MS to MCMC models appears appropriate.

Interventions: The MS performed network meta-analyses on classes of treatments (i.e. SGLT2s, DPP4s, SUs, TZDs), rather than comparing individual treatments. Such 'lumping' of evidence is a concern as regards the assumption of consistency, leading to heterogeneity, difficulties in interpreting results and potential conflict between the direct and indirect evidence. The MS states that the rationale for considering the treatments as a class was due to the limited evidence base for some treatments, that previous NICE clinical guidelines had indicated that they could be considered as a class and that heterogeneity among some individual studies in terms of study characteristics within a class of treatments meant that comparison of individual studies may be affected by a risk of bias. The MS should have considered a network meta-analysis of individual treatments as well as presenting one of class effects. This would have shown results similar to the Assessment Group NMA, where dapagliflozin has slightly less effect than empagliflozin 10mg and canagliflozin 100mg, the other starting doses. Although it is not clear which treatment was the reference treatment in the network meta-analyses, results are presented for comparisons of the treatment classes with both placebo and SGLT2 only.

Outcomes: Continuous outcomes of mean change from baseline in HbA_{1c}, weight and SBP (mean difference scale) and count based outcomes of proportion of patients experiencing hypoglycaemia (odds ratios) were used in the network meta-analysis. Although data for the continuous outcomes was for ITT population using LOCF, any missing data were based on estimates from the primary study. Data time points ranged from 18 to 30 weeks.

Participants: Comparison of the baseline characteristics of the 32 studies showed variability. Although the MS stated that the trials were generally similar in baseline characteristics, it identified that 9 RCTs were conducted only in Asian patients, 1 RCT had a higher mean age, 1 RCT had a higher mean baseline HbA_{1c}, 8 RCTs had higher mean baseline weights and that average duration of diabetes and baseline BMI varied. It should be noted that the included studies were conducted between 1994 and 2014 with study duration ranged from 18 to 102 weeks. Although the effects of baseline HbA_{1c} was assessed through meta-regression and those associated with the Asian only studies through exclusion of the studies in a sensitivity analysis, possible heterogeneity associated with the other factors was not considered further.

Evidence networks: The MS presents network diagrams of the decision space for the classes of treatment. It is not clear the number of RCTs linking each treatment class and subsequent Forrest plots are presented for comparisons with placebo only. It is difficult to judge whether sparse evidence networks or zero values were a concern, although the 'lumping' of evidence into treatment classes may well have overcome this issue. It is also unclear which treatment was used as the reference treatment.

Summary: The MS clearly specified the approach it had taken to the majority of the elements of its network meta-analyses. It lacked details concerning the prior distributions and link functions used, its assessment of autocorrelation in MCMC models and sensitivity analyses concerning the elements of the models themselves (e.g. prior distributions, link functions and priors for parameters). Although it assessed some possible causes of heterogeneity, others were not considered (e.g. participant characteristics, length of study follow-up). It appropriately examined consistency of the outcomes from the network meta-analyses. The MS identified several limitations underlying its analysis, including high placebo effects associated with the assessment of body weight in a dapagliflozin monotherapy study and a study focusing on Asian patients, a lack of evidence on specific patient groups (i.e. metformin intolerant), limited duration of follow-up, different definitions of hypoglycaemia and inconsistent reporting of safety outcomes. However, the key limitation that affects the network meta-analysis is the lack of evidence on individual treatments. As a result, the MS 'lumps' together the evidence by treatment class. This can cause concerns with regards to the assumption of consistency, lead to heterogeneity, difficulties in interpreting results and potential conflict between the direct and indirect evidence.

Boehringer Ingelheim

The Boehringer NMA is shaded as confidential. It was very complex and included 37 studies, including some which the Assessment Group rejected for our NMA. All the sulfonylureas trials were

pooled into one node, which we think is undesirable given the mix of drugs from tolbutamide to gliclazide. The NMA includes both the Saleem 2011 and Jibran 2006 trials with their striking similarities.

Review of statistical methods for NMA for Empagliflozin (Jardiance) – Boehringer Ingelheim

Model type: The MS correctly used both fixed- and random- effects meta-analyses to assess the continuous and count based outcome variables. It also used hierarchical Bayesian regression modelling for analysing the continuous outcomes, assumed to be due to the different ways in which the continuous outcomes are reported (e.g. change from baseline per treatment (arm level data) and change from baseline compared to a reference treatment (study level data)), although this was not clearly stated. Meta-regression models were fitted to explore the influence of possible effect modifiers in terms of explaining any heterogeneity, specifically baseline values of continuous variables at the trial level. These effect modifiers were centred on the average baseline value and any effects were assumed to affect all treatments linearly. Decisions regarding the fit of the different models (i.e. which was the most appropriate) were made using both Deviance Information Criterion (DIC) (differences of between 3 to 5 points being statistically significant) and the residual deviance (comparison with the number of data points with a ratio of 1 considered a good model). A parsimonious approach appeared to be adopted. Fixed-effects models were fitted initially with random-effects and/or meta-regression models adopted only if they reduced the DIC significantly and suggested a good model through the residual deviance. Heterogeneity and consistency were not specifically assessed, although heterogeneity was examined through sensitivity analyses. The overall modelling strategy used in the MS seemed appropriate.

Distributions & Priors: The MS produced network meta-analyses for both continuous and count based outcome measures. It appropriately made the assumption that the continuous outcomes should be normally distributed and used an identity link function. Also, that the outcomes measuring counts should use a binomial model with a logit link function. The MS stated that vague priors were used for random-effects models. Vague priors tend to be recommended for trial specific baselines (μ_i), trial specific treatment effects (d_{1k}) and for the between-study variance (where appropriate), unless the model is either binomial with a logit link function or a rate model with log link function (where a uniform prior is used for the standard deviation) or where data are sparse and the model fails to converge (where vague gamma priors are used for precision). Although the MS used vague priors for both the count based outcome measures and when there were sparse networks, it undertook some sensitivity analyses. These focused on examining different prior distributions when the random-effects models failed to converge, although limited information is provided on the specific distributions used. The MS also provided limited information concerning model convergence such as burn-in simulations, iterations used for the modelling or the diagnostic statistics and plots. It only identified the number of iterations on the occasions that model convergence was not achieved.

Interventions: The MS appropriately selected placebo as the reference treatment for all the network meta-analyses undertaken, presenting all comparisons of treatments against placebo. No comparisons were made between the different active treatments and it is assumed that the evidence network was insufficient to support such analyses.

Outcome measures: Continuous outcome measures included changes in HbA_{1c} and weight from baseline. These outcomes were reported in different forms as change from baseline per treatment, change from baseline compared with a reference treatment and as baseline and endpoints. To ensure comparability the outcome of mean change from baseline was calculated for each trial, using specific steps to derive the outcome and common measures of variability around the point estimates. The steps taken in the MS appeared appropriate. Count based outcomes included measures of the incidence of hypoglycaemia, UTI and GTI. The outcome measures were reported as being assessed at 24 weeks and 52 weeks, however as noted in the MS the 24 week time-point varied by 6 weeks and the 52 week time-point by 4 weeks. Such heterogeneity may have affected the outcomes reported and these differences were not encompassed in any sensitivity analysis.

Participants: The systematic review that underlies the network meta-analysis included 5 studies that had patients who were elderly and/or had a renal impairment. These studies differed from the other included studies and may have had some influence on the outcomes of the network meta-analyses, although their effects were not considered in sensitivity analyses.

Evidence network: The MS identified concerns about sparsely populated networks and zero events, both of which were evident in the current network meta-analyses. Where trial evidence is limited, the posterior distribution of the standard deviation will be poorly identified and likely to include extreme values (i.e. unexpectedly wide credible intervals). It is also possible that models, particularly random-effects models, will not converge. The MS identified that the networks may be sparse and, where random-effects models did not converge, estimated fixed-effects models only. Inevitably fixed-effects models assume that all studies are estimating exactly the same underlying effect size, which may be unrealistic. As such, the sparse evidence network and the fixed-effects models may be affected by uncertainty around the point estimate and credible intervals. Given the sparse network, it was likely that there may be zero values in the categorical variables. Although the Bayesian Markov Chain Monte Carlo network meta-analyses can accommodate zero values, if the data are too sparse and/or several trials have zero values, then the model may fail to converge or produce high standard deviations. The MS correctly employed a continuity correction, although it did not specify the actual correction used.

Summary: Although the MS undertook many of the steps in conducting an appropriate network meta-analysis, its reporting was not completely transparent. It lacked some clarity as regards: the use of hierarchical regression models; the rationale for not exploring other underlying study characteristics (i.e. participants and outcomes) as causes of heterogeneity; the sensitivity analyses around prior distributions and priors; and, the reasoning behind only presenting comparative results against placebo rather than the active treatments. Also, the

analysis did not present information concerning the convergence of the different models. However, the key issue underlying the network meta-analysis is the sparsity of the evidence in the network itself. Although numerous different active treatment options are included, limited evidence is available for many of the comparisons made. The lack of an evidence base prevented many of the random-effects and meta-regression models from converging, limiting the analyses to the less conservative fixed-effects models. As such, there remains uncertainty around the outcomes of the network meta-analyses and the variance in the treatment effects.

Janssen

The Janssen NMA included 40 studies, including some which the AG did not think relevant, such as dapagliflozin 5mg. It included four DPP4 inhibitors and 4 sulfonylureas. It did not include repaglinide but this was included in a sensitivity analysis.

Review of statistical methods

A Bayesian hierarchical model was used for the network meta-analysis. Although not explicitly stated, it is evident that both fixed-effects and random-effects models were estimated. No analysis was undertaken of possible effect modifiers using meta-regression, instead sensitivity analyses excluded trials with different characteristics. The MS used Deviance Information Criterion (DIC) to assess the goodness of fit of the models, selecting the model with the lowest DIC as the most appropriate. A threshold of 3 points on the DIC is used to judge significant change. Where a random-effects model was selected as the base case analysis, a fixed-effects model was estimated in a sensitivity analysis. Given other statements in the MS, it is assumed that random-effects models may have also been estimated as a sensitivity analysis when a fixed-effects model was the base case. Where trials had multiple arms, the MS correctly made adjustments to the statistical approach to account for the correlation between treatment effects from the same trials. The approach taken was based on a conditional distribution formulation of the multivariate normal distribution. The influence of heterogeneity was assessed through an analysis of the direct pairwise comparison of treatments using Cochran's Q test ($p=0.1$), I^2 statistic (threshold >50%), comparisons using forest plots and comparison of the characteristics of the trials. Consistency of the direct and indirect evidence was compared using the difference in the respective point estimates and their p values, testing whether they differed statistically significantly from zero. As well as producing point estimates (and credible intervals) of the mean difference and odds ratios, the MS ranked the probability of the different treatments as being the most effective based on the Surface Under the Cumulative Ranking (SUCRA). SUCRA produces probabilities that range from 100%, showing the treatment ranks first, to 0%, which shows it ranks last. These rankings formed the basis of the comparison of the different treatments, along with an assessment of the probability that canagliflozin performed better than the other treatments. The comparative ranks were interpreted on the basis that a treatment with >70% was judged the best,

between 30% and 70% no difference between treatments, and <30% the alternative treatment was considered best. Although the analysis lacked an assessment of heterogeneity through meta-regression, the overall modelling strategy used in the MS appeared appropriate.

For the network meta-analyses of continuous outcomes, the MS correctly assumed that a Normal distribution and identity link function should be used. Similarly, for binary outcomes, the MS appropriately selected a binomial distribution and logit link function. The MS states that it uses non-informative priors for unknown parameters. Priors for the Normal distributions for treatment effects $(0, 10^4)$ and the uniform distributions for between-trial standard deviations (binary outcomes range (0,2); continuous outcomes range based on outcome scale with assessment of posterior distribution to select prior distribution) were specified. While the priors are considered suitable, issues concerning sparse data may require other priors to be considered, particularly if the model fails to converge. Although not specifically stated in the MS, this issue appears to have considered as a sensitivity analysis on the prior distributions for between-trial precision uses a gamma distribution (0.001, 0.001) for the random-effects model. No other prior distributions appear to have been examined in sensitivity analyses.

The network meta-analyses used Markov Chain Monte Carlo simulation in WinBUGS running 3 chains with different starting values. It assessed convergence through history and Gelman-Rubin plots, although these are not presented. Fixed-effects network meta-analyses used a burn-in of 20,000 iterations, which were discarded, and a further 20,000 iterations to monitor the parameters. Random-effects network meta-analyses used a burn-in of 100,000 iterations (which were discarded) and monitored parameters for a further 100,000 iterations. Where convergence was not achieved, iterations were increased (numbers of iterations used not stated).

Treatments included in the network meta-analysis had to be in common use in the UK. The network meta-analyses assessed both treatment- and dose-specific outcomes in the classes of SGLT-2, thiazolidinedione and DPP-4, with those for sulfonylurea pooled to reflect dose adjustments on a per-patient basis. The MS appropriately selected placebo as the reference treatment for all of the evidence network diagrams, however all results were compared with canagliflozin. No comparisons were made between the other active treatments, which may reflect the sparse nature of the evidence.

Continuous outcomes measured the change from baseline in each treatment arm for $HbA_{1c,}$ FPG, weight, BMI and SBP. If data were missing, values were estimated as the difference between the final value and the value at baseline, with the variance calculated using an approach recommended by the NICE DSU. Sensitivity analyses were conducted on the approach to estimating the variance of the mean change (i.e. within-patient correlation varied from base case of 0.5 to 0.7). Binary outcomes used the number of events and total patients in each treatment arms for calculating the proportion of patients reaching HbA_{1c} <7%, proportion of patients with ≥ 1 hypoglycaemic event and proportion of patients reaching HbA_{1c} <6.5%. Handling of missing data from binary outcomes is not discussed. Outcomes were assessed at 26 weeks ± 4 weeks with a sensitivity analysis of 26 weeks ± 10 weeks.

This variation may have led to heterogeneity in the outcomes reported, although the MS states that these were based on expert clinical opinion. Additional sensitivity analyses were also conducted including studies reporting outcomes from 16 to 21 weeks and/or 31 to 36 weeks.

There appeared to be some heterogeneity in the participant characteristics. Patients in the included studies ranged in age from 48 to 72 years; the proportion of males from 11% to 80%; the proportion who were Caucasian/white from 6% to 80%; and, in duration of their diabetes 1.1 years to 13 years. In many instances studies did not report the characteristics of their participant populations. As a result, heterogeneity was identified in the network meta-analyses and sensitivity analyses were undertaken.

The MS presented evidence networks for the different comparisons undertaken. It was evident from the network diagrams that some of the treatments were in parts of the network that were unconnected and these were excluded from the analyses. Other parts of the evidence networks were sparsely populated with only 1 trial. Such limited data may have resulted in posterior distributions of the standard deviations that included extreme values and the possibility of non-convergence of the model. This increased the uncertainty around the outcome of the network meta-analyses. Trials including binary outcomes were affected by zero events. Where this occurred, the MS appropriately used a continuity correction (0.5 added to all cells counts of studies with at least one arm with a zero). Trials with no event in any arm or that were considered to affect convergence (basis of exclusion not stated) were excluded from the analysis.

The trials included in the evidence network were assessed through sensitivity analyses that excluded trials considered a source of heterogeneity or inconsistency, identified as lower quality (not double blind), where it was unclear if it assessed monotherapies, assessed a single ethnic group, or published in a non-peer reviewed journal or as part of a regulatory process. Further sensitivity analyses were conducted that included an unpublished trial (DIA3011) assessing canagliflozin 100mg and canagliflozin 300mg and repaglinide trials that included metformin and sulfonylurea.

The MS clearly outlined the key aspects of the network meta-analyses. It estimated fixed- and random-effects Bayesian hierarchical models using MCMC simulation in WinBUGS, evaluating the fit of the models through DIC. Prior distributions and values were correctly assumed, with an alternative assessed through sensitivity analysis to examine the effects of sparse data. The MS discussed the simulation process in terms of chains run, iterations for burn-in and monitoring parameters, and the process for assessing convergence. The analysis also assessed heterogeneity, inconsistency between direct and indirect meta-analyses and made adjustments for multiple treatment arms. The network meta-analyses presented point estimates and credible intervals for outcomes and ranked treatments as to which performed the best. Treatments were compared to canagliflozin, with no comparisons of the other active treatments. Missing data were appropriately estimated for continuous measures, however there is no discussion of missing data for binary outcomes. Outcomes were assessed at 26 weeks ± 4 weeks with a sensitivity analysis at 26 weeks ± 10 weeks, which may have resulted in some heterogeneity. It was evident that the network was sparsely populated in certain

comparisons and that there were zero values for binary outcomes. Although the zero values were handled appropriately through a continuity correction, the effects of sparse data for the continuous variables may lead to increased uncertainty around the estimates. The MS produced a range of sensitivity analyses to explore the robustness of the models. Overall the methods used in the network meta-analyses appeared appropriate and identified most limitations in the evidence. The sparse evidence base may influence the outcomes produced.

Comments

Despite the different approaches and inclusions, some findings from the different meta-analyses were similar. For example, the differences in effect sizes of HbA1c of canagliflozin 100mg and dapagliflozin 10mg were reported as 0.33% (Janssen), 0.365% (Boehringer) and 0.36% (Assessment group).

There appears to be a systematic difference between results of the Assessment Group NMA and the Boehringer NMA, with effects on HbA1c being higher in the latter one, with the AG results being closer to the trial results. The Janssen figures are similar to the AG ones. This is shown in Table 14.

Table 14 Reductions in HbA1c at 24 weeks compared to placebo

	Reduction in HbA1c %			
Drug	Boehringer NMA	Janssen*	Assessment group	Trial
Dapaglifozin 10mg	[redacted]	0.64	0.59	0.66 (Ferrannini[74])
Empagliflozin 10mg	[redacted]	0.74	0.76	0.74 (Roden[79])
Empagliflozin 25mg	[redacted]	0.85	0.88	0.86 (Roden[79])
Canagliflozin 100mg	[redacted]	0.97	0.95	0.91 (CANTATA-M[72])
Canagliflozin 300mg	[redacted]	1.20	1.19	1.17 (CANTATA-M[72])

Janssen figures derived from their Figure 8.
However the relative differences between drugs are similar, and those are what matter in the modelling.

Chapter 5 Cost effectiveness

Approach to modelling

There are several issues to consider in choosing sequences, including;

- The assumption that in most patients, the condition will progress, requiring intensification of therapy by adding a second glucose-lowering agent – dual therapy – and later one or more others
- Whether the second drug should vary according to what the first was. For example, after a flozin as first drug, the choice of second drug includes sulfonylureas, gliptins, and pioglitazone
- Whether these drugs could also come in at later stages. For example, if dual therapy with canagliflozin and gliclazide is failing, one option might be to add sitagliptin. Others include pioglitazone, insulin and a GLP-1 analogue
- We assume that if intensification to dual therapy is required, the doses of empagliflozin and canagliflozin will already have been raised to 25mg and 300mg respectively.

These options could create a need for a very large number of pathways which is beyond the scope of this report. We also need to keep regimens after monotherapy as similar as possible in order to focus on the differences arising from the initial monotherapy.

Dual therapy

The draft NICE guideline on type 2 diabetes, for patients who cannot take metformin, has been reproduced earlier in this report. It envisages dual therapy with one of the following combinations;

- Pioglitazone and a sulfonylurea
- Pioglitazone and a gliptin
- Sulfonylurea and a gliptin

In the interest of simplicity, we have chosen the sulfonylurea as the second drug, except after gliclazide monotherapy, when we use pioglitazone. The sulfonylurea was preferred to pioglitazone because of the latter's safety record. Pioglitazone is preferred to a DPP4 inhibitor only on cost grounds.

We have assumed that patients are at the maximum tolerated dose of each monotherapy drug before moving to dual therapy.

Triple therapy

Moving to triple therapy is more complicated, since after some of the dual regimens, pioglitazone and a gliptin are still available, and the GLP-1 analogues and insulin enter the frame. It is not possible to review all options.

At this stage, the draft NICE guideline recommends that insulin-based treatment should be considered.

In the interests of simplicity, our base case is therefore to bring in NPH insulin for triple therapy. We therefore have sequences as follow;

- Empagliflozin 25mg > empagliflozin + gliclazide > empagliflozin + gliclazide + NPH insulin
- Canagliflozin 300mg > canagliflozin + gliclazide > canagliflozin + gliclazide + NPH
- Dapagliflozin 10mg > dapagliflozin + gliclazide > dapagliflozin + gliclazide + NPH
- Sitagliptin 100mg > sitagliptin + gliclazide > sitagliptin + gliclazide + NPH
- Pioglitazone 45mg > pioglitazone + gliclazide > pioglitazone + gliclazide + NPH
- Glic> glic + pio > glic + pioglitazone + NPH

Some patients will progress to needing short-acting insulin to control blood glucose after meals. We assume that once patients move to a basal-bolus insulin regimen, the sulfonylurea will be stopped. Note that we have not introduced any of the flozins beyond monotherapy since those situations were dealt with in the three STAs.

An alternative to bringing in insulin as third drug, is to consider the GLP-1 analogues. These are simpler for patients to manage, involving a once a week injection, and a low risk of hypoglycaemia.

NICE has adopted a very restrictive position on the GLP-1 analogues, based on a minimum BMI, and stopping rules requiring both a 1% reduction in HbA1c and 3% weight loss, but that was not based on any cost-effectiveness analysis and is due for review.

Only one long-acting GLP-1 analogue has been appraised by NICE – long-acting exenatide. If we bring that in as 3rd drug, basal insulin would be the fourth drug, with sequences as follow;

Empa 25mg > empa + gliclazide > empa + glic + exenatide LA > empa + glic + exen + NPH insulin

Cana 300mg > cana + gliclazide > cana + glic + exenatide LA> cana+ glic + exen +NPH

Dapa > dapa + gliclazide > dapa + glic + exenatide LA > dapa + glic+ exen +NPH

Sita 100mg > sita + glic > sita + glic + exenatide LA > sita+ glic+ exen+ NPH

Pio 45mg > pio+ glic > pio + glic + exenatide LA > pio + glic + exen + NPH

One problem with deriving effect sizes for modelling, is that most trials recruit patients with rather poorer control than would be expected amongst patients who are being followed up according to NICE guidelines which state (draft 2)

> *1.6.1 In adults with type 2 diabetes, measure HbA1c levels at 3–6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy*

So if the above guideline is being followed, patients whose HbA1c rises above the 7.5% intensification threshold, should have that detected within a few months, before it has gone much higher. Their HbA1c levels might be in the 7.5% to 8.0% range. Whereas most trials of intensification to dual or triple therapy recruit patients with much higher HbA1c, often in the 8.7-9.05 range, but sometimes well over 9%.

The importance of this is that reductions in HbA1c tend to be larger when baseline HbA1c is higher. So the effect sizes in HbA1c seen in most trials will be larger than expected in management of type 2 diabetes according to the NICE guideline, with close monitoring and prompt intensification.

So we need to be selective in the trials from which we extract data, rather than using effect sizes from broad-spectrum meta-analysis.

The generalisability of trials to routine care has been examined by Thomsen and colleagues in Denmark.[7] They looked at the effects of adding a second drug to metformin in a large population-based cohort, and concluded that the results were similar to those seen in the trials. The mean HbA1c at intensification was 8.0%. They observed reductions in median HbA1c of 1.2% with sulfonylureas, 0.8% with DPP4 inhibitors, 1.3% with GLP-1 receptor agonists and 2.4% with insulin. However, these differences reflect different baseline HbA1cs, notably 9.5% to 10% amongst those who started insulin. Despite intensification, 41% had not achieved HbA1c <7.5% six months later.

Thomsen and colleagues[7] also noted that the threshold for intensification had fallen over the years, from about 8.8% in 2000-2003 to about 8.1% in 2010-2012 (estimated from graph in supplementary material figure 3). If this has also occurred in the UK, it reinforces the need to be selective in extracting effect sizes for modelling. In past studies, patients with type 2 diabetes were often left poorly controlled for several years before intensification[181, 182] but this may be happening less nowadays, with improved control promoted by the Quality Outcomes Framework of payments to general practices for demonstrating performance against HbA1c control indicator s[183], including DM007 for the HbA1c indicator. The three bands are now 59, 64 and 75 mmol/mol. All of them (not just the tightest) probably encourage initiation of insulin in practice.

AG cost effectiveness literature review

Only one paper was identified that addressed the cost effectiveness of flozin monotherapy in the patient group under consideration. Neslusan et al[184], available only in abstract, used the ECHO-T2DM model to compare the cost effectiveness of monotherapy canagliflozin 100mg and canagliflozin 300mg with lifestyle management within the US. Patients could intensify to sulfonylurea and then on to insulin, both apparently with an 8.0% intensification threshold. By the 10th year the use of canagliflozin had delayed the intensification to insulin such that 27% of the canagliflozin 100mg and 19% of the canagliflozin 300mg group were receiving insulin, compared to 66% of those who started with lifestyle management. Canagliflozin was reported to lower total costs and result in improved quality of life over a 30 year time horizon, and so dominated lifestyle management.

The UKPDS and the UKPDS OM models

By way of background, for much cost effectiveness modelling in T2DM the results of the UKPDS have been used. Until recently the main UKPDS publication relevant to cost effectiveness modelling was the UKPDS68.[185] This outlines a number of equations for estimating the progression of the risk factors of HbA1c, SBP, TC:HDL and smoking status through time. Given the evolution of these risk factors the UKPDS68 also specifies a number of equations that calculate the annual risk of experiencing first "events", these events being the macro-vascular complications of diabetes such as stroke and the micro-vascular complications of diabetes such as blindness. The UKPDS68 also permits the calculation of annual probabilities of death. The UKPDS68 was used by Oxford University to develop an electronic cost effectiveness model, the OM1.

The UKPDS68 has recently been partially updated by the UKPDS82[186], the latter incorporating longer follow-up data of the UKPDS. This provides an alternative set of equations to estimate the probability of events and deaths, and also permits the estimation of the probability of some second events: MI, stroke and amputation. Oxford University is developing an updated electronic model, the OM2. As far as the AG is aware, this currently relies upon the UKPDS68 for the evolution of the risk factors and the UKPDS82 for the probabilities of events and deaths. The AG has not had access to the OM2 during the course of the assessment.

The UKPDS82 provides the following table (Table 15) to outline the differences in the predicted number of events at 10 years for patients of different ages.

Table 15 Table 2 of UKPDS82: Ten year event rates (%): OM1 vs OM2

	50-54 years		60-64 years		70-74 yrs		All ages	
	OM1	OM2	OM1	OM2	OM1	OM2	OM1	OM2
1st MI	14.9	7.5	22.5	10.3	29.6	13.3	21	9.9
2nd MI	n/a	0.9	n/a	1.0	n/a	1.1	n/a	1.0
Ulcer	n/a	1.5	n/a	1.9	n/a	2.2	n/a	1.8
Blindness	2.2	2.2	3.5	3.1	4.9	4.0	3.3	2.9
IHD	8.6	6.9	10.3	8.3	10.5	9.0	9.5	7.8
1st stroke	3.3	3.3	7.9	6.4	14.2	10.7	7.6	6.2
2nd stroke	n/a	0.3	n/a	0.7	n/a	1.5	n/a	0.7
Renal failure	0.9	0.3	1.4	0.6	1.6	0.8	1.3	0.5
1st amputation	1.7	1.3	2.0	1.6	1.7	1.8	1.8	1.5
2nd amputation	n/a	0.4	n/a	0.6	n/a	0.4	n/a	0.4
Heart failure	3.0	2.5	5.9	4.3	9.9	6.4	5.7	4.0
Death	14.5	11.1	32.1	22.3	58.8	43.3	31.6	22.5

IHD includes angina and consequences of procedures to relieve it such as angioplasty and coronary artery bypass grafting.

The OM1 predicts roughly double the number of myocardial infarctions over ten years, and the rates of IHD are also noticeably higher. Possibly mainly as a consequence of the higher rate of myocardial infarction predicted by the OM1, the ten year death rate predicted by the OM1 is also noticeably higher. The OM1 will tend to over predict event rates compared to the OM2. The OM1 is now likely to overstate the benefits and cost savings arising from any avoidance of the complications of diabetes that are associated with the more effective treatment.

It is anticipated that the longer follow-up data of the UKPDS associated with the UKPDS82[186] will result in additional publications, one of which will update the evolution of the risk factors. The costs associated with events have already been updated, the UKPDS84[187] being an update of the UKPDS65.[188] The quality of life estimates have also been updated in Alva et al.[189] But the format of the analysis of Alva et al is less closely aligned with the events of the UKPDS84 when compared with the alignment of the quality of life estimates of the UKPDS62[190] with the events of the UKPDS68.[185]

Company submissions

There are three company submissions.

- Boehringer Ingelheim for empagliflozin
- Astrazeneca for dapagliflozin
- Janssen for canagliflozin

An overarching summary of the companies' and the AG's modelling assumptions, inputs and results is presented at the end of the economics, permitting an easy read across. Readers may wish to work through this overarching summary first, before turning to the more detailed summaries presented below for more clarity around specific points of the individual modelling exercises.

All the submissions contain modelling exercises with long term time horizons of around 40 years, which for the majority of patients will be a lifetime horizon. They all undertake a cost utility analysis using the appropriate perspectives of the NHS and PSS for costs and the patient for benefits, and discount costs and benefits at 3.5%.

Boehringer Ingelheim designed a front end to the UKPDS OM1 model. The Boehringer Ingelheim submission has a great deal in common with the modelling of recent NICE clinical guidelines for T2DM and the AG modelling for the current assessment, both of which design a front end to the UKPDS OM1.

Astrazeneca uses the CARDIFF diabetes model (CDM) which uses many of the UKPDS68[185] equations and so has much in common with the UKPDS OM1 model, but updates the calculation of the probabilities of having an event to use the UKPDS82[186] which is the basis of the OM2.

Janssen differs from Astrazeneca and Boehringer Ingelheim in using the ECHO-T2DM model. Its base case has assumptions which differ quite noticeably from those of the other two submissions. There is also relatively little detail in the Janssen submission, with most of the detail being contained in the appendices to the submission and the submitted electronic copy of the model.

In the light of the above, the review of the company submissions below provides a reasonably in depth review of the Janssen modelling. This is followed by shorter reviews of the Boehringer Ingelheim the Astrazeneca modelling, which are more in line with the AG modelling.

Janssen economic modelling

The ECHO-T2DM model is an individual patient simulation model developed by staff of the Swedish Institute for Health Economics. It has been routinely submitted to the Mt. Hood challenges. The Mt. Hood challenges are intermittent events at which the main diabetes models are challenged to use a set of real world clinical inputs to predict the longer term incidences of the various complications of diabetes without having access to the actual longer term incidences of the various complications. Their predictions are then compared with the actuals. But the ECHO-T2DM submissions to the Mt.

Hood challenges were probably with different assumptions than those used for the Janssen submission, in particular with regards the evolution of HbA1c.

The model was run with a 40 year time horizon and a cycle length of 1 year. Costs and benefits were discounted at 3.5%. The perspective was that of the patient for health impacts and of the NHS/PSS for costs.

1,000 PSA iterations were run for the base case, with each PSA iteration modelling 2,000 patients. It appears that each patient was run through the model only once, with no internal loops to reduce Monte-Carlo error. For the scenario analyses the number of patients was reduced to 1,500. The submission did not present any analysis of model convergence over the number of patients modelled. It appears that only results of analyses performing the 1,000 PSA iterations were presented and that no deterministic analyses, i.e. analyses with no sampling of second order uncertainty, were undertaken. This could have permitted more than 2,000 patients to be simulated and some analysis of convergence of results as patient numbers were increased to be presented. Note also that it appears that only pairwise comparisons are permitted in the ECHO-T2DM model. Consequently, it is unclear whether the characterisation of uncertainty within the PSAs across all the comparators is correct; i.e. whether each PSA iteration used the same sampled parameter values across the various pairwise comparisons. This should not affect the central estimates of the probabilistic analysis but the characterisation of the uncertainty around it would be affected.

The model simulates the evolution of the severity of the micro-vascular complications of diabetes, based mainly upon WESDR data:

- Retinopathy
- Chronic kidney disease (CKD)
- Neuropathy, this also encompassing peripheral vascular disease

CKD health states range from stage 1 with an eGFR > 90ml/min/1.73m^2 to end stage renal disease with an eGFR < 15ml/min/1.73m^2 for over one year.

The appendices to the Janssen submission state that four macro-vascular complications are included:

- Ischaemic Heart Disease (IHD)
- Myocardial infarction (MI)
- Stroke; and
- Congestive heart failure (CHF).

The model also incorporates:

- Patient weight;
- Severe hypoglycaemia;
- Non-severe hypoglycaemia;
- UTIs;
- GTIs;
- Peripheral oedema; and,
- Discontinuations.

Patient characteristics

Patient characteristics at baseline were drawn from a pooled analysis of the CANTATA-M [72, 87] and Japanese canagliflozin [73] studies, resulting in baseline estimates of 56 years of age, 52% male, 8.016% HbA1c, 128mmHg SBP, 29.7 BMI, 200mg/dl total cholesterol, 118mg/dl LDL, 48mg/dl HDL, 175mg/dl triglycerides and a mean eGFR of 86ml/min/1.73m^2. Note that the inclusion of the Japanese study pulls down the mean BMI because the mean BMI was 25.6 kg/m^2. Those in CANTATA-M had a higher BMI, mean 31.6 kg/m^2.

Based upon the submitted electronic model input sheets, the mean disease duration was 4.6 years and was assumed to range uniformly between 0 years and 9.2 years. The proportion of patients with background diabetic retinopathy was 0.7%, with micro-albuminuria was 0.1% and with symptomatic neuropathy was 1.5%. The proportion of patients with IHD was 1.2%, MI 0.8%, stroke 0.1% and amputation 0.1%. The other complication rates were zero.

Sequences modelled and treatment effectiveness

The Janssen submission modelled the following treatment sequences (see Table **16**).

Table 16 Janssen model treatment sequences

Monotherapy	1st intensification	2nd intensification	3rd intensification	4th intensification
Flozin	Flozin + SU	NPH insulin	NPH + Aspart	None
Pioglitazone	Pioglitazone + SU	NPH insulin	NPH + Aspart	None
Gliclazide	Sitagliptin + SU	NPH insulin	NPH + Aspart	None
Sitagliptin	Sitagliptin + SU	NPH insulin	NPH + Aspart	None
Repaglinide	Pioglitazone	Pioglitazone + SU	NPH insulin	NPH + Aspart

Repaglinide was only included as a scenario analysis. For canagliflozin 100mg it appears that two arms were modelled: one that intensified by adding gliclazide and another that permitted a dose increase to canagliflozin 300mg [redacted].
But the Janssen submission is slightly ambiguous about this.

Clinical effectiveness estimates for the monotherapies were mainly drawn from the 26 week NMA, though infection rates were drawn from the canagliflozin trials with the flozins being assumed to have the same rate as canagliflozin 100mg and the other comparators the same rate as the placebo arm. Based upon the electronic input sheets submitted by Janssen and the model having an annual cycle, the 26 week estimates were assumed to apply at the end of the first cycle. Note also that the estimates of the electronic input sheets are stated as being relative to placebo, and that there does not appear to be a placebo effect within the electronic input sheets. As a consequence, it appears that the treatment effects relative to placebo rather than the absolute treatment effects have been applied within the Janssen modelling.

The appendices to the submission present two NMAs: with and without repaglinide. The central estimates of these appear to the AG to be virtually identical, with the exception of the rates of severe and non-severe hypoglycaemic events for pioglitazone and sitagliptin. Why these should differ between the two analyses is not clear (see Table 17).

Table 17 Janssen central clinical effectiveness estimates including repaglinide

Drug	Cana		Dapa	Empa		Glicl.	Pio	Sita	Repa.
Dose	100mg	300mg	10mg	10mg	25mg	160mg	30mg	100mg	2mg
HbA1c	-0.97	-1.2	-0.64	-0.73	-0.85	-0.59	-0.78	-0.72	-1.28
SBP	-3.71	-5.41	-3.21	-2.60	-3.40	0.191	0.880	0.800	0.191
BMI	-0.85	-1.21	-0.57	-0.61	-0.65	0.220	0.833	0.293	0.220
TC	4.512	7.544	4.512	4.512	4.512	..	..	..	..
LDL	1.655	6.156	1.655	1.655	1.655	..	..	..	..
HDL	3.447	3.236	3.447	3.447	3.447	..	..	..	..
Triglycerides	-25.0	-24.0	-25.0	-25.0	-25.0	..	..	..	..
AEs									
Female GMI	0.208	0.161	0.208	0.208	0.208	0.065	0.065	0.065	0.065
Male GMI	0.047	0.165	0.047	0.047	0.047	0.015	0.015	0.015	0.015
Upper UTI	0.008	0.000	0.008	0.008	0.008	0.000	0.000	0.000	0.000
Lower UTI	0.107	0.109	0.107	0.107	0.107	0.071	0.071	0.071	0.071
Severe hypo	0.008	0.000	0.003	0.008	0.008	0.034	0.002	0.002	0.010
Non-severe hypo	0.046	0.065	0.057	0.046	0.046	0.508	0.027	0.031	0.156
1st year disc.	0.025	0.020	0.025	0.025	0.025	0.011	0.011	0.011	0.011
Periph. oedema									
Year 1	0.119	0.119	0.119	0.119	0.119	0.119	0.254	0.119	0.119
Subsequent	0.058	0.058	0.058	0.058	0.058	0.058	0.085	0.058	0.058

As already noted, the definition of hypoglycaemia used a cut-off of below 4.0mmol/l, which is above the foot of the normal range of 3.5mmol/l.

The submission appears to state that when a patient intensified by adding another therapy that the clinical effectiveness estimates of that therapy were applied. When a patient intensified therapy by switching to another therapy, rebound was assumed with the clinical effectiveness estimates of the initial therapy being removed prior to applying the clinical effectiveness estimates of the therapy that was being switched to. Rebound consequently appears to be to take the patients back to their baseline values for the risk factors. And the clinical effectiveness of a treatment was assumed to be the same whether it was being used as a monotherapy or was being added to other therapies.

At the progression to insulin the following clinical effectiveness estimates were applied, the values being taken from the copy of the electronic model input sheet that was submitted. The source of these estimates (see Table 18) was not clear to the AG

Table 18 Janssen central clinical effectiveness estimates for insulin

Drug	NPH	Aspart
HbA1c	-0.9	-1.509
SBP	..	..
BMI	0.496	1.009
TC	..	..
LDL	..	..
HDL	..	..
Triglycerides	..	..
AEs		
Severe hypo	0.0049	0.04
Non-severe hypo	0.67	44.95

Treatment intensification and discontinuation

Treatment intensification occurred if the patient breaches the 7.5% HbA1c treatment intensification threshold.

[redacted]

[redacted]

[redacted]

[redacted].

Patients could also discontinue their current treatment due to adverse events and contraindications. It is unclear to the AG whether those discontinuing one treatment were assumed to intensify to monotherapy with another agent or to dual therapy with another agent.

The submission states that the treatment effects associated with discontinuations were immediately reversed at discontinuation. If treatment effects were limited to; e.g. one off reductions in HbA1c it is easy to see how this treatment effect could be reversed and rebound occur. But treatment effects are not limited to one-off effects. The evolution of HbA1c after the initial one-off effect is also treatment specific so has to be counted as a treatment effect. The AG assumption is that rebound was to baseline values, but this is not unambiguous and may have been treated differently for different risk factors; e.g. HbA1c and weight.

The Janssen submission is ambiguous about whether the model handles treatment intensifications and treatment discontinuations in the same manner. It is important to know whether rebound also occurs when treatments are withdrawn at treatment intensification, particularly for the intensification from repaglinide to pioglitazone, and for the intensification to insulin when patients are assumed to discontinue their oral therapies. Appendix 4 to the main submission states that:

> *Treatment intensification algorithms triggered when biomarker threshold levels are exceeded determine AHA and concomitant medication use (i.e. anti-hypertensive, dyslipidaemia) over time. Each drug (or drug combination) is described by a profile that includes price, initial treatment effects, bio-marker evolution, "rebound" effects applied upon discontinuation, AE rates, non-compliance rates, contraindications, and disutility (if any). A treatment sequence of rescue medications can be specified by the user, including at least one line of rescue insulin therapy. Agents can be continued or discontinued at bio-marker failure (HbA1c for AHA, SBP for anti-hypertensive agents, and any of the cholesterol components for anti-dyslipidaemia agents).*

To the AG this suggests the intensifications, or discontinuation at biomarker failure of HbA1c in the above, may be treated in the same manner as discontinuations and treatment switches and have rebound applied if specified by the user.

This raises the possibility of repaglinide rebounding at treatment failure, so adding 1.28% to the then current 7.5% patient HbA1c. Intensifications to pioglitazone with its -0.78% effect and then the subsequent intensification to add gliclazide and its effect of -0.59% may not reverse this rebound, given the incorporation of annual drift. If this applied, patients on repaglinide could spend little to no time on subsequent oral intensifications before intensifying to insulin. But the AG assumption is that rebound is to the baseline value rather than to the baseline value plus annual drift, and that this rebound applies to all the risk factors and not just HbA1c.

It is not obviously reasonable to assume that there will be rebound when patients start insulin. The clinical effectiveness estimates for insulin may reflect the overall effect of a switch to insulin including any discontinuations of existing therapy.

HbA1c evolution

A major difference in assumptions in the Janssen submission compared to the other submissions and the AG modelling is that rather than apply the UKPDS68[185] equation to evolve HbA1c, treatment specific linear evolutions were assumed. The argument for this is that though most NICE assessments in diabetes have used the UKPDS68 equations to evolve HbA1c these evolutions encompass treatment intensifications. As a consequence, if treatment effects are being associated with treatment intensifications in the modelling, using the UKPDS68 evolution will tend to double count these treatment effects.

The values of these for the monotherapies were based upon values taken from the ADOPT trial as reported in Kahn et al.[169] The majority of the monotherapies under consideration were not used in the ADOPT trial, which used rosiglitazone, metformin and glyburide (the Amrican name for glibenclamide). Janssen assumes that values from treatments within the ADOPT trial apply to the monotherapies under consideration as below (Table 19).

Table 19 Janssen annual rates of HbA1c drift by monotherapy

Monotherapy	ADOPT equivalent	Annual HbA1c drift
Flozin	Metformin	0.14%
DPP IV: Sitagliptin	Metformin	0.14%
SU: Gliclazide	SU: Glyburide	0.24%
Repaglinide	SU: Glyburide	0.24%
Pioglitazone	Rosiglitazone	0.07%

Applying the glibenclamide progression rate to gliclazide may be pessimistic given the 6-year difference in start of insulin on gliclazide and glibenclamide, in favour of gliclazide.[13]

Given the annual rates of drift and the initial HbA1c treatment effects estimated in the NMA, it is apparent that the annual rates of drift are likely to be as, if not more, important than the HbA1c treatment effects estimated in the NMA. Due to the NMA estimating HbA1c from 24 week data, half the annual drift is added to the estimated treatment effect to provide the 52 week estimate.

At intensification, if another treatment is added the annual rate of HbA1c drift is assumed to be the average of the HbA1c annual drifts of the two treatments being used as dual therapy (Table 20).

Table 20 Janssen annual rates of HbA1c drift by dual therapy

Dual therapy	Annual HbA1c drift
Flozin + Sulfonylurea	0.19%
DPP IV + Sulphonylurea	0.19%
Pioglitazone + Sulphonylurea	0.16%

For those intensifying to insulin, Janssen derive an annual rate of drift of 0.15% from the UKPDS82.[186]

The impact of these different annual drifts in HbA1c is applied in tandem with the initial treatment effects. For instance, at the central Janssen treatment effect estimates and a baseline value for HbA1c of 8.0% it appears that for those who do not discontinue for other reasons the following evolutions are implied up to the point at which HbA1c rises above 7.5% and treatment is intensified (see Figure 10).

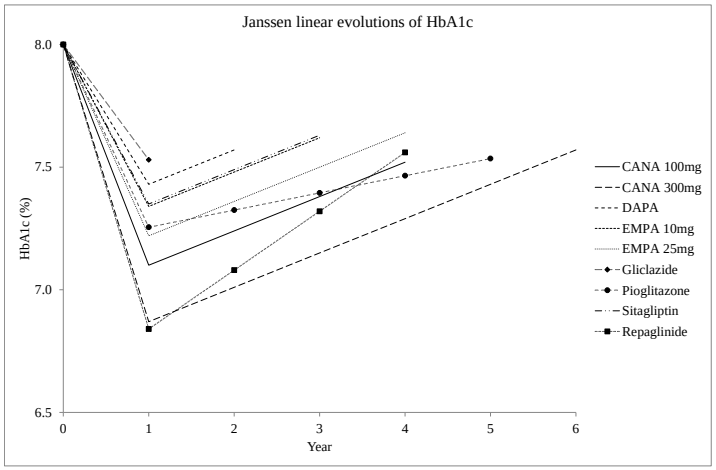

Figure 10 Janssen modelled HbA1c drift by treatment at central values

Immediately apparent is that for gliclazide (the topmost line) the treatment effect of -0.59% when coupled with half of the annual drift; i.e. an increase of 0.12%, means that the patient is above 7.5% at the end of the first cycle.

Turning to canagliflozin 100mg (the solid line) despite its initial treatment effect of -0.97% being somewhat less than the -1.28% of repaglinide they both breach the 7.5% HbA1c intensification threshold at the fourth year due to the differences in annual drift. The slower drift for canagliflozin 300mg also means that despite an initial treatment effect of -1.20% it breaches the 7.5% HbA1c intensification threshold two years later.

Thereafter, it should be borne in mind that repaglinide is assumed to be replaced by pioglitazone. Due to the withdrawal of treatment the current AG reading of the Janssen submission is that in the model this causes the HbA1c to rebound to the original baseline value of 8.016%, and not to have the full rebound of the repaglinide 1.28% treatment effect applied. The -0.59% pioglitazone effect is then applied with the pioglitazone specific HbA1c rate of drift applied, with a further intensification to pioglitazone + SU after this. In other words, in the repaglinide arm there is the initial repaglinide evolution of HbA1c, in the above example for 4 years, which is then followed by exactly the same HbA1c evolution as in the pioglitazone arm, only with this being lagged by 4 years.

The same annual drifts apply for empagliflozin, dapagliflozin and sitagliptin as for canagliflozin. They also intensify by adding gliclazide, and then on to insulin. Again ignoring discontinuations for other reasons, the linear evolution of HbA1c means that any difference in the timings of the first intensification is also reflect in the timings of the intensification to insulin. It appears that the assumption of a linear evolution of HbA1c will maintain absolute differences in HbA1c between treatments, at least until the patient intensifies to insulin. Upon intensification to insulin it appears that the ECHO-T2DM model applies the linear evolution for HbA1c, but then permits the patient to increase their insulin dose in order to stabilise their HbA1c. The Janssen submission is not particularly clear on this point, but it appears that this means that HbA1c may eventually converge between treatments once the patient has started insulin.

Pioglitazone benefits from a slower annual rate of drift, and continues to derive some benefit from this source even after the intensification of adding gliclazide. At central parameter values and again ignoring discontinuations it will have a permanent HbA1c benefit over all the other comparators with the possible exception of canagliflozin 300mg.

Reconciling the above with the evolutions of HbA1c reported in the Janssen submission is difficult, given the annual cycle of the model. But it should be borne in mind that the Janssen curves are

averaged over a large number of patients and PSA iterations, and include the effects of discontinuations for other reasons (see Figure 11).

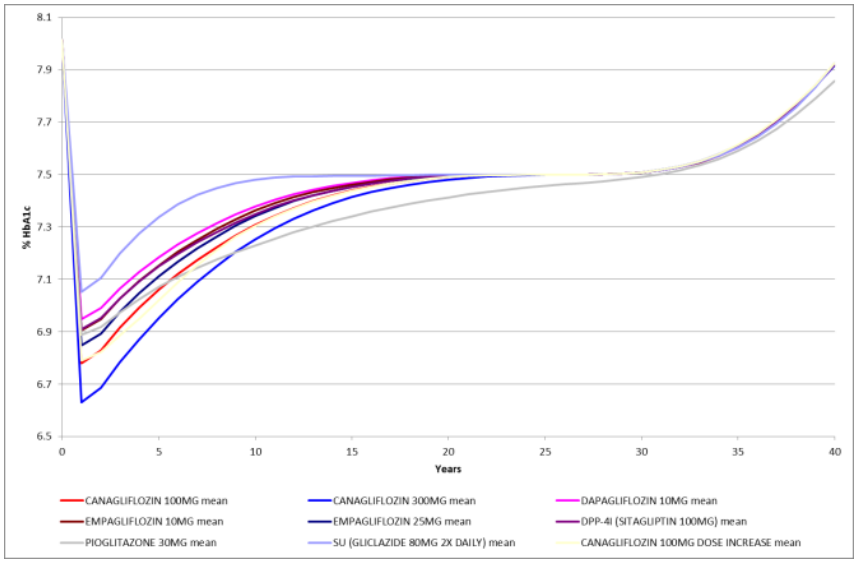

Figure 11 Janssen Figure 13: submission reported evolutions of HbA1c

For instance, the mean first year effect for the gliclazide arm as shown by the topmost curve is around a 0.95% reduction in HbA1c, which is somewhat greater than the -0.59% mean estimate for gliclazide. Those discontinuing for reasons other than HbA1c apparently in effect switch to pioglitazone, the estimate for which is -0.78%. Similarly, the reduction of around 1.4% in HbA1c for canagliflozin 300mg as shown by the bottom curve is also difficult to reconcile with its central estimate of -1.20%. Perhaps both discontinuations and their treatment effects and intensifications and their treatment effects are included in the year 1 estimates, though this timing could be questionable given the annual cycle of the model. It remains difficult to reconcile the above with the central estimates for treatment effectiveness.

At central estimates around a third of the canagliflozin 300mg patients would be required to not to receive a boost of the -0.59% estimate for the intensification to gliclazide to achieve the reduction of 1.4% shown in the above figure. This also requires that none discontinue, rebound and receive a lesser treatment effect from whatever alternative they switch to. Any discontinuations in the canagliflozin 300mg arm would seem to require an even larger boost to the 1.2% canagliflozin 300mg treatment effect among those not discontinuing if the reduction of around 1.4% is to be arrived at.

Even with the effects of 2nd order sampling, it is not clear to the AG how the above central estimates for the evolutions of HbA1c have been arrived at. Perhaps there are additional placebo treatment effects in addition to the treatment effects relative to placebo and the AG has not managed to identify these. In the light of the above, while having read the Janssen submission and its appendices, the AG does not really understand how the model is implementing the changes in HbA1c and how the central

estimate for canagliflozin 300mg is to on average reduce the patient HBA1c from 8.016% at baseline to around 6.63% at one year: a reduction of around 1.4%.

The above figure also sees the HbA1c values converge between the arms. Janssen states that this is "*Because of differences in the timing of requirements for rescue medication, HbA1c, SBP, and lipid curves tend to converge as patients with higher values benefit from treatment-related improvements earlier*". To the AG this does not obviously explain the convergence, or why the curve for gliclazide converges by essentially having zero increase from the 10th to the 30th year. A possible explanation might be the intensification to insulin with patients then being permitted to increase their insulin dose in order to stabilise their HbA1c.

The argument that the UKPDS68 equation 11 includes the effects of treatment intensifications does have some force. But it should be borne in mind that the UKPDS68 equation 11 explicitly includes a parameter for whether the patient is in their second year of diagnosis. This could be viewed as a proxy for the clinical effectiveness of the first treatment for diabetes being introduced, though the second year of diagnosis might be a little early for some patients. As a consequence, modelling could as an alternative apply treatment specific effects and still apply the UKPDS68 equation 11 thereafter, only ignoring the parameter related to whether the patient is in their second year or not. For the patient baseline characteristics outlined in the Janssen submission the annual increases implied by the UKPDS68 equation 11 in the years shortly after the second year are around 0.18% which is broadly central to the rates Janssen takes from theADOPT study as reported in Kahn et al.[169] This may be preferable to extrapolating linear rates from the ADOPT trial, particularly since these rates are being applied to treatments which were not used in the ADOPT trial, and to periods beyond the 5 year follow up of the ADOPT trial, and with some distinctly ad hoc averaging for the rates for dual therapy.

The AG has some sympathy with the argument that HbA1c drift may initially be treatment specific. A linear evolution might even be the most reasonable functional form, particularly given the coefficients reported by Kahn et al.[169] But the AG does not view it as reasonable to assume a linear evolution of HbA1c throughout and that there will be no convergence between treatments, or at least none until a patient starts insulin therapy. This may artificially preserve differences between treatments, when the UKPDS68 evolution clearly implies a convergence. The AG is also uncomfortable with the assumed linear rates of drift that have been imputed from Kahn et al, given that none of the monotherapies under consideration were studied by Kahn et al.

A scenario analysis where the model applies the UKPDS68 evolution of HbA1c was presented.

Evolution of other risk factors

Linear drifts were also assumed for the other biomarkers but these were not differentiated by treatment: 0.30mmHg for SBP, 0.03mg/dl for lipids resulting in a flat TC:HDL evolution. These annual rates of drift were apparently derived from the UKPDS. The UKPDS was conducted largely before the use of statins, and it can be argued that alternative evolutions to those of the UKPDS are now appropriate. But given that the annual rates of drift were apparently derived from the UKPDS, it is unclear to the AG why the equations of the UKPDS68 were not applied.

For a patient's SBP, the common annual rate of drift will tend to maintain the absolute differences between the arms. As far as the AG can ascertain, it also appears that unlike HbA1c this absolute difference for SBP will be maintained even after insulin therapy has been started.

Weight was associated with an annual gain of 0.1kg. Table 12 of the submission states that weight drifts upwards but there is no suggestion of a base case assumption of convergence. Table 13 goes on to suggest that for the base case the patient's weight was assumed to converge at treatment discontinuation with this being in line with figure 26 of the appendix. If this convergence applied, it is unclear whether it was at the 1st intensification or was when the oral therapies were being discontinued and the patient switched to insulin. A scenario analysis of a slower convergence over two years after treatment discontinuation was also presented.

Treatment discontinuation: Renal impairment

In accordance with the canagliflozin SmPC, canagliflozin 100mg was modelled as being discontinued if the eGFR fell below 45ml/min/1.73m^2. Canagliflozin 300mg was modelled as being discontinued if the eGFR fell below 60ml/min/1.73m^2. The SmPC states that if the eGFR falls below 60ml/min/1.73m^2 the patient should have their dose adjusted to 100mg. Those intensifying from canagliflozin 100mg to canagliflozin 300mg would have already failed on canagliflozin 100mg. The license states that canagliflozin 100mg should always be used before canagliflozin 300mg. So dose reduction may be of limited relevance and discontinuation of canagliflozin 300mg may be the appropriate assumption.

Empagliflozin has similar restrictions in its SmPC, with it being possible to increase the dose from 10mg to 25mg if the eGFR is more than 60ml/min/1.73m^2. If the eGFR falls below 60ml/min/1.73m^2 the patient should have their dose adjusted to 10mg, and if the eGFR falls below 45ml/min/1.73m^2 the patient should discontinue empagliflozin.

The dapagliflozin SmPC has slightly different restrictions and is not recommended for patients with an eGFR of less than 60ml/min/1.73m^2.

The sitagliptin SmPC does make the administered dose depend on renal impairment, requiring it to be reduced to 50mg in those with moderate renal impairment and to 25mg in those with severe renal impairment. But discontinuation does not appear to be required.

As far as the AG can see the submission does not state what assumptions if any have been made about discontinuing empagliflozin and dapagliflozin based upon the patient's eGFR. Table 12 of the submission is explicit in its consideration of the canagliflozin SmPC for discontinuations related to renal impairment and to the pioglitazone SmPC for discontinuations related to CHF, but makes no reference to the empagliflozin SmPC or the dapagliflozin SmPC. Appendix 4 of the submission mentions that empagliflozin and dapagliflozin also have treatment rules based upon eGFR. The input sheets to the electronic model suggest that empagliflozin 10mg, empagliflozin 25mg and dapagliflozin are assumed to be discontinued as per canagliflozin: if the eGFR drops below 60ml/min/1.73m^2. This appears to be incorrect for empagliflozin 10mg, and illogical for empagliflozin 25mg.

The use of the ECHO-T2DM model was in part justified by Janssen on grounds of the need to properly account for discontinuations due to renal impairment. In the light of this, a scenario analysis that does not apply these discontinuations would have been useful in order to assess the importance of attempting to model this.

Treatment discontinuations: Adverse events

Patients could discontinue treatments due to adverse events. It is not clear to the AG what was assumed to happen to these patients. They may have discontinued their current treatment and switched to whatever is next in the sequence; e.g. from flozins to SU and then on to NPH insulin, or they may switch to an alternative monotherapy, or they may have switched to an alternative dual therapy.

Hypoglycaemic events

Hypoglycaemia event rates were derived from the pooled 26 week data of the two canagliflozin trials. The NMA 26 week data provided the estimates for the other comparators with the exception of gliclazide. No hypoglycaemia rates were available for gliclazide, and as a consequence rates for glimepiride were adjusted by relative risks of 0.43 for symptomatic and 0.45 for severe hypoglycaemia. The AG is unclear whether these rates were adjusted to be annual rates and so to be in line with the annual model cycle.

Hypoglycaemia event rates were further modified by increasing the risk of hypoglycaemia for low HbA1c values. The relationship underlying this was based upon a large data set of the DCCT study among patients with type 1 diabetes. A 1% drop in HbA1c below the mean value of the clinical study was associated with an increased hazard of hypoglycaemia of 1.43. However patients in the DCCT

intensive arm were on either multiple daily injections or continuous subcutaneous insulin infusion via insulin pumps.

Adverse events

UTI and GTI event rates were derived from the pooled 26 week data of the two canagliflozin trials. The AG is unclear whether these rates were adjusted to be annual rates and so to be in line with the annual model cycle. The other flozins were assumed to have the same rates as canagliflozin 100mg, with the other comparators being assumed to have the same rate as the pooled placebo arms of the canagliflozin trials.

Quality of life

A systematic literature review was conducted with Janssen preferring the CODE-2 data of Baghust and Beale[191] over the UKPDS62[190] due to it providing greater richness for the micro-vascular complications. Baghust and Beale is also the source for quality of life coefficient for BMI.

Janssen report that no appropriate studies were identified for adverse events, and as a consequence a time trade-off study (TTO) among 100 members of the UK general public was conducted to determine the quality of life impacts from UTIs and GTIs. This TTO study also explored hypoglycaemia, GI symptoms and hypovolaemic events, but the estimates for these were disregarded (see Table **21**).

Table 21 Janssen TTO AE quality of life report mean values

	Mean	s.d.	Disutility
T2DM	0.92	0.10	..
and Mild/ moderate UTIs	0.83	0.14	0.09
and Severe UTIs	0.73	0.20	0.19
and Mycotic infection	0.67	0.26	0.25
and Moderate hypoglycaemia	0.81	0.19	0.11
and Severe hypoglycaemia	0.77	0.21	0.15
and Fear of hypoglycaemia	0.77	0.17	0.15
and GI symptoms	0.68	0.24	0.24
and Hypovolaemic events	0.84	0.14	0.08

Based upon the references cited, these values apparently contributed to a regression analysis which arrived at the final QALY decrements. Unfortunately, the AG has not been able to source this regression analysis.

The health state descriptors suggest that the estimates relate to ongoing infection and are not time limited as is appropriate in a TTO study, but this implies that event health states need to be adjusted by the average duration of UTIs and GMIs as occurs in the Janssen submission. The method of this adjustment does not appear to have been presented. At mean values 1 week of a moderate UTI would roughly correspond with a -0.0012 QALY decrement, 2 weeks of a severe UTI would roughly correspond with a -0.0073 QALY decrement and 1 week of a mycotic infection would roughly correspond with a -0.0046 QALY decrement.

The quality of life values applied for the baseline characteristics and micro-vascular complications are presented below. Those for macro-vascular complications, obesity, hypoglycaemic events and adverse events are presented in the overarching summary comparison of the companies' and AG's inputs (see Table **22**).

Table 22 Janssen QoL values: Baseline and micro-vascular

State	QoL	Source
Baseline	1.027	CODE 2
Patient Characteristics		
Age (per 10 Years)	-0.0235	CODE 2
Female	-0.0930	CODE 2
Duration of T2DM (per 10 Years)	-0.0163	CODE 2
Micro-vascular Complications		
Retinopathy (BDR, MO, PDR, and combinations)	0.000	CODE 2
Blindness (one or both eyes, incl. combinations)	-0.057	CODE 2
Gross Proteinuria	-0.048	CODE 2
ESRD	-0.175	CODE 2
Symptomatic Neuropathy	-0.084	CODE 2
Peripheral Vascular Disease (PVD)	-0.061	CODE 2
Symptomatic Neuropathy & PVD	-0.085	CODE 2
Diabetic Foot Ulcer	-0.170	CODE 2
One lower extremity amputation	-0.272	CODE 2
Two lower extremity amputations	-0.272	CODE 2

Costs

Direct drug costs were sourced from the BNF69 and are not presented here for reasons of space. Note that the Janssen analysis in common with the other company analyses applies the £608 cost for canagliflozin 300mg, due to the submission predating the equalisation of the canagliflozin list prices at the canagliflozin 100mg list price of £477.

The costs of blindness, IHD, MI, CHF and stroke were derived from the UKPDS84[187] but are not presented here again for reasons of space. Similar costs are presented within the section on the AG modelling. A variety of other costs are sourced from a variety of NICE guidelines and other sources. Again for reasons of space and because they have very little impact upon the modelling these are not presented here. A full table of event costs is presented in the appendices of the Janssen submission in table 33 starting on page 69. Costs are also summarised in the overarching comparison of the companies and AG modelling exercises.

Adverse events costs were based upon the following (see Table 23).

Table 23 Janssen adverse event costs

Adverse event	Cost	Description and Reference
Non-severe hypoglycaemic event	£0.00	Assumption
Severe hypoglycaemic event	£380.00	Value taken from NICE draft CG
lower UTIs (male)	£93.01	2 GP visits plus trimethoprin 200mg twice daily
lower UTIs (female)	£47.01	1 GP visits plus trimethoprin 200mg twice daily
upper UTIs (male)	£94.02	2 GP visits plus trimethoprin 200mg twice daily
upper UTIs (female)	£94.02	2 GP visits plus trimethoprin 200mg twice daily
GMI (male)	£52.86	1 GP visit plus fluconazole for 7 days
GMI (female)	£49.45	1 GP visit plus 1 500mg clotrimazole pessary

Some additional costs for GTIs might be anticipated if a patient's partner is also treated.

Results

The QALY losses in the model are presented in tables 42 and 43 of the appendices which is summarised below (see Table 24). The AG interpretation of this is that canagliflozin 100mg has been taken as the reference for survival with the absolute QALY losses associated with the various events also being presented. The net absolute QALY difference between canagliflozin 100mg and each of the comparators is then presented, with the percentage contribution of the various events to this net QALY effect being presented alongside. Since the complications of diabetes other than neuropathy make little contribution to this, they have been grouped together for reasons of space.

Table 24 Janssen base case sources of QALY differences

	Loss	Survival	Hypo	AEs	Weight	Neurop.	Other
Cana. 100	1.258	..	0.213	0.015	0.553	0.358	0.119
Absolute QALY differences relative to canagliflozin 100mg, and proportionate contribution by source							
Cana. 300	+0.044	38%	11%	1%	42%	5%	3%
Cana. 100/300	+0.012	49%	12%	1%	36%	2%	0%
Dapa.	-0.033	26%	7%	1%	51%	9%	6%
Empa. 10mg	-0.029	28%	6%	1%	49%	10%	6%
Empa. 25mg	-0.015	7%	8%	1%	70%	8%	6%
Pioglitazone	-0.041	27%	33%	0%	36%	1%	4%
Gliclazide	-0.090	27%	19%	2%	40%	8%	5%
Sitagliptin	-0.058	23%	2%	3%	62%	4%	5%

The AG considers it odd that neuropathy should be so different between gliclazide and pioglitazone, but it is not possible to see how this is handled within the model.

The above shows that within the modelling survival differences account for a reasonable proportion of the estimated differences in mean QALYs between the comparators: about one quarter for the non-canagliflozin comparators. But the direct quality of life impacts of weight, hypoglycaemia and to a lesser extent neuropathy account for the majority of the differences. The QALY losses from the other complications of diabetes are relatively insignificant. A similar analysis can be presented for the cost differences (see Table 25).

Table 25 Janssen base case sources of cost differences

	Total	Oral Tx	Insulin	Hypo	AEs	Neurop.	Other
Cana. 100	£23,525	£3,190	£5,604	£142	£179	£6,350	£8,060
Absolute cost differences relative to canagliflozin 100mg, and proportionate contribution by source							
Cana. 300	£777	73%	21%	1%	0%	2%	3%
Cana. 100/300	£144	61%	33%	0%	0%	0%	4%
Dapa.	£69	46%	45%	1%	0%	2%	5%
Empa. 10mg	£55	47%	44%	0%	0%	3%	6%
Empa. 25mg	£3	49%	43%	0%	1%	3%	5%
Pioglitazone	-£3,261	68%	23%	1%	1%	1%	7%
Gliclazide	-£305	53%	39%	0%	1%	2%	4%
Sitagliptin	-£82	49%	30%	1%	3%	2%	14%

As can be seen from the above, the main differences in cost arise from difference treatment costs for both the oral drugs and insulin, with these being in part driven by the survival differences alluded to

above. The only real exceptions to this are for the comparison with pioglitazone, where an additional £156 treatment cost for CHF is anticipated compared to canagliflozin 100mg.

Ranking treatments in order of increasing total costs, the Janssen base case cost effectiveness results are as below. Note that the following table presents the ICERs relative to the cheapest comparator among those being considered. Not all these ICERs are presented by Janssen, with some having been derived be the AG, so are subject to rounding errors (see Table **26**).

Table 26 Janssen base case cost effectiveness estimates

			vs Pioglitazone			vs Gliclazide			vs Sitagliptin		
	Cost	QALY	Δ £	Δ Q	ICER	Δ £	Δ Q	ICER	Δ £	Δ Q	ICER
Pioglitazone	£20,264	9.998									
Gliclazide	£23,220	9.949	£2,956	-0.049	Dom						
Sitagliptin	£23,443	9.981	£3,179	-0.017	Dom	£223	0.032	£6,969			
Cana. 100	£23,525	10.039	£3,261	0.041	£79,537	£305	0.090	£3,377	£82	0.058	£1,414
Empa. 25mg	£23,528	10.024	£3,264	0.026	£125,538	£308	0.075	£4,107	£85	0.043	£1,977
Empa.10mg	£23,580	10.010	£3,316	0.012	£276,333	£360	0.061	£5,902	£137	0.029	£4,724
Dapa.	£23,594	10.006	£3,330	0.008	£416,250	£374	0.057	£6,561	£151	0.025	£6,040
Cana. 100/300	£23,669	10.051	£3,405	0.053	£64,245	£449	0.102	£4,402	£226	0.070	£3,229
Cana. 300	£24,302	10.083	£4,038	0.085	£47,456	£1,082	0.134	£8,075	£859	0.102	£8,422
Dom: dominated by pioglitzone.											

Pioglitazone is the cheapest due to its acquisition cost. As a consequence, while other treatments are estimated to be more effective compared to pioglitazone their cost effectiveness is poor. Both gliclazide and sitagliptin are estimated to be dominated by it. Sitagliptin being dominated by pioglitazone may be due to its assumed faster rate of HbA1c drift. Canagliflozin 100mg is estimated to have an ICER of £79,537 per QALY compared to pioglitazone. Canagliflozin 100mg also provides more QALYs at a cheaper cost than empagliflozin and dapagliflozin, so dominating them. Canagliflozin 100mg followed by canagliflozin 300mg has a better cost effectiveness against pioglitazone than canagliflozin 100mg, so extendedly dominates canagliflozin 100mg. But it is in turn extendedly dominated by canagliflozin 300mg which is estimated to have a cost effectiveness compared to pioglitazone of £47,456 per QALY.

The cost effectiveness of sitagliptin and the flozins is estimated to be more reasonable when compared to gliclazide. But canagliflozin 100mg extendedly dominates sitagliptin and dominates empagliflozin and dapagliflozin.

Across the nine comparators, the probabilistic modelling suggested that if the willingness to pay is zero, pioglitazone has a 100% probability of being the most cost effective treatment. This probability declined as the willingness to pay increased, until at around a willingness to pay of £55k it ceased to have the highest probability of being the most cost effective treatment. At this point canagliflozin 300mg overtook it, with a probability of being the most cost effective of around 25%.

At high willingness to pay values of £200k per QALY it appears that the probabilities of being the most cost effective have stabilised. Canagliflozin 300mg remains the highest with a probability of around 33%.

The others increase their probabilities as the willingness to pay rises, but still only converge to values under 20%, with the values for empagliflozin 10mg, dapagliflozin 10mg, sitagliptin 100mg and gliclazide never rising above 10%.

Sensitivity analyses

The univariate sensitivity analyses presented by Janssen vary parameters by an arbitrary ±20% and are consequently of limited interest. Full results of these are presented in tables 46 to 48 of the appendices to the submission. The main result of interest is that the modelling is sensitive to the annual rate of HbA1c drift that is assumed for canagliflozin: deterministic sensitivity analyses (DSA) number 6 lower value and upper value (6L and 6U) which respectively decrease and increase the base case 0.14% annual rate of drift by 20%. The cost effectiveness estimates under DSA 6L and DSA 6U for canagliflozin 100mg compared to:

- pioglitazone are £45,862 per QALY and £211k per QALY respectively
- gliclazide are £593 per QALY and £8,751 per QALY respectively
- sitagliptin are dominance and £8,528 per QALY respectively

In the opinion of the AG these changes are likely to be due more to the time spent on therapy and its immediate effects upon treatment cost, weight, adverse events and hypoglycaemia than to any changes in the modelled complications of diabetes. An exception to this might be the modelled rates of neuropathy.

Scenario analyses

A range of scenario analyses as summarised in table 13 on page 52 of the Janssen submission is presented, with summary results for all of these in tables 19 and 20 of the Janssen submission. The main points of interest identified by the AG are summarised below.

For the comparison with empagliflozin and dapagliflozin the main scenario analyses of interest are those that:

- revise the patient characteristics at baseline from those that Janssen pools from its trials to those of the THIN database, which is the database that underlies the patient characteristics of the modelling for the draft NICE CG: Sc5;
- apply the UKPDS68 HbA1c evolution equation and UKPDS62 quality of life values, while also assuming that patients can intensify to NPH insulin but not to basal-bolus insulin: Sc6; and,
- apply the UKPDS68 HbA1c evolution equation: Sc14.

These scenario analyses remove the dominance of canagliflozin 100mg over empagliflozin and dapagliflozin with the costs effectiveness estimates typically changing to lie between £5k and £10k per QALY.

Scenario analysis 14 is rather more dramatic in terms of the cost effectiveness estimates. But it would probably be more accurate to describe it as showing broad clinical equivalence but additional costs from canagliflozin compared to dapagliflozin, empagliflozin 10mg and empagliflozin 25mg of £198, £150 and £65 respectively.

Including repaglinide: Sc1

The analysis which includes repaglinide differs little from the base case analysis, but with repaglinide being estimated to have total costs of £22,170 and total QALYs of 9.967. As a consequence it is dominated by pioglitazone. If pioglitazone is excluded from this analysis gliclazide is still dominated, only now by sitagliptin. Sitagliptin with a cost effectiveness of £79,400 per QALY compared to repaglinide is in turn extendedly dominated by canagliflozin 100mg, which has a cost effectiveness of £21,050 per QALY compared to repaglinide. Empagliflozin and dapagliflozin remain dominated by canagliflozin 100mg. Canagliflozin 100mg followed by canagliflozin 300mg has a cost effectiveness estimate compared to repaglinide of £20,816 per QALY, which is again extendedly dominated by canagliflozin 300mg which has a cost effectiveness of £20,200 per QALY compared to repaglinide.

Same annual HbA1c drift across the monotherapies: Sc2

Unfortunately table 50 of the Janssen submission appendices does not provide the estimates for the canagliflozin 300mg arm. But the estimates for canagliflozin 100mg and canagliflozin 100 / 300 mg are extremely similar to those of the base case, and as a consequence the AG has used the estimates of the base case for canagliflozin 300mg for the following table. The reported ICERs are all compared to repaglinide (see Table **27**).

Table 27 Janssen scenario analysis: common HbA1c annual drift

	Cost	QALY	ICER
Repaglinide	£20,982	10.03	
Pioglitazone	£21,485	9.95	Dom
Gliclazide	£22,589	10.01	Dom
Sitagliptin	£23,615	9.99	Dom
Cana. 100	£23,732	10.05	£137,500
Empa. 25mg	£23,732	10.03	Dom
Emap. 10mg	£23,739	10.02	Dom
Dapagliflozin	£23,786	10.02	Dom
Cana. 100/300	£23,853	10.06	£95,700
Cana. 300	£24,594	10.09	£63,368
Dom: dominated by repaglinide			

If the annual HbA1c drift across the monotherapies is set equal to that of canagliflozin 100mg, this somewhat worsens the cost effectiveness of pioglitazone to the extent that it is now dominated by repaglinide. The cost effectiveness estimate for canagliflozin 100mg compared to pioglitazone improves to £24,233 per QALY

Assuming the same annual rate of HbA1c drift across the comparators improves the cost effectiveness of repaglinide and somewhat worsens the costs effectiveness estimates for canagliflozin compared to repaglinide. But the cost effectiveness estimate for canagliflozin compared to pioglitazone improves.

Lower BMI disutility: Sc4

Revising the disutility per BMI point from 0.0061 to 0.0038 has quite a large impact upon some results, as would be anticipated. The cost effectiveness estimate for canagliflozin 100mg compared to pioglitazone worsens to £146k per QALY and compared to repaglinide to £26,378 per QALY. The other costs effectiveness estimates are not particularly affected. Canagliflozin 100mg is still estimated to dominate the other flozins.

UKPDS68 HbA1c evolution coupled with UKPDS62 QoL: Sc6

This scenario applied the UKPDS68 HbA1c evolution and some of the UKPDS62 quality of life values.[185] It also assumed that there was no intensification to basal bolus insulin. The rationale for these grouped changes is not obvious, and as a consequence the AG prefers scenario analysis 14.

UKPDS HbA1c evolution: Sc14

Applying the UKPDS HbA1c evolution isolates the effects of this compared to scenario 6. The full results for this scenario do not appear to be reported in the Janssen appendices. As already reported above, for the comparisons with the other flozins there is broad clinical equivalence but additional costs from canagliflozin 100mg compared to dapagliflozin, empagliflozin 10mg and empagliflozin 25mg of £198, £150 and £65 respectively. Similarly there is broad clinical equivalence with gliclazide but a rather larger incremental cost of £744. The cost effectiveness of canagliflozin 100mg compared to pioglitazone improves somewhat to £31,945 per QALY.

The assumptions around the evolution of HbA1c are clearly central to the Janssen modelling. In the opinion of the AG this is not due to the complications of diabetes being modelled as changing. In the opinion of the AG it is likely to be mainly due to the amount of time a patient is modelled as spending on the various oral therapies changing. This primarily affects the direct drug costs of treatment, patients' weights, hypoglycaemia and adverse events.

Astrazeneca economic modelling

The CARDIFF Diabetes Model (CDM) is an individual patient level model that has been used for previous NICE assessments. It has been routinely submitted to the Mt. Hood challenges. But these submissions to the Mt. Hood challenges were with different assumptions than those used for the AstraZeneca submission.

The modelling of the complications of diabetes within the CDM was previously largely based upon the UKPDS68 risk equations, these being the basis of the UKPDS OM1 model. For the Astrazeneca submission, the CDM modelling of the complications of diabetes has been updated to use the UKPDS82 risk equations, these being the basis of the UKPDS OM2 model. Note that for the probabilistic modelling the UKPDS researchers have made available the 1,000 bootstraps of the equations underlying the UKPDS OM1 model to the Mt Hood challenge modellers. As far as the AG is aware the corollary of these has not been made available for the equations underlying the UKPDS OM2 model. As a consequence, it is not clear how the CDM of the Astrazeneca submission has implemented the probabilistic modelling.

During the STA of dapagliflozin the ERG noted various errors in the CDM implementation formulae for the evolution of the risk factors, which were subsequently corrected during the course of the STA. The AG assumption is that within the Astrazeneca submission these errors have been corrected.

The model was run with a 40 year time horizon and a cycle length of 6 months. Costs and benefits were discounted at 3.5%. The perspective was that of the patient for health impacts and of the NHS/PSS for costs.

It appears that for a deterministic model run 30,000 patients were run. It appears that each patient was run through the model only once, with no internal loops to reduce Monte-Carlo error. Probabilistic modelling was based upon 1000 PSA iterations, each with 30,000 patients being simulated. The submission did not present any analysis of model convergence over the number of patients modelled. The CDM only permits pairwise comparisons. As a consequence, the uncertainty around the cost effectiveness estimates is not presented across all the comparators but only in a pairwise fashion.

The AstraZeneca submission notes that among those receiving monotherapy, among the comparators within the NICE scope sulfonylurea has the largest market share of [redacted]. The gliptins share is stated as being [redacted] followed by [redacted] for the glitazones. Astrazeneca argue that the main comparator for the flozins will be the gliptins, which if true would justify the concentration upon pairwise comparisons.

The CDM models the incidence of the following micro-vascular complications:

- Amputation
- Nephropathy
- Blindness

Four macro-vascular complications are included:

- Ishaemic Heart Disease (IHD)
- Myocardial infarction (MI)
- Stroke; and
- Congestive heart failure (CHF).

The model also incorporates:

- Patient weight;
- Severe hypoglycaemia;
- UTIs;
- GTI; and,
- Discontinuations.

Patient characteristics

Patient characteristics at baseline were mainly drawn from the NMA, resulting in baseline estimates of 55 years of age, 54.6% male, 7.5% HbA1c due to NICE clinical guidelines though the NMA mean of 8.2% was used as a scenario analysis, 128.3mmHg SBP, 195mg/dl total cholesterol, 46mg/dl HDL and a weight of 80kg.

The submission does not appear to state what the baseline prevalence of the complications of diabetes was. The submitted electronic model sets these to zero.

Sequences modelled and treatment effectiveness

The comparators were grouped into their class as per the AstraZeneca NMA, e.g. the cost effectiveness of flozins as a group was estimated compared to the gliptins as a group. Note that of the glitazones only pioglitazone was considered, rather than a class effect being applied. Repaglinide was not considered as a comparator due to a lack of evidence.

Astrazeneca argues that allowing the intensifications to differ between the arms would not permit a fair assessment of the cost effectiveness of alternative monotherapies, but would rather be a comparison of the cost effectiveness of alternative treatment sequences. Consequently, the Astrazeneca submission modelled the following treatment sequences despite this not reflecting UK clinical practice (see Table **28**).

Table 28 Astrazeneca model treatment sequences

Monotherapy	1st intensification	2nd intensification
Flozin	NPH insulin	Intensified NPH
Gliptin	NPH insulin	Intensified NPH
Pioglitazone	NPH insulin	Intensified NPH
Sulfonylurea	NPH insulin	Intensified NPH

Intensified insulin was assumed to involve a 50% dose escalation.

Clinical effectiveness estimates for the monotherapies were drawn mainly from the 24 week NMA. Infection rates were not meta-analysed but were drawn from a weighted pooled mean of incidence data at 24 weeks from the papers included in the NMA. Clinical effectiveness estimates for insulin were drawn from Monami et al[192] for NPH and from Waugh et al[193] for intensified NPH (see

Table **29**). (The AG does not know how these figures for "intensified NPH" were obtained. Usually if NPH was insufficient, short-acting insulin would be added at meal-times.)

Table 29 Astrazeneca central clinical effectiveness estimates

Drug	Flozin	Glitpin	Pio	SU	NPH	Int. NPH
HbA1c	-0.74	-0.64	-0.90	-0.95	-1.10	-1.11
SBP	-5.87	-1.53	-1.31	-0.65	..	..
Weight (kg)	-2.81	-0.13	2.61	0.07	1.08	1.90
AEs						
UTI	0.092	0.022	0.153	..	..	..
GTI	0.074	0.002	..	..	..	..
Severe hypo	0.010	0.016	0.024	0.055	0.0004	0.0136
Non-severe hypo	..	..	..	..	0.0104	0.6024
1st cycle disc.	0.034	0.039	0.177	0.061	..	..

Treatment intensifications and discontinuations

A patient is modelled as intensifying treatment, first to NPH and then to intensified NPH, when their HbA1c breaches the 7.5% intensification threshold. The AG assumption is that the monotherapies are withdrawn at treatment intensification, but this is not explicit within the Astrazeneca submission.

Patients may also discontinue due to adverse events. The AG was unable to identify what was assumed for these patients: whether they switched to an alternative monotherapy and if so which, or whether they intensified to NPH insulin.

HbA1c evolution

In common with the AG modelling, the evolution of HbA1c is based upon equation 11 of the UKPDS68. Treatment intensification occurs if a patient's HbA1c breaches the 7.5% intensification threshold. This leads to a sawtooth evolution of HbA1c, as described in more detail in the section on the AG modelling.

Evolution of other risk factors

The evolution of SBP and the TC:HDL ratio was also based upon equations 12 and 13 of the UKPDS68. The section on the AG modelling describes this in some detail so it is not further described here.

Weight loss with the flozins is assumed to be maintained for two years after which it is assumed that patients rebound to their starting weight. A similar assumption appears to have been made for the gliptins, though the weight loss is only maintained for one year. The weight increases associated with the other treatments are assumed to be retained. Weight is also assumed to increase by 0.1kg annually.

Quality of life

The quality of life for a patient without any complications is a function of patient age, as drawn from analysis of EQ-5D data from the Health Survey for England 2003[194]:

$$QoL = 1.2066 - 0.0184 * Age + 0.0004 * Age^2 - 0.0000026 * Age^3$$

This results in a baseline quality of life of 0.882, with this slowly declining over time.

Quality of life decrements associated with the complications of diabetes were drawn from the UKPDS62[190] with the exception of that for End Stage Renal Disease (ESRD) which was drawn from the standard UKPDS OM1 source . Quality of life decrements for hypoglycaemic events were drawn from Currie et al[195], but note that it appears that the coefficient for symptomatic event was applied to the number of symptomatic events rather than to their logarithm. The quality of life impacts of increasing BMI was drawn from Baghust and Beale.[191] These sources and values are all as per the AG modelling so are not tabulated here for reasons of space.

Note that the submission suggests that the BMI disutility is applied for all BMI changes and is not limited in its effects to changes in BMI when the patient BMI is greater than $25kgm^{-2}$. If this applies it may have biased the analysis in favour of the flozins by valuing reductions on patients' BMI among those with a BMI of less than $25kgm^{-2}$. But given the mean BMI at baseline of $29.2kgm^{-2}$ this may not be a particular concern.

A systematic literature review was conducted for UTI and GTI QoL decrements. For UTIs the average of the values of Barry et al[196] of -0.3732 for pyelonephritis and of -0.2894 for dysuria appears to have been coupled with an assumed duration of around three days to yield a QALY decrement of -0.00283 per UTI. Apparently no values were found for GTIs and as a consequence these had the same disutility applied.

Costs

The direct drug costs were sourced from the British National Formulary (BNF) 69. For both the flozins and the gliptins weighted average costs based upon their UK market share were used. This resulted in a mean annual flozin cost of £482 and a mean annual gliptin cost of £429. The annual cost of pioglitazone was £19 and the annual sulfonylurea cost was based upon gliclazide at an annual cost of £66. The cost of gliclazide suggests to the AG that modified release gliclazide has been assumed, as the standard version would be around half the cost that was applied.

The costs of the complications of diabetes in the first year and for subsequent years for blindness and amputation were based upon the UKPDS84.[187] This is the same source as the AG though the AG arrives at somewhat lower values. There may be a suggestion that indexation by AstraZeneca was

based on 2007 prices, when the UKPDS84 is in 2012 prices. But the source of the discrepancies is unclear.

AG calculations suggest that the UKPDS84 average inpatient costs and outpatient costs for those without any of the modelled complications have not been included within the AstraZeneca modelling. If this is the case it would be a quite serious omission, and would tend to bias the analysis in favour of the more effective treatment.

Astrazeneca may have used the UKPDS84 bespoke costing template to derive costs for a representative baseline patient, but this seems to be unlikely to be the source of the discrepancies between Astrazeneca and the AG. The Astrazeneca mean age at baseline is 55, while the AG has in order to be able to implement the costs probabilistically taken the costs example of the UKPDS82[186] for a 60 year old man. Costs are typically increasing in age in the UKPDS84.[187]

Table 5.10 of the AstraZeneca submission also does not include a cost for fatal IHD events despite these being within the UKPDS84 and seeming to be associated with deaths in the UKPDS82 and the UKPDS OM2. The UKPDS65 that goes along with the UKPDS68 and the UKPDS OM1 does not itemise a cost for fatal IHD events. But the AG understanding is that the AstraZeneca CDM modelling is based upon the UKPDS82 and as a consequence does not understand why fatal IHD events have had a zero cost assigned.

For reasons that are unclear, AstraZeneca chose to revert to the costs of the UKPDS65 for the ongoing costs among those with a history of IHD, CHF and stroke, and probably MI as well. This seems peculiar to the AG, given that the UKPDS82 and the UKPDS65 are very similar in their format with the UKPDS82 also presenting cost estimates for those with a history of IHD, CHF, stroke and MI.

ESRD was costed using the estimate of Baboolal et al.[197] for continuous ambulatory peritoneal dialysis. Previous NICE assessments have also used this reference, though have also tended to use the higher cost estimates within Baboolal et al for hospital haemodialysis. Astrazeneca argued that the use of the peritoneal dialysis cost was conservative.

Severe hypoglycaemia was costed using the Hammer et al (2009) reference, which is the reference used for the AG modelling. UTIs and GTIs were assumed to involve one GP appointment, costed at £46 using the PSSRU Unit Costs of Health and Social Care 2014.[198]See Table **30**.

Table 30 Astrazeneca costs of complications and adverse events.

	1st year		
Event	Fatal	Non-fatal	Subs. Years
Ischaemic Heart Disease		£12,762	£1,395
Myocardial Infarction	£2,605	£7,938	£2,177
Congestive Heart Failure		£5,180	£1,656
Stroke	£5,188	£11,450	£1,378
Amputation		£13,499	£4,618
Blindness		£6,502	£2,307
ESRD (including dialysis)		£18,776	£18,776
Severe hypoglycaemia		£424	£424
UTI		£46	£46
GTI		£46	£46

Results

The CDM modelling for the base case results in the following (see Table **31**). The AG assumption is that this is based upon deterministic modelling; i.e. with no second order sampling.

Table 31 Astrazeneca base case results: pairwise comparisons

	Flozins	Gliptins	net	Pioglitazone	net	SU	net
Drug costs	£5,638	£5,449	£190	£4,066	£1,572	£4,128	£1,510
Macro. compl.	£9,179	£9,251	-£72	£9,319	-£140	£9,226	-£47
Micro. compl.	£12,924	£12,938	-£14	£12,433	£491	£12,935	-£11
Hypoglycaemia	£175	£184	-£9	£197	-£22	£244	-£69
Other AE costs	£63	£51	£12	£53	£10	£49	£14
Total costs	£27,979	£27,873	£106	£26,067	£1,912	£26,582	£1,397
QALYs	13.206	13.188	0.018	13.111	0.095	13.179	0.027
ICER			£5,904		£20,089		£52,047

Within the pairwise comparisons, compared to the sulfonylureas the flozins offer some additional benefit of 0.027 QALYs but there are reasonable additional costs of £1,397 associated with this resulting in a cost effectiveness estimate of £52,047 per QALY.

The gains from the flozins compared to pioglitazone are larger at 0.095 QALYs which may be sufficient to justify the additional cost of £1,912 which results in a cost effectiveness estimate of £20,089 per QALY.

When compared with the gliptins, the flozins provide only a small additional gain of 0.018 QALYs but this is also at a relatively modest additional £106 cost which results in a cost effectiveness estimate of £5,904 per QALY.

The probabilistic pairwise modelling suggests that the flozins have a probability of being cost effective compared to the gliptin of 66%, compared to pioglitazone of 51% and compared to the sulfonylureas of 13%.

Ranking results in order of increasing cost sees the following (Table **32**).

Table 32 Astrazeneca base case results

	Cost	net	QALY	net	ICER
Pioglitazone	£26,067		13.111		
SU	£26,582	£515	13.179	0.068	£7,574
Gliptins	£27,873	£1,291	13.188	0.009	£143,444
Flozins	£27,979	£106	13.206	0.018	£5,904

As would be anticipated from the pairwise comparisons, it appears that the sulfonylureas have an acceptable cost effectiveness compared to pioglitazone of £7,574 per QALY. The gliptins offer minimal patient benefit compared to the sulfonylureas, 0.009 QALYs or the equivalent of around an additional 4 days survival, but with a reasonable increase in costs of £1,291 and a cost effectiveness estimate of £143k per QALY. As already noted, the flozins cost effectiveness estimate compared to the gliptins is good at £5,904 per QALY, but is poor against the sulfonylureas at £52,047 per QALY.

A variety of univariate sensitivity analyses were presented which varied the clinical effectiveness estimates to their upper and lower confidence interval limits, the disutilities for BMI changes to their upper and lower confidence interval limits, varied the disutilities for complications by ±10% and varied the total non-drug costs by ±25%.

Only the changes to the BMI disutility had any marked impact, with these impacts being mainly for the comparisons with pioglitazone and sulfonylurea. The lower confidence limit for the disutility of weight gains improved the cost effectiveness estimate compared to pioglitazone from £20,089 per QALY to £14,626 per QALY, while the upper confidence limit worsened it to £32,065 per QALY. The lower confidence limit for the utility of weight losses worsened the cost effectiveness compared to the sulfonylureas from £52,047 per QALY to £62,810 per QALY, while the upper confidence limit improved it to £4,434 per QALY.

Due to the CDM of AstraZeneca only modelling pairwise comparisons, the probabilistic modelling is only presented for the pairwise comparisons.

Compared to the gliptins, at willingness to pay values of £0, £20k and £30k per QALY the flozins are estimated to have a probability of being the most cost effective of around 42%, 65% and 68% with the CEAC converging to a little over 70% at high willingness to pay values.

Compared to pioglitazone, at willingness to pay values of £0, £20k and £30k per QALY the flozins are estimated to have a probability of being the most cost effective of around 0%, 50% and 80% with the CEAC converging to a little over 95% at high willingness to pay values.

Compared to sulfonylurea, at willingness to pay values of £0, £20k and £30k per QALY the flozins are estimated to have a probability of being the most cost effective of around 0%, 12% and 26% with the CEAC still slowly increasing to a little over 60% at a willingness to pay of £100k per QALY.

Scenario analyses

A range of scenario analyses were undertaken, mainly varying the HbA1c values at baseline and HbA1c thresholds for intensifying treatment, altering the assumptions around maintenance of weight effects and the drug costs that were applied (see Table **33**).

Table 33 Astrazeneca scenario analyses: cost effectiveness estimates for the flozins

	vs Gliptins			vs Pioglitazone			vs SUs		
	Δ £	Δ Q	ICER	Δ £	Δ Q	ICER	Δ £	Δ Q	ICER
HbA1c base. 7.5%, thresh. 8.0%	£225	0.021	£10,799	£3,059	0.106	£28,970	£2,335	0.037	£63,783
HbA1c base. 8.19%, thresh. 8.19%	£198	0.023	£8,694	£3,327	0.101	£32,982	£1,846	0.021	£88,934
HbA1c base. 7.5%, thresh 7.5, 8.0%	£100	0.020	£4,977	£1,902	0.101	£18,884	£1,382	0.026	£53,057
Flozin wgt maintain 1 year	£22	0.014	£1,583	£1,828	0.091	£20,077	£1,313	0.023	£57,839
Comparator wgt maintain 2 year	£115	0.014	£8,137	£1,913	0.101	£19,032	£1,435	0.028	£51,166
Flozin & Pio wgt conv. final int.	..	..	..	£1,818	0.048	£38,199	..	..	..
No discontinuations	£69	0.023	£3,035	n.a.	n.a.	n.a.	£1,431	0.028	£51,718
No AE disutility	£106	0.019	£5,685	n.a.	n.a.	n.a.	£1,397	0.028	£50,456
Cana 100 and 300 mkt share [redacted]	£137	0.018	£7,585	£1,943	0.095	£20,407	£1,427	0.027	£53,176
Sitagliptin price	£90	0.018	£4,996	..	..	..	..	..	..
Alogliptin price	£410	0.018	£22,756	..	..	..	..	..	..
20 year time horizon	£100	0.020	£5,093	£1,841	0.089	£20,611	£1,399	0.028	£49,275

The scenario analyses around adverse events and discontinuations for the comparison with pioglitazone were reported as having the same values as the corresponding analyses for sitagliptin, so appear to be typos.

Less stringent thresholds for intensification of therapy tended to worsen the cost effectiveness estimates. This seems likely to be mainly due to patients remaining on their monotherapy for longer and the associated increase in the direct drug costs, and not due to differences in the modelled complications of diabetes.

Weight convergence between the flozins and pioglitazone somewhat worsens the cost effectiveness estimate, due to this removing the weight gains associated with pioglitazone. Not that this convergence is only imposed at around the seventh or eighth year of the modelling.

Results compared to the gliptins are not particularly sensitive to whether the sitagliptin price is applied rather than the gliptins' prices weighted by their market shares, due to Astrazeneca estimating sitagliptin to have a market share of the gliptin monotherapy of [redacted] with the similarly prices saxagliptin and linagliptin having market shares of [redacted] and [redacted] respectively. Alogliptin is notably cheaper but is estimated to have less than a [redacted] market share.

Boehringer Ingelheim economic modelling

Boehringer Ingelheim presented the results of two modelling exercises: model A and model B.

Model A simulated the effects of one year of treatment. Thereafter the path of the patient was determined by the UKPDS OM1. This appears to have limited the direct treatment effects for elements such as treatment cost and the direct treatment effects upon adverse events and the quality of life impact of weight changes to one year's duration. At the end of the first year the AG assumption is that the treatment effects upon HbA1c, SBP, the TC:HDL ratio and weight were fed into the UKPDS OM1 to model the lifetime impact of the monotherapy. But the AG has not been able to identify how the model A does this and this assumption is based upon the written Boehringer Ingelheim submission which states that "*Model A… approach… patients undergo different comparator therapies for a year… the UKPDS model then undergoes a full 40 year … run*".

The AG understanding, which may not be correct, is that in effect this assumed that the patient remained on the monotherapy for the patient lifetime. And that it also assumed that the direct treatment costs, adverse events and direct quality of life impacts from weight changes would only apply during the first year.

Model B was somewhat more involved, and took a similar modelling approach to that of the modelling for the draft NICE CG for T2DM and the AG modelling for the current assessment. An excel front end was designed for the UKPDS OM1, which modelled the initial treatment effects and then used the UKPDS risk equations to model the evolution of the risk factors and the complications of diabetes. When patients' HbA1c breached the 7.5% intensification threshold they could first intensify by adding another oral drug, with a second intensification to NPH insulin also being possible. The survival curve of the OM1 coupled with the timing of intensifications permitted model B to calculate treatment specific treatment costs, adverse event rates and quality of life impacts from weight changes to add to the outputs of the OM1 model.

Boehringer Ingelheim noted that the model B ran the OM1 one year at a time, and that this can lead to an underestimation of the total costs and total QALYs over the 40 year time horizon. Boehringer Ingelheim suggested that this will tend to have underestimated the cost effectiveness of empagliflozin. Note that the AG approach was to run the OM1 model over the 40 year time horizon for each patient simulated.

Patient characteristics

Patient characteristics were drawn from patients within the Clinical Practice Research Datalink (CPRD). This identified 9,211 UK patients with who started their first oral antidiabetic treatment in 2014. While not all of the codes used for the search appear to have been specific to T2DM; e.g. diabetes mellitus, the minimum age at diagnosis was 23 with a mean of 60 and a standard deviation of 12 and the requirement to be starting an oral therapy should have restricted the sample to T2DM patients.

The average duration of diabetes was 2.9 years, 57% being male. The mean HbA1c was 8.49%, SBP 134mmHg, HDL 1.2mmol/l and LDL 4.0mmol/l. The mean BMI was 31kgm^{-2}.

The presence of existing complications was included: 6.63% for atrial fibrillation, 3.18% for PVD, 2.21% for MI, 1.92% for CHF, 1.62% for stroke, 6.13% for IHD, 0.29% for amputation, 0.23% for blindness, and 0.05% for renal failure.

Sequences modelled and treatment effectiveness

Model A only considers the first year of treatment with monotherapy and then adds the UKPDS costs and complications to this.

Model B considers the following treatment sequences, with patients intensifying to the next line of therapy when their HbA1c breaches the 7.5% intensification threshold (see Table **34** and Table **35**).

Table 34 Boehringer Ingelheim sequences modelled: 52 week data

Monotherapy	1st intensification	2nd intensification
Repaglinide 1mg	+Gliclazide	+ NPH insulin
Gliclazide	+Sitagliptin	
Pioglitazone 45mg	+Gliclazide	
Sitagliptin 100mg	+Gliclazide	
Empagliflozin 10mg	+Gliclazide	
Empagliflozin 25mg	+Gliclazide	

Pioglitazone 45mg was chosen due to it being the most commonly prescribed dose. The differences in cost between pioglitazone 30mg and pioglitazone 45mg are minimal.

AG comment. If repaglinide was insufficient, it would be replaced since for dual use, it is licensed only with metformin. So it would not be logical to add gliclazide to repaglinide since they act largely on the same receptors. Note also that 1mg is a small dose of repaglinide.

Table 35 Boehringer Ingelheim sequences modelled: 24 week data

Monotherapy	1st intensification	2nd intensification
Dapagliflozin 5mg	+Gliclazide	+ NPH insulin
Dapagliflozin 10mg	+Gliclazide	
Canagliflozin 100mg	+Gliclazide	
Canagliflozin 300mg	+Gliclazide	
Empagliflozin 10mg	+Gliclazide	
Empagliflozin 25mg	+Gliclazide	

Clinical effectiveness data was based upon 52 week data where available though this was apparently not available for canagliflozin or dapagliflozin. Sitagliptin clinical effectiveness estimates were apparently based upon 24 week data, though the submission does not state that 52 weeks data was not available. The effect upon SBP and rates of UTIs were also based upon 24 week data due to 52 week data not being available.

Hypoglycaemia rates were based upon sulfonylurea 16.4% annual rate of the NMA (for pooled sulfonylureas) coupled with odds ratios for each of the comparators against sulfonylurea. A ratio of non-severe to severe hypoglycaemia event rate of 17.2 was based upon the 0.009 annual rate of severe hypoglycaemia event rates of Leese et al (2003) coupled with the overall rates of hypoglycaemia in the NMA.

UTI event rates were based upon the annual placebo rates of 3.5% from the NMA coupled with odds ratios for each of the comparators.

Table 36 Boehringer Ingelheim monotherapies effectiveness: 24 week data

	Cana		Dapa		Empa	
	100mg	300mg	5mg	10mg	10mg	25mg
HbA1c	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TC:HDL	..	..	..	..	..	..
Hypos OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSHypos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shypos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTIs OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 37 Boehringer Ingelheim monotherapies effectiveness: 52 week data

	Empa		Pio	Repa	Sita	Gliclazide
	10mg	25mg	45mg	1mg	100mg	
HBA1c	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SBP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TC:HDL	..	..	..	..	..	..
Hypos OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NSHypos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Shypos	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTIs OR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTIs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The above table (Table **36** and Table **37**) reports the SBP effects and hypoglycaemia odds ratios from the written submission, and the hypoglycaemia event rates of the electronic model B.

Based upon a comparison of the written submission with the electronic model B it appears that the values relative to placebo have been inputted to the model. It appears that the placebo effects have not been included which may tend to have underestimated the absolute treatment effects from baseline to 24 or 52 weeks. This is with the exception of the hypoglycaemia and UTI rates.

Table 38 Boehringer Ingelheim intensification effectiveness data

	1st		2nd
	+SU	+Glitpin	NPH
HBA1c	[redacted]	[redacted]	[redacted]

SBP	[redacted]	[redacted]	[redacted]
Weight	[redacted]	[redacted]	[redacted]
TC:HDL	..	..	..
Hypos OR	[redacted]	[redacted]	..
NSHypos	[redacted]	[redacted]	[redacted]
Shypos	[redacted]	[redacted]	[redacted]
UTIs OR	[redacted]	[redacted]	..
UTIs	[redacted]	[redacted]	[redacted]

Note that for the intensifications the hypoglycaemia event odds ratios are apparently relative to placebo, while the UTI odds ratio is relative to the sulfonylurea. The UTI rate of NPH insulin was taken from the placebo arm of the NMA of the submission for empagliflozin combination therapy (see Table **38**).

Treatment intensifications and discontinuations

Within model A there are no treatment intensifications. Treatment with the monotherapies is for one year only, after which it appears that the UKPDS OM1 model is appended to this.

Within model B treatment is intensified when a patient is modelled as breaching the 7.5% HbA1c threshold.

It appears that discontinuations of therapy for reasons other than breaching the HbA1c threshold of 7.5% have not been modelled.

HbA1c evolution

The evolution of HbA1c is based upon equation 11 of the UKPDS68.

Within model A it appears that the patient's baseline HbA1c has the treatment effect of the initial monotherapy applied, with the UKPDS OM1 and hence relevant equation of the UKPDS68 being used to model its evolution thereafter. But as stated in the introduction, the AG has not been able to identify how model A interacts with the UKPDS OM1.

Within model B it appears that the patient's baseline HbA1c has the treatment effect of the initial monotherapy applied. Equation 11 of the UKPDS68 is then used to model the evolution of the patient's HbA1c until it breaches the 7.5% intensification threshold, at which point the treatment effect of the 1st intensification is applied. Equation 11 of the UKPDS68 is then applied until the 2nd intensification occurs with the associated treatment effect. HbA1c is then modelled as progressing as per equation 11 of the UKPDS68.

Evolution of the other risk factors

The evolution of SBP and the TC:HDL is based the UKPDS OM1 and hence relevant equation of the UKPDS68.

Within model A, it appears that the patient's baseline SBP had the treatment effect of the initial therapy applied, with equation 12 of the UKPDS68 being used to model its evolution thereafter. For the TC:HDL ratio due to there being no treatment effects estimated, it appears that equation 13 of the UKPDS68 was used to model the evolution throughout. But again, as stated in the introduction, the AG has not been able to identify how model A interacts with the UKPDS OM1.

Within model A the direct impacts of weight changes upon quality of life were only evaluated during the first year. For the UKPDS modelling it appears that weight losses were assumed to rebound to baseline after one year, while weight gains were assumed to remain indefinitely.

Within model B it appears that the patient's baseline SBP had the treatment effect of the initial therapy applied, with equation 12 of the UKPDS68 being used to model its evolution except for when a treatment intensification took place at which point the treatment effect of the intensification was applied. For the TC:HDL ratio due to there being no treatment effects estimated, it appears that equation 13 of the UKPDS68 was used to model the evolution throughout.

Within model B, weight losses from treatment were assumed to apply at 52 weeks and then to rebound to baseline at 104 weeks. Weight gains from treatment were assumed to be maintained indefinitely. A 0.1kg annual weight gain from natural history was also applied.

Quality of life

The quality of life at baseline and the quality of life decrements associated with the complications of diabetes were drawn from the recent paper by Alva et al[189] which reanalysed the updated UKPDS data set and in some sense updated the values of the UKPDS62 which is the paper that the AG modelling relies upon. The values and a commentary upon this are presented later in the comparison of modelling inputs used by the companies and the AG.

In common with the other companies, the quality of life impact of hypoglycaemic events was drawn from Currie et al.[195] Similarly, the quality of life decrement of -0.0061 per BMI point above 25kgm^{-2} was drawn from Baghust and Beale.[191]

The quality of life decrement of -0.00283 per UTI was based upon the estimates of Barry et al.[196]

Costs

Treatment costs were based upon the March 2015 MIMs.

The costs of diabetes without complications and the costs of the complications of diabetes were taken from the UKPDS84. Boehringer Ingelheim appears to have only applied the inpatient costs of the UKPDS84, and to have ignored the outpatient costs.

A cost of £380 per severe hypoglycaemic event was drawn from the draft NICE CG for T2DM, which is similar to that of the other company submissions and AG value.

UTIs were associated with a £36 cost, based upon the ERG report[199] for the previous STA of dapagliflozin for T2DM combination therapy.

Results

For model A, table 65 of the Boehringer Ingelheim submission presents the disaggregate costs and QALYs. Tables 66 and 67 present net quantities for the 52 week analyses relative to empagliflozin 25mg and empagliflozin 10mg respectively. Tables 68 and 69 present net quantities for the 24 week analyses relative to empagliflozin 25mg and empagliflozin 10mg respectively. The following presents a summary of these. For clarity:

- Model A is the one year decision tree model with the UKPDS OM1 tacked onto the end of it
- Model B is the Boehringer Ingelheim designed front and back end to the UKPDS OM1
- The 52 week analysis compares empagliflozin with the non-flozin comparators
- The 24 week analysis compares the flozins with one another

The combination of the above yields four sets of results.

Table 39 Boehringer Ingelheim results: Model A: 52 weeks analysis

			vs. pioglitazone		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Pio 45mg	[redacted]	[redacted]			
Gliclazide	[redacted]	[redacted]	£4	0.008	£500
Repag. 1mg	[redacted]	[redacted]	£30	0.009	£3,333
Empa. 25mg	[redacted]	[redacted]	£283	0.050	£5,634
Empa. 10mg	[redacted]	[redacted]	£304	0.043	£7,070
Sita. 100mg	[redacted]	[redacted]	£363	0.014	£25,929

Table 40 Boehringer Ingelheim results: Model A: 24 weeks analysis

			vs. canagliflozin 100mg		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Cana. 100mg	[redacted]	[redacted]			
Empa. 25mg	[redacted]	[redacted]	£26	-0.008	Dominated
Empa. 10mg	[redacted]	[redacted]	£43	-0.015	Dominated
Dapa. 10mg	[redacted]	[redacted]	£44	-0.018	Dominated
Dapa. 5mg	[redacted]	[redacted]	£55	-0.020	Dominated
Cana.300mg	[redacted]	[redacted]	£64	0.021	£3,048

The tables above (Table **39** and Table **40**) may have some rounding errors due to the AG constructing the ICERs versus pioglitazone.

In model A, empagliflozin 25 mg is estimated to dominate both empagliflozin 10mg and sitagliptin. Its cost effectiveness compared to pioglitazone is estimated to be £5,364 per QALY, compared to gliclazide is estimated to be £6,643 per QALY, and compared to repaglinide is estimated to be £6,171 per QALY. Pioglitazone, gliclazide and repaglinide are essentially estimated to all involve the same costs and patient benefits. Among the flozins, canagliflozin 100mg is estimated to dominate the other flozins with the exception of canagliflozin 300mg.

For Model B, table 71 of the submission presents the disaggregated results with tables 72 and 73 presenting the aggregate results. The AG has not managed to reconcile these to sources, so the results of both are presented below (Table **41**).

Table 41 Boehringer Ingelheim results: Model B costs: 52 week analysis

	Table 71					Table 72
	UKPDS	Tx	S Hypo	UTI	Total	Total
Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empa.10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pio 45mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Repa 1mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sita. 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gliclazide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note that the UKPDS costs of Model B that are reported in table 71 are around half those of Model A that are reported in table 65. This is a cause of some concern, and the reason for these discrepancies is far from obvious.

Table 42 Boehringer Ingelheim results: Model B QALYs: 52 week analysis

	Table 71						Table 72
	UKPDS	BMI	NSHypo	S Hypo	UTIs	Total	Total
Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empa.10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pio 45mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Repa 1mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sita 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gliclazide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The UKPDS QALYs of Model B are much more in line with those of Model A, the values in table 71 being around 90% of those in table 65 (Table **42**).

Table 43 Boehringer Ingelheim results: Model B: Table 71 : 52 week analysis

			vs pioglitazone		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Pio 45mg	[redacted]	[redacted]			
Repa 1mg	[redacted]	[redacted]	[redacted]	[redacted]	£57,416
Gliclazide	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	£35,223
Empa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	£43,987
Sita. 100mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom

Pioglitazone is estimated to be the cheapest comparator, and to dominate both gliclazide and sitagliptin. Repaglinide costs an additional [redacted] than pioglitazone and yields an additional [redacted] QALYs, resulting in a cost effectiveness estimate of £57,416 per QALY compared to pioglitazone. But repaglinide is extendedly dominated by empagliflozin 25mg which while costing [redacted] more than pioglitazone results in an additional [redacted] QALYs, hence a cost effectiveness estimate of £35,223 per QALY. Empagliflozin 25mg is estimated to dominated empagliflozin 10mg and sitagliptin 100mg.

But the AG assumption is that the correct cost effectiveness estimates are those of table 72, as reported below (Table **44**) since it is these that Boehringer Ingelheim has chosen to concentrate upon.

Table 44 Boehringer Ingelheim results: Model B: Table 72 : 52 week analysis

			vs pioglitazone		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Pio 45mg	[redacted]	[redacted]			
Repa 1mg	[redacted]	[redacted]	£635	0.025	£25,349
Gliclazide	[redacted]	[redacted]	£1,527	0.013	£122k
Sita. 100mg	[redacted]	[redacted]	£2,504	0.015	£164k
Empa. 25mg	[redacted]	[redacted]	£2,834	0.061	£46,480
Empa. 10mg	[redacted]	[redacted]	£2,837	0.056	£50,892

With the exception of repaglinide, none the other comparators appear to be cost effective compared to pioglitazone at conventional thresholds. But empagliflozin 25mg is estimated to cost an additional [redacted] when compared to sitagliptin 100mg and to cause an additional [redacted] QALYs, so have a cost effectiveness of £7,228 per QALY (Table 45, Table 46 and Table **47**).

Table 45 Boehringer Ingelheim results: Model B Costs: 24 week analysis

	Table 71					Table 72
	UKPDS	Tx	S Hypo	UTI	Total	Total
Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cana. 300mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cana. 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa. 5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 46 Boehringer Ingelheim results: Model B QALYs: 24 week analysis

	Table 71						Table 73
	UKPDS	BMI	NSHypo	S Hypo	UTIs	Total	Total

Empa. 25mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cana. 300mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cana. 100mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dapa. 5mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 47 Boehringer Ingelheim results: Model B: table 71: 24 weeks

			vs empagliflozin 25mg		
	Cost	QALY	Δ Cost	Δ QALY	ICER
Empa. 25mg	[redacted]	[redacted]			
Empa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Cana.100mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Dapa. 10mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Dapa. 5mg	[redacted]	[redacted]	[redacted]	[redacted]	Dom
Cana. 300mg	[redacted]	[redacted]	[redacted]	[redacted]	£62,442

Based upon table 71, empagliflozin 25mg is estimated to be the cheapest of the flozins and to dominate the other flozins with the exception of canagliflozin 300mg. Canagliflozin 300mg is estimated to cost an additional [redacted] compared to empagliflozin 25mg but also yield an additional [redacted] QALYs so have a cost effectiveness estimate of £62,442 per QALY.

But the AG assumption is that the correct cost effectiveness estimates are those implied by table 73, as reported below (Table **48**).

Table 48 Boehringer Ingelheim results: Model B: table 73: 24 weeks

			vs dapagliflozin 10mg			vs canagliflozin 100mg		
	Cost	QALY	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Dapa. 10mg	[redacted]	[redacted]						
Cana. 100mg	[redacted]	[redacted]	£1	0.033	£39			
Dapa. 5mg	[redacted]	[redacted]	£43	0.001	£31,840	£42	-0.032	Dom
Empa. 25mg	[redacted]	[redacted]	£46	0.021	£2,172	£45	-0.012	Dom
Empa. 10mg	[redacted]	[redacted]	£68	0.007	£9,835	£67	-0.026	Dom
Cana. 300mg	[redacted]	[redacted]	£970	0.056	£17,363	£969	0.023	£42,951

While dapagliflozin 10mg is technically the cheapest, being only £1 less than canagliflozin 100mg it is essentially the same cost but inferior to it. Canagliflozin 100mg is the more natural baseline. This dominated the other comparators, with the exception of canagliflozin 300mg. Canagliflozin 300mg

costs £969 more than canagliflozin 100mg but yield an additional 0.023 QALYs, resulting in a cost effectiveness estimate of £42,951 per QALY.

Sensitivity analyses

Boehringer Ingelheim did not present any sensitivity analyses.

Assessment group economic modelling

The model

The protocol specified that either the UKPDS outcomes model 1 (OM1) or the UKPDS outcomes model 2 (OM2) would be used by the AG. For some of its outputs the OM1 is quite different from the OM2 in its predictions. But the OM2 was not made available to the AG in time for the assessment and so as specified in the protocol the OM1 has been used.

As already noted, the OM1 predicts roughly double the number of myocardial infarctions over ten years, and the rates of IHD are also noticeably higher than those of the OM2. The ten year mortality is also higher with the OM1. Compared to the OM2, the OM1 will tend to over predict event rates and so overstate the benefits and cost savings arising from any avoidance of the complications of diabetes that are associated with the more effective treatment. Being more recent and more reflective of current practice, the OM2 would consequently have been much preferable had it been available to the AG.

The OM1 was used for the modelling that underlies the current draft NICE CG for diabetes. During its development the GDG reviewed in detail ten T2DM cost effectiveness models. These included the JADE and CORE models, but not the ECHO-T2DM model. Based upon validation and consistency with the NICE reference case the GDG very much preferred the OM1, in no small part due to it being based upon a single RCT rather than drawing a range of modelling inputs from disparate sources.

The AG has developed a front and back end to the OM1. Briefly, for each patient and treatment strategy that is simulated the AG front end models the patient's progression from monotherapy through the various treatment intensifications over a 40 year time horizon in annual cycles. This in turn introduces the patient's evolutions of HbA1c, SBP, TC:HDL, BMI, hypoglycaemia event rates, adverse events and treatment costs. The evolutions of the patient's HbA1c, SBP and TC:HDL are then fed into the OM1 which models the complications of diabetes and patient lifespan, and outputs the costs and quality of life impacts of living with diabetes and the patient's survival curve. The AG back end takes the OM1 survival curve and uses this to condition the evolutions of the patient's BMI, hypoglycaemia event rates, adverse events and treatment costs. The cost and quality of life impacts of these are then summed with the cost and quality of life impacts outputted by the OM1.

In slightly more detail, patients start on monotherapy but intensify their treatment if their HbA1c is modelled as breaching the 7.5% threshold. Intensifications typically add another treatment to a patient's existing treatment(s). This permits treatment sequences to be modelled, starting with monotherapy but with subsequent treatment intensifications, these intensifications eventually leading to first basal insulin and then basal-bolus insulin. Each treatment within a sequence is associated with treatment costs, weight changes, hypoglycaemic events and adverse events. The AG modelling also

permits treatments to be associated with a discontinuation rate in their first year, with patients who discontinue being assumed to switch to another treatment at the same line of therapy.

For each patient that is modelled, the modelled treatment sequences lead to a modelled evolution of HbA1c, SBP and TC:HDL ratio. These, together with the patient's baseline characteristics, are fed into the OM1. The OM1 then models the rates of the complications of diabetes, such as CHF, and the patient survival, which results in estimates for the discounted costs and QALY impacts of the complications of diabetes over the modelled lifetime of the patient. A survival curve is also drawn from the OM1 model. Due to the model being an individual patient simulation any given patient is run through the model many times, say 1,000 inner loops, in order to reduce Mote-Carlo sampling error. In effect this is the same as running a cohort of 1,000 identical patients through the model. The OM1 survival curve is the proportion of this cohort, or 1,000 inner loops, that is modelled as surviving. This survival curve conditions the AG front end evolutions of treatment sequences and the cost and QALY impacts of their treatment costs, weight changes, hypoglycaemic events and adverse events.

For the deterministic model run the OM1 correctly outputs the relevant survival curve. Unfortunately, for the PSA iterations it appears that the OM1 does not output the relevant survival curve. As a consequence, the relevant survival curve has had to be imputed from the OM1 annual discounted QALY estimates by an initial run of the model with the baseline quality of life set equal to unity and the quality of life decrements of the complications all set to zero. The resulting annual discounted QALYs were then undiscounted to arrive at the patient specific survival curve. (For the PSA each patient was run with 100 inner loops, and as a consequence the imputed survival curve had a granularity of 1%) But this also meant that the PSA had to run the OM1 model twice for each strategy for a given patient for a given PSA iteration. This also required that the same random number seed be used for each of these model runs in order for the imputed survival curve to be consistent with the second run of the model that estimated the strategy's costs and benefits. The OM1 only permits the random number seed to be 1 of 100 values. The AG model randomly assigned this value during the PSA, keeping this value constant between the two model runs for a given patient for a given PSA iteration. Having to run the model twice for a given patient for a given PSA iteration also significantly increased the time it took to run the PSA.

An element that the OM1 cannot address is the requirement for patients receiving a flozin to have their dose of it reduced or discontinued based upon renal function and eGFR rates. While the AG has a number of issues with the Janssen modelling, the use of the ECHO-T2DM model did permit this to be explored though the AG has not reviewed the implementation of this in any detail. It would be interesting to know the impact that turning off these discontinuations would have upon the cost effectiveness estimates of the Janssen modelling. If this is significant enough to affect the conclusions

that would be drawn from the Janssen modelling it could suggest additional modelling uncertainty from the AG use of the OM1.

The AG visual basic modelling has the advantage of permitting up to twelve treatment strategies to be simultaneously compared with one another, with the correlation between treatments' effects being properly taken into account. Each PSA iteration also uses the same set of parameter values and random number seed across all the treatment strategies being modelled. This in turn permits the correct characterisation of uncertainty within the probabilistic modelling.

Model runs

The draft NICE CG for diabetes concluded after a number of model runs that with a patient cohort of 35,000 or more there was little to be gained from running more than 100 inner loops to reduce Monte-Carlo sampling error. As a consequence, probabilistic results were based upon 1,000 PSA iterations each with a patient cohort of 50,000 with 100 inner loops. For deterministic model runs, i.e. those without any second order sampling, the modelling for the CG increased the number of inner loops to 1,000 as recommended within the OM1 manual.

The AG has adopted the same approach.

Probabilistic sampling

The risk factor evolution parameters of equations 11, 12 and 13 of the UKPDS68 were received as 1,000 bootstrap samples from the UKPDS group (Personal communication Prof Alastair Gray University of Oxford June 2015). The UKPDS OM1 also only permits 1,000 bootstraps.

The other parameters within the modelling were sampled by the AG. Clinical effectiveness was sampled within the NMA, with this outputting 10,000 lookup values for the various clinical effectiveness parameters. But due to the OM1 only permitting 1,000 bootstraps and the time taken to run the PSA, a subset of 1,000 were sampled from the 10,000 lookup values of the NMA. It was checked that these subsets had means that were similar to the central estimates of the NMA.

Other parameters were sampled by the AG using the distributions outlined below.

Patient characteristics at baseline

The patient characteristics at baseline are taken from the current draft NICE CG for diabetes. This undertook extensive analysis of the THIN data base, supported by some additional data from the Health Survey for England (see Table **49**).

Table 49 NICE CG baseline risk factors and baseline complication rates

Age	59.8	Atrial fibrillation	0.81%
Duration diabetes	2.0	PVD	0.51%
Male	57%	MI	0.80%
BMI	31.9	CHF	0.50%
HbA1c	8.40%	Stroke	0.50%
SBP	137.5	IHD	2.70%
TC	4.96	Amputation	0.10%
HDL	1.18	Blindness	0.40%
Current smoker	18.1%	Renal failure	0.20%
Past smoker	34.0%		

These were sampled once for the modelling using the full variance-covariance between the characteristics, as per the modelling for the current draft NICE CG for diabetes.

The AG has adopted these values with the exception of the baseline the baseline TC:HDL ratio. TC:HDL has been assumed to be 3.0 due to NICE guidelines on atorvastatin use in people with diabetes. This change in therapy may be partly the cause of the differences between the OM1 and the OM2. A scenario analysis applies the values of the NICE CG and evolves these according to the UKPDS 68 equation 13.

Astrazeneca argued that the baseline HbA1c should be 7.5% in order to be in line with NICE guidelines. But the patients modelled are starting their first drug treatment after on average having been diagnosed with diabetes for 2.0 years. The mean HbA1c at diagnosis was estimated to be 8.2%. It seems unlikely that most patients will have successfully controlled their diabetes through diet and exercise and got below 7.5% if they were above it at diagnosis, only to subsequently lose this control. As a consequence, the base case will apply the baseline HbA1c values as estimated within the draft NICE CG. A scenario analysis applies a common 7.5% HbA1c at baseline across the 50,000 patients simulated.

Sequences modelled

As outlined in the assessment protocol, in line with NICE guidelines patients will intensify their treatment if their HbA1c breaches the 7.5% intensification threshold. As a consequence, the modelling needs to take into account the clinical effects and costs of these intensifications. Based upon expert opinion the AG has modelled the following treatment sequences (Table **50**).

Table 50 AG treatment sequences modelled

Monotherapy	1st intensification	2nd intensification	3rd intensification

Repaglinide	-Repaglinide +Pioglitazone +Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Gliclazide	+Pioglitazone	+NPH insulin	-Gliclazide +Bolus insulin
Pioglitazone	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Sitagliptin	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Dapagliflozin	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Empagliflozin	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin
Canagliflozin100	+Gliclazide	+NPH insulin	-Gliclazide +Bolus insulin

Clinical effectiveness

The clinical effectiveness estimates are drawn from the Warwick AG NMA as presented in the clinical effectiveness section and from a review of the literature. Events rates are annual unless otherwise stated (Table **51** and Table **52**).

Table 51 AG monotherapy clinical effectiveness estimates: non-flozins

	Gliclazide		Pio.		Repag.		Sita.	
	μ	s.e.	μ	s.e.	μ	s.e.	μ	s.e.
HbA1c	-1.301	0.014	-1.200	0.011	-1.200	0.360	-0.723	0.019
SBP	-0.600	0.520	-1.400	0.500	-1.000	0.000	0.394	0.048
Weight	1.397	0.013	2.962	0.009	0.100	0.670	-0.003	0.275
Sev. Hypo	0.10%	0.04%	0.00%	0.00%	2.00%	0.70%	0.00%	0.00%
Symp. Hypo	1.30%	0.40%	0.00%	0.00%	13.00%	1.70%	0.00%	0.00%
UTI	4.00%	1.00%	4.00%	1.00%	4.00%	1.00%	4.00%	1.00%
GTI	1.00%	0.49%	1.00%	0.49%	1.00%	0.49%	1.00%	0.49%
Disc.	3.30%	0.82%	9.00%	0.74%	5.00%	3.00%	4.00%	1.30%

Note that in the above the rates of hypoglycaemia, UTIs and GTIs are annual.

Table 52 AG monotherapy clinical effectiveness estimates: flozins

	Dapa. 10		Empa. 25		Cana.300	
	μ	s.e.	μ	s.e.	μ	s.e.
HbA1c	-0.704	0.016	-0.870	0.016	-1.153	0.032
SBP	-2.931	0.024	-3.743	0.054	-1.338	0.048
Weight	-2.457	0.006	-2.471	0.008	-3.577	0.012
Sev. Hypo	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
Symp. Hypo	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
UTI	5.50%	1.97%	5.40%	1.50%	6.60%	1.80%
GTI	4.50%	1.80%	3.60%	0.64%	5.00%	2.00%
Disc.	3.00%	1.50%	1.80%	0.91%	2.00%	1.00%

For the flozins the UTIs rates and GTIs rates are half-yearly.

For the intensifications, due to a lack of data the addition of a treatment is assumed to have the same clinical effectiveness regardless of what it is being added to (see Table **53** and Table **54**).

Table 53 AG 1st intensification clinical effectiveness estimates

	+Pio		+Glicl.		-Repag. +Glicl. +Pio.	
	μ	s.e.	μ	s.e.	μ	s.e.
HbA1c	-1.200	0.011	-1.010	0.011	-1.200	0.011
SBP	-1.400	0.500	-0.600	0.520	-1.400	0.500
Weight	2.800	0.160	1.300	0.070	2.800	0.160
Sev. Hypo	0.00%	0.00%	0.00%	0.00%	0.10%	0.18%
Symp. Hypo	10.70%	1.80%	11.20%	2.10%	10.70%	1.80%
GMI	4.0%	1.0%	4.0%	1.0%	4.0%	1.0%
UTI	1.0%	0.5%	1.0%	0.5%	1.0%	0.5%

Table 54 AG 2nd and 3rd intensification clinical effectiveness estimates

	+NPH		+Bolus	
	μ	s.e.	μ	s.e.
HbA1c	-1.200	0.300	-0.660	0.060
SBP	-0.500	1.200	0.000	0.000
Weight	3.600	0.500	0.800	0.200
Sev. Hypo	0.40%	0.17%	0.7%	0.5%
Symp. Hypo	14.0%	5.1%	38.0%	2.9%
UTI	0.0%	0.0%	6.0%	1.4%
GTI	0.0%	0.0%	0.0%	0.0%

Adjusting the HbA1c effect for a patient's baseline HbA1c

The NICE CG modelling estimated two alternative models for the change at one year in HbA1c. The first corresponded to the base case approach of the AG, though metformin was the reference treatment in the NICE CG NMA rather than placebo as in the AG NMA.

- estimate a reference treatment's absolute change in HbA1c from baseline, t_0, to the end of the first cycle, t_1: Δ_{abs}
- estimate the difference between the reference treatment and the other treatments at the end of the first cycle: ΔTx_{rel}
- $H_1 = H_0 + \Delta_{abs} + \Delta Tx_{rel}$

For instance, suppose that the change between t_0 and t_1 for metformin $\Delta_{abs} = -1.49$ and that the difference between metformin and canagliflozin at t_1 was $\Delta Tx_{rel} = -0.51$. A patient with a baseline H_0=9.00 would be estimated to have $H_1 = 9.00 – 1.49 – 0.51 = 7.00$, whereas a patient with a baseline H_0=7.00 would be estimated to have H1 = 7.00 – 1.49 – 0.51 = 5.00.

But a strong correlation was observed between the trials' metformin absolute effect between t_0 and t_1 and their mean baseline HbA1c. As a consequence the NICE CG explored adding an additional term to Δ_{abs} to make the change also a function of the baseline HbA1c, H_0. This led to the following adjusted model for the HbA1c at the end of the first cycle:

$$H_1 = H_0 + (\Delta_{abs} + \beta (H_0 - 7.5)) + \Delta Tx_{rel}$$

with ΔTx_{rel} being taken from the NICE CG NMA.

The Δ_{abs} and β were not estimated during the NMA, but were separately estimated using the same data for metformin as was used in the NMA. The adjusted model simplifies to the unadjusted model by setting β=0. This resulted in the following coefficients (see Table **55**):

Table 55 NICE CG adjustment to reference treatment HbA1c effect by baseline HbA1c

	Unadjusted (95% CrI)	Adjusted (95% CrI)
Δ_{abs}	-1.49 (-2.16,-0.90)	-0.78 (-1.65, 0.03)
β	..	-0.50 (-0.78, -0.21)

and the following unadjusted and adjusted treatment effects for metformin (see Figure **12**).

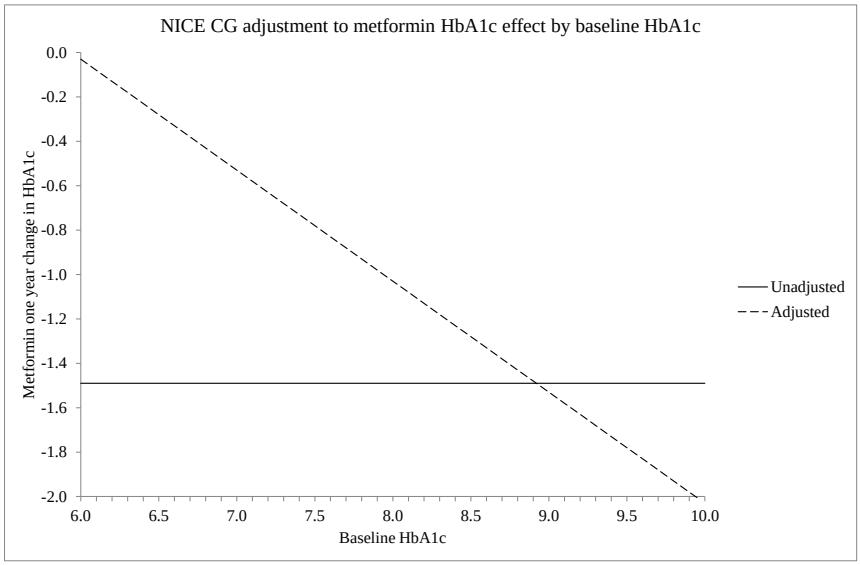

Figure 12 NICE CG adjustment to reference treatment HbA1c effect by baseline HbA1c

In essence, the adjusted function adds the difference between the two intercepts -1.49 and -0.78, or a constant 0.71, and the β (H_0 -7.5) to the unadjusted H_1. In other words for a given baseline H_0 the H_1 of the adjusted function is a constant difference from the H_1 of the unadjusted function, regardless of the treatment effect relative to metformin ΔTx_{rel}. Since β = -0.50 is negative the reduction in HbA1c between t_0 and t_1 is larger for those with a high baseline H_0. The application of the adjusted function means that more patients will see a treatment reduce their HbA1c to below the NICE treatment intensification threshold of 7.5%. It also prevents patients with a low baseline H_0 being modelled as falling to perhaps unrealistically low values of HbA1c.

The adjusted function was preferred for the NICE CG due to a superior information criterion and because the influence of β was judged to be significant with its 95% credible interval all lying below zero.

For the patient with a baseline H_0 = 9.00 the adjusted model estimates that under canagliflozin their H_1 = 9.00 – 0.78 – 0.50 * (9.00 – 7.50) – 0.51 = 6.96 in contrast to the estimate of H_1 = 7.00 of the unadjusted model. Similarly, for the patient with a baseline H_0 = 7. 00 the adjusted model estimates that under canagliflozin their H_1 = 7.00 – 0.78 – 0.50 * (7.00 – 7.50) – 0.51 = 5.96 in contrast to the estimate of H_1 = 5.00 of the unadjusted model.

The NICE CG function is for metformin monotherapy. It was also estimated using a very different data set than the current AG NMA. Any read across from it to the current assessment is consequently almost submerged in caveats. But if a hypothetical placebo in the monotherapy metformin trials would have a reasonably constant relative effect, Tx_{rel}, at t_1 compared to metformin, and this placebo effect could reasonably be read across to the current patient group it would be reasonable to explore the impact of the above relationship in the current assessment. For a deterministic analysis this simply requires 0.71 - 0.50 (H_0 -7.5) to be added to the overall unadjusted H_1 treatment effect estimated for each of the active treatments within the AG NMA. This will be explored as a scenario analysis.

Treatment discontinuations

Those discontinuing in the first year for reasons other than their HbA1c not falling below the 7.5% threshold are assumed to switch to another monotherapy:

- From flozins to gliclazide
- From sitagliptin to gliclazide
- From pioglitazone to gliclazide
- From gliclazide to pioglitazone
- From repaglinide to pioglitazone

Note that those discontinuing are in effect assumed to switch to the alternative monotherapy, and its associated subsequent sequence of treatments. These sequences were retained in part due to data availability and in part due to a desire not to introduce new sequences with a different number of possible intensification steps.

But these subsequent sequences may also contain the treatment that the patient was intolerant of as a monotherapy. This only affects those discontinuing from pioglitazone and those discontinuing from gliclazide. In the light of this, a scenario analysis will be undertaken where among those discontinuing and switching treatment the intensification step to a treatment the patient was intolerant of as a monotherapy is omitted.

The modelling of the evolution of the risk factors

For HbA1c the base case applies the treatment effect in the first year of therapy. HbA1c is then evolved according to the UKPDS68 equation 11. But this is with the proviso of the UKPDS68 equation 11 parameter for a patient being in their second year since diagnosis not being applied. Given the average patient duration of 2 years since diagnosis, the AG is of the opinion that including the UKPDS68 equation 11 parameter for a patient being in their second year since diagnosis would

tend to double count the treatment effect of starting a monotherapy. HbA1c is evolved according to the UKPDS68 equation 11 until the treatment intensification threshold of 7.5% is breached.

At this point, the patient intensifies treatment and receives the associated treatment effect. HbA1c is then once more evolved according to the UKPDS68 equation 11 until the treatment intensification threshold of 7.5% is breached, at which point another treatment intensification occurs. When the patient is on the last line of treatment HbA1c evolves according to the UKPDS68 equation 11 with no further treatment intensifications.

Should a patient discontinue and move onto an alternative treatment at the same line of therapy, the treatment effect of the first line of therapy of the first year is removed, one year's evolution according to the UKPDS68 equation 11 added and the treatment effect of the alternative treatment applied.

The paragraphs that follow are purely for illustration. The data are hypothetical and bear no realtion to the actual inouts used in the AG modelling.
The figure below (Figure **13**) shows how this results in a sawtooth evolution of HbA1c. It applies to a patient aged 40 with a current baseline HbA1c of 7.6%, who at diagnosis was aged 30 and had an HbA1c of 7.0%. It assumes four strategies, with initial reductions in HbA1c of 1.8%, 1.6%, 1.4% and 1.2% for strategies 1, 2, 3 and 4 respectively. It also assumes that two further treatment intensifications are possible, these having the reductions in HbA1c of 2.0% and 1.5% across the four strategies.

The modelled evolution of strategies 2, 3 and 4 are very similar with the first treatment intensification at year 6. The slightly greater initial reduction in HbA1c of strategy 1 is sufficient for HbA1c not to breach the treatment intensification threshold of 7.5% until 1 year later, and as a consequence the first treatment intensification does not occur until year 7.

The other figure below (Figure **13**) illustrates how a discontinuation could affect the modelled evolution of HbA1c for strategy 1. This still assumes a reduction in HbA1c from the original treatment of 1.8% but from the alternative treatment that the patient discontinues to of only 0.5%. As before, this also assumes that two further treatment intensifications are possible, with reductions in HbA1c of -2.0% and -1.5% in the sequence that the patient has discontinued to.

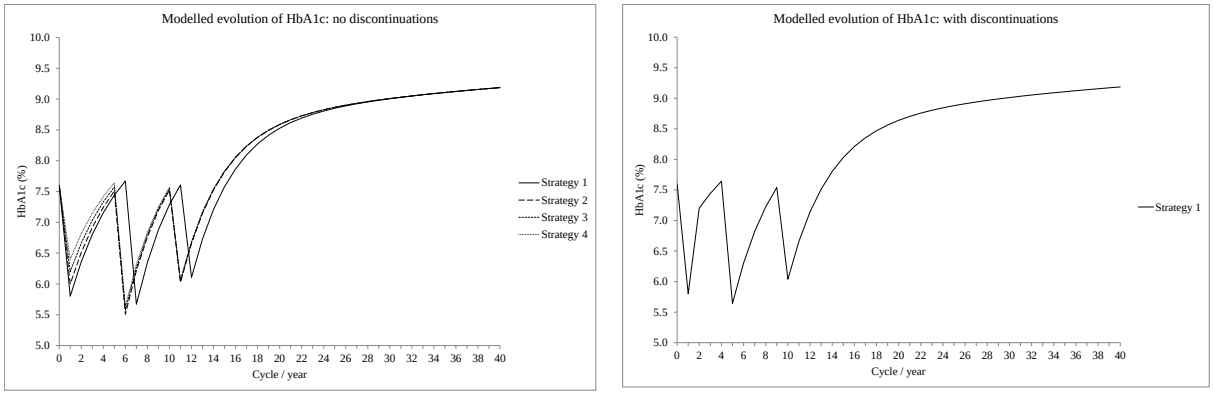

Figure 13 Example of the modelled evolution of HbA1c: UKPDS68

In the light of the Janssen submission, the model has been constructed to permit a scenario analysis of HbA1c having a linear increase and for the annual rate of increase to be treatment specific. The following illustrates the same initial treatment effects for strategies 1, 2, 3 and 4 but for the annual linear increase while on first line treatment to be 0.1%, 0.2%, 0.3% and 0.4% respectively. For those discontinuing from strategy 1, the annual linear increase while on the first line treatment is assumed to be 0.05%. Subsequent to treatment intensification the evolution of HbA1c is assumed to revert to the UKPDS68 equation 11, but the model has the facility to impose treatment specific annual linear increases in HbA1c at any or all treatment lines (see Figure **14**).

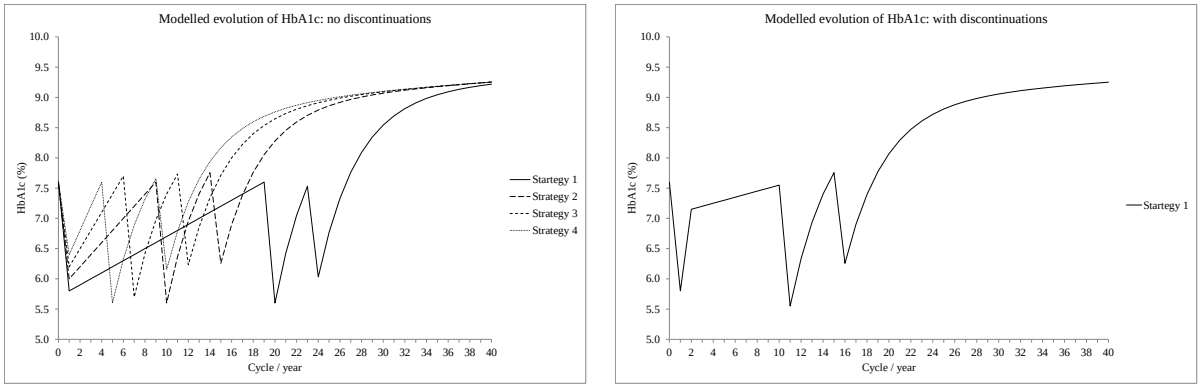

Figure 14 Example of the modelled evolution of HbA1c: Linear evolution

A similar approach is taken for the modelling of the evolution of SBP and can be for the TC:HDL ratio, though the base case holds the TC:HDL ratio constant at 3.0. The UKPDS 68 specifies equation 12 and equation 13 respectively. Treatment intensifications are still determined by the modelled HbA1c.

The figures below (Figure **15**) illustrate the modelled evolution of SBP for the same patient as before with HbA1c being modelled to evolve according to the UKPDS68 equation 11, with an SBP at

baseline of 130mmHg and at diagnosis of 120mmHg. It assumes initial treatment effects of -20mmHg, -15mmHg, -10mmHg and -5mmHg for strategies 1, 2, 3 and 4 respectively. The intensifications result in treatment effects of -15mmHg and -10mmHg. For the patient modelled as discontinuing during strategy 1, the alternative treatment effect is -5mmHg.

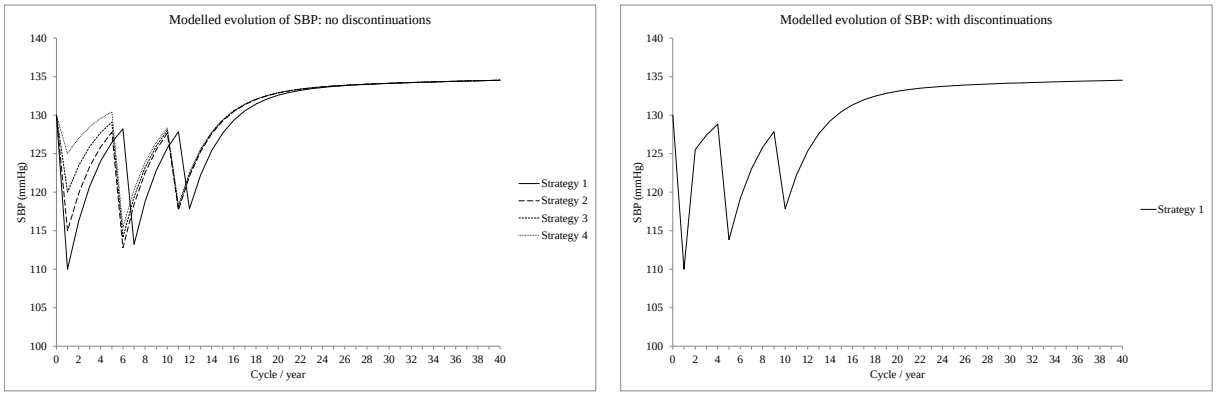

Figure 15 Example of the modelled evolution of SBP

The figures below (Figure **16**) illustrate the UKPDS modelled evolution of the TC:HDL ratio for the same patient as before with HbA1c being modelled to evolve according to the UKPDS68 equation 11, with a TC:HDL ratio at baseline of 4.0 and a ratio at diagnosis of 3.5. It assumes initial treatment effects of -1.0, -0.8, -0.6 and -0.4 for strategies 1, 2, 3 and 4 respectively. The intensifications result in treatment effects of -0.8 and -0.6. For the patient modelled as discontinuing during strategy 1, the alternative treatment effect is -0.4.

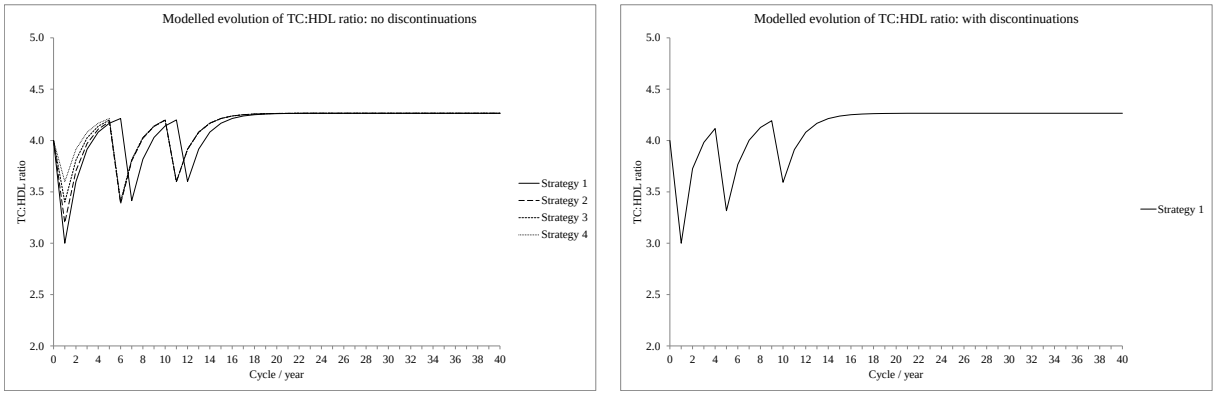

Figure 16 Example of the modelled evolution of the TC:HDL ratio

The modelled evolution of HBA1c, SBP and the TC:HDL ratio for a range of inputted patient characteristics was cross checked with that modelled by the UKPDS OM1 at central UKPDS68

parameter values. The modelled evolutions values were typically around 99.99% of the values simulated by the UKPDS OM1 model.

The evolution of the patient BMI is based upon a mean annual increase in weight of 0.1kg as has typically been used in previous NICE assessments of treatments for diabetes and is apparently originally sourced from the 2006 NICE CG on obesity. Over the course of NICE assessments and guidelines development for treatments for T2DM, quite a lot of discussion has focussed upon what is reasonable to assume about the duration of weight effects. There has been some argument that initial weight losses associated with treatment may tend to be transient, while initial weight gains associated with treatment may tend to be more permanent. In the light of this five scenarios are modelled:

- Treatment weight changes maintained with no rebound to natural history
- Treatment weight gains maintained, weight losses rebound to natural history after one year
- Treatment weight gains maintained, weight losses rebound to natural history at intensification
- Treatment weight changes rebound to natural history after one year
- Treatment weight changes rebound to natural history at intensification

The following figures (Figure **17** and Figure **18**) illustrates weight changes being maintained for a patient of 85kg at baseline. Initial hypothetical treatment effects are +5kg, -5kg, +10kg and -4kg for strategies 1, 2, 3 and 4 respectively. The intensifications result in treatment effects of +3kg and +7kg. For the patient modelled as discontinuing during strategy 1, the alternative treatment effect is +4kg with the additional weight gains in the alternative sequence thereafter being assumed to be the same as in the original sequence.

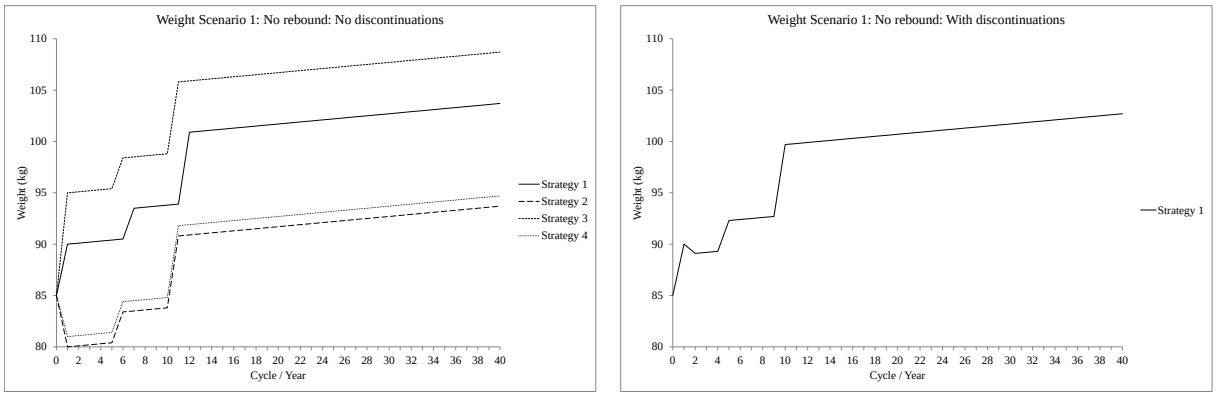

Figure 17 Example of the modelled evolution of patient weight: no rebound

The above is largely self-explanatory. Within the evolution of weight for the patient under strategy 1 who discontinues there is a drop in weight between year 1 and year 2. This arises due to the patient being assumed to come off their original treatment which would have increased their weight by 5kg

and to move onto the alternative treatment which only increases their weight by 4kg. Quite when the patient would discontinue and as a consequence quite what the balance would be in practise between the 5kg increase and the 4kg increase during the first line of treatment is a moot point.

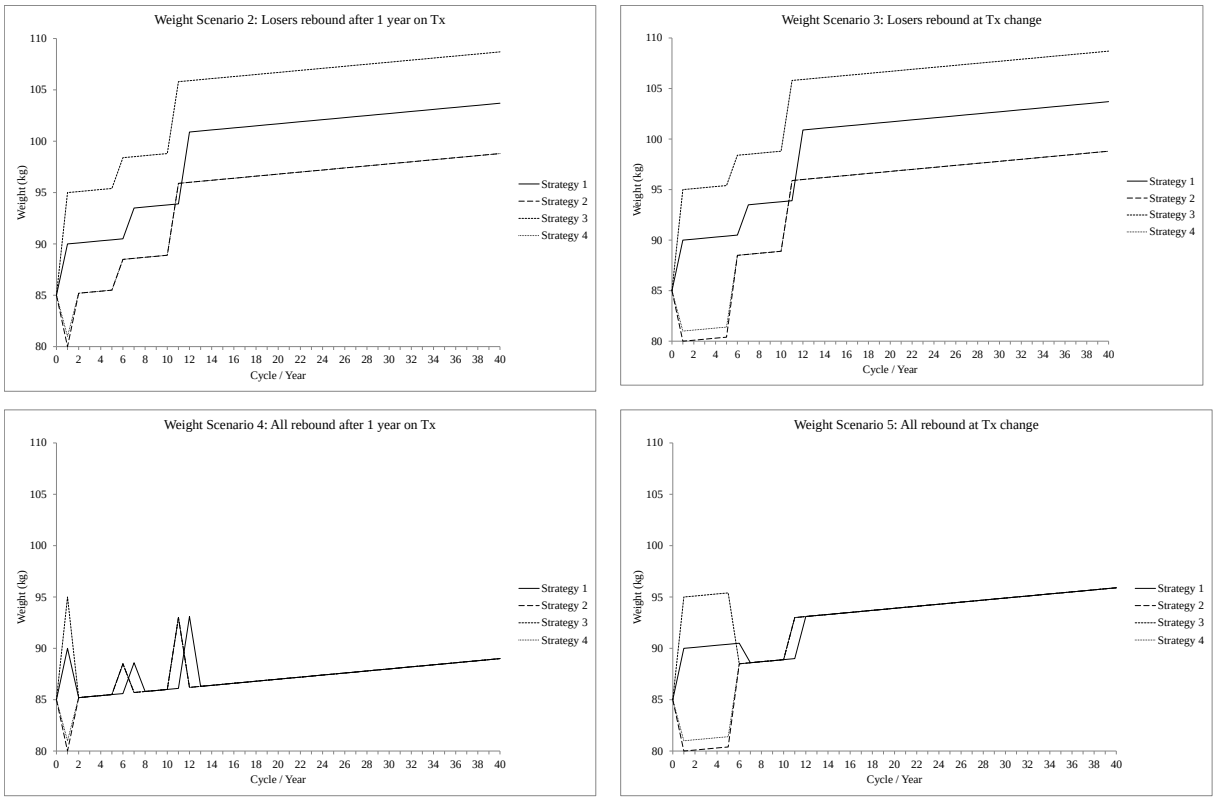

Figure 18 Example of the modelled evolution of patient weight: rebound scenarios

BMI scenarios 2 and 3 which have weight losses rebounding to natural history do not affect strategy 1 and strategy 2 as they only incur weight gains.

BMI scenario 2 sees weight losses rebound to natural history after one year. So at year 2 both strategy 2 and strategy 4 have rebounded to natural history and 85.2kg weight. Thereafter they follow the same weight profile since their treatment intensifications also occur at the same time: year 6 and year 11.

BMI scenario 3 sees weight losses rebound to natural history at treatment intensification. To model this, the rebound to natural history that would have applied in the previous year is first calculated, 85.5kg, to which the intensification treatment effect of +3.0kg is added to give a weight of 88.5kg at year 6. An alternative way of looking at this is to view the intensification treatment effect of +3.0 kg being composed of two parts: +0.1kg natural history and +2.9kg additional treatment effect.

BMI scenario 4 sees all weight changes rebound to natural history after one year. The figure is largely self-explanatory, with all initial treatment effects being removed at year 2. Thereafter, strategies 2, 3 and 4 intensify treatment at years 6 and 11, and see the weight gains associated with intensifications rebound to natural history at years 7 and 12. Strategy 1 intensifies later at years 7 and 12, hence the later rebounds to natural history.

BMI scenario 5 sees all weight changes rebound to natural history at treatment change. Strategies 2, 3 and 4 intensify treatment at years 6 and 11, so rebound to natural history the following year. But the weight gains associated with the intensifications are then added to where the patients rebound to. As a result, after the first intensification at year 6 the patient weight is 88.5kg for strategies 2, 3 and 4. For strategy 1 the intensification is one year later, with it joining the other strategies at a weight of 88.6kg in year 7. Much the same happens at the subsequent intensification.

Note that the BMI scenarios 4 and 5 may be felt to be literally unrealistic, with weight gains rebounding to natural history after one year or at the next treatment change. But they may be better thought of as causing weight to converge between strategies either after one year or at treatment change. In terms of the modelling of the impact of BMI upon quality of life this will not be exactly arithmetically correct due to the floor of 25kgm^{-2} on the BMI quality of life coefficient of -0.0061. Given the baseline BMI of 31.6kgm^{-2} (s.d. 6.0kgm^{-2}) around 13% of patients are modelled as having a BMI of less than 25kgm^{-2}. For some of these patients, the rebounds of scenarios 4 and 5 may not be exactly equivalent in their quality of life impacts to weight converging between the strategies by some other means, e.g. at the value of strategy with the higher BMI. But the AG is of the opinion that any differences are likely to be minor.

Note that there is a minor error within the implementation of weight in the AG modelling. The UKPDS 68 requires that the BMI at diagnosis is used and this has been implemented correctly. But the AG modelling assumes that the BMI at diagnosis also applies at baseline. It can be argued that the BMI at baseline should be the BMI at diagnosis plus the natural history increase that would be implied by the duration at baseline. But since the mean duration of diabetes at baseline is estimated to be 2.0 years and that this adjustment would only affect results for the subset of patients during the cycles they bordered the 25kgm^{-2} threshold, this error will have negligible effects upon net results.

Diabetic ketoacidosis

There has been some suggestion that the flozins may increase the risk of diabetic ketoacidosis (DKA). But rates are low in absolute terms, with the EMA reporting 101 cases over about 500,000 patient years of flozins use.

The Diabetics With Eating Disorders surveyed England's PCTs in 2010.[200] Among the 45 PCTs that responded the mean cost per DKA event was £1,438, or £1,552 in 2014 prices. But given an event rate of 1 per 5,000 patient years the average increase in costs associated with this is minimal: around 30p per year of treatment. The typical duration of DKA events is also quite short, certainly less than one week, though there may be recurrence. But even with quite a large quality of life decrement, given the absolute event rate and the short duration any overall average QALY impact will also be minimal.

There remains the possibility of an increased mortality with DKA among those with T2DM. This could have more of an impact upon the modelled average QALY in the flozin arms. But there is no simple means of incorporating this mortality into the OM1 modelling, this being a black box to the AG.

For the above reasons DKA has not been incorporated into the economic modelling.

Quality of life: Diabetes and the complications of diabetes

Given the use of the OM1 model, the AG draws the quality of life value for those without any complications and quality of life impacts for the complications of diabetes from the UKPDS62 as below (Table **56**). A value for renal failure is not given in the UKPDS62 and as a consequence the AG has used the OM1 default value of -0.263 as drawn from Kiberd and Jindal.[201]

Table 56 Quality of life values for OM1 complications

	Mean	S.E.	Distribution
No complications	0.785	0.005	Beta
MI	-0.055	0.006	LogNormal
IHD	-0.090	0.018	LogNormal
Stroke	-0.164	0.030	LogNormal
CHF	-0.108	0.031	LogNormal
Amp	-0.280	0.056	LogNormal
Blind	-0.074	0.033	LogNormal
Renal	-0.263	0.020	LogNormal

Quality of life: Weight

In common with most NICE assessments of treatment for T2DM and the draft NICE T2DM CG the AG applies the utility decrement of -0.0061 (s.e. 0.001) of Baghust and Beale.[191] Within Baghust and Beale, this decrement applies if the patient BMI is above 25kgm^{-2}.

The mean BMI within the UKPDS RCT was 27.7kgm^{-2} and it is from here that the mean baseline utility of 0.785 is drawn. As a consequence, since the modelling applies the -0.0061 quality of life decrement when the patient BMI rises above 25kgm^{-2}, it can be argued that the baseline utility of 0.785 should have 0.0061* 2.7 = 0.0165 added to it. This modification is adopted for the AG base case.

Quality of life: Treatment discontinuations

Based upon the draft NICE T2DM CG treatment discontinuations were assigned a QALY decrement associated with nausea as drawn from Matza et al.[202] The with and without nausea quality of life values of 0.89 and 0.85 were taken to apply yielding a mean decrement of 0.04, which the GDG thought a six week duration would be most reasonable estimate, this yielding a mean QALY decrement of -0.00462.

Quality of life: Adverse events

The 2012 NICE clinical guideline on infection, CG139[203], undertook a systematic review of the literature for studies of the quality of life impacts of symptomatic UTIs. This identified 11 studies, but a number of these are of limited relevance to the current assessment due to; e.g. being among patients with spinal cord injuries. Of the 11 studies, 5 appear most relevant to the current assessment.

CG139 also undertook economic modelling of treatments for UTIs. But due to the available clinical effectiveness estimates being largely limited to those with spinal cord injury, the quality of life values applied are of limited relevance to the current assessment. This modelling also considered progression from symptomatic UTIs through to 1st line drug resistance and multi drug resistance with these causing increased costs and mortality.

The AG modelling for the current assessment only considers the quality of life and cost impacts of treating UTIs and GTIs, with the assumption that none will progress to a more serious condition. So there are caveats around these estimates and for a given set of inputs they could be seen as being biased and on the low side.

Barry et al[196] used the Index of Wellbeing (IWB) to estimate quality of life among young women with UTIs. The IWB is a generic QoL instrument. The mapping function from the IWB to quality of life values was apparently based upon 62 American nurses and non-medical graduate students ranking health states on a sixteen point scale. Barry et al report that the IWB includes hospitalisation, self-care and ambulatory status and permits the inclusion of the following symptoms: pain, bleeding, itching discharge from sexual organs, painful burning or frequent urination, burning or itching rash on large areas of the body, taking medication, fever or chills with aching all over and pain in the chest,

stomach, sides, back or hips. But Barry et al do not describe quite how the quality of life values for the health states for their model have been derived. It appears to be based upon an index patient with a set of symptoms; i.e. expert opinion linked to the IWB. They estimated disutilities of 0.3732 for pyelonephritis, and 0.2894 for vaginitis and persistent dysuria. Their duration was estimated to be 10 days, 5 days and 5 days respectively.

Gold et al[204] catalogued 130 health states using the Health and Activity Limitation Index (HALex) with the score being based upon the answers to two questions of the US National Health Interview Survey. A multi-attribute utility model resulted in quality of life estimates of 1.00 for perfect health, and 0.73 for bladder infection and 0.66 for kidney infection. The derivation of these weights is not particularly clear within the paper.

Ackerman et al[205] used the standard gamble to estimate quality of life values among 13 men with moderate to severe benign prostatic hyperplasia. A variety of health states were described, with the quality of life impacts of severe UTIs being estimated among these. The six risk averse men reported an average value of 0.972 for a severe UTI, while the seven non-risk averse men reported an average value of 0.893. Over the 13 respondents this suggests an average disutility per severe UTI of 0.071.

Ellis and Verma[206] measured the impact of UTIs among 118 otherwise healthy Canadian women through a case controlled analysis using the SF-36 with a recall period of 1 day. The mapping from the SF-36 to the EQ-5D quality of life values based upon the algorithm of Ara and Brazier[207] appears to have been undertaken by the NICE CG, since Ellis and Verma only report the mean values for the eight main elements of the SF-36. This resulted in those with no UTI having a mean quality of life of 0.922 compared to 0.724 for those with a UTI.

Ernst et al[208] used the Quality of Wellbeing (QWB) to estimates the quality of life among 146 American women diagnosed with acute cystisis, and the effect of treatment upon quality of life. Those with T2DM were excluded from the study. The QWB was administered 3, 7, 14 and 28 days after the initial visit. The quality of life at baseline was 0.68 (s.d. 0.03) compared to 0.81 (s.d. 0.11) at the 28 day point. Quality of life among those cured compared to those not cured was statistically significantly different at the 5% level at day 3, 7 and 14 with respective QWB scores of 0.77 vs 0.72, 0.82 vs 0.71 and 0.83 vs 0.76. See Table **57**.

Table 57 Quality of life estimates for infections

Source	Barry et al[196]		Gold et al[204]	Ackerman et al[205]		Ellis & Verma[206]	Ernst et al[208]
Year	1997		1998	2000		2000	2005
Country	USA		USA	USA		Canada	USA
N	n.a.		n.a.	13 men		118 women	146 women
Method	IWB		HALex	SG		SF-36	QWB
Condition	Pyelonephritis	Vaginitis / Dysuria	Bladder	Kidney	UTIs	UTIs	Cystitis
Disutility	0.3732	0.2894	0.27	0.33	0.028-0.107	0.198	0.05-0.13

Of the above papers, Ackerman et al[205] could be argued as coming closest to the NICE reference case. But the usefulness of these estimates is compromised by the small sample size. As a consequence, the AG will use the results of the Janssen TTO study for the base case of quality of life impact of -0.19 for a UTI and -0.25 for a GTI. Nicolle et al[93] estimated median durations of UTIs of between 11.0 days and 12.5 days, and as a consequence the base case will assume 2 weeks average duration.

Quality of life: Hypoglycaemia

Following the lead of the current draft NICE CG for T2DM, the source for the base case for the quality of life decrements associated with hypoglycaemia events will be Currie et al.[195] This used two separate 3 month recall surveys among patients with diabetes (n=408 and n=897) undertaken at different time points, though 145 patients responded to both surveys.

The first survey was used to estimate a relationship between a patient's score on the Hypoglycaemic Fear Survey (HFS) and the number of non-severe and severe hypoglycaemic episodes with coefficients of 1.773 (s.e. 0.230) and 5.881 (s.e. 1.553) respectively. The second survey was used to estimate the relationship between the HFS and the EQ-5D quality of life with a coefficient of -0.008 (s.e. 0.001).

Given the 3 month recall period, the mapping between non-severe hypoglycaemia event rates and the patient's score on the Hypoglycaemic Fear Survey requires that rates be converted to 3 monthly rates before the 1.773 HFS coefficient can be applied to arrive at the correct QALY decrement.

The authors of the draft NICE CG for T2DM also point out that the table 4 coefficient of Currie et al for non-severe hypoglycaemia events is based upon the natural logarithm of the event rate rather than the event rate. As such it is non-linear. To account for this the AG has followed the method of the authors of the draft NICE CG for T2DM and applied a Poisson distribution to give the spread of possible patient event rates prior to applying the coefficients of Currie et al.[195]

The 5.881 HFS coefficient of table 4 of Currie et al[195] for severe hypoglycaemic events was derived on a dichotomous basis, equal to 1 if there were any events reported during the previous 3 months and equal to 0 if there were none reported. The draft NICE clinical guideline gives a quite complicated formula for accounting for this using a binomial distribution, but this apparently simplifies to the quarterly probability times the utility decrement (Personal communication, Gabriel Rogers, NICE, 17 Aug 2015).

The following (
Table **58**) present a range of estimates based upon this method.

Table 58 AG QALY decrements by hypoglycaemia event rates.

	Severe	Non-severe					
Annual	1.00	10	20	30	40	50	60
Quarterly	0.22	2.50	5.00	7.50	10.00	12.50	15.00
HFS	1.30	1.39	2.65	3.44	3.98	4.40	4.74
Annual QALY loss	-0.010	-0.011	-0.021	-0.032	-0.035	-0.038	-0.040

But the values of Currie et al[195] come with some major caveats. As Currie et al note regarding the two data sources "*These studies were commissioned by the pharmaceutical industry to inform drug developments around new treatments for diabetes that were found to reduce the frequency of hypoglycaemia*". The paper authorship also includes staff of Novo Nordisk and Sanofi-Aventis.
The values are based on results from two surveys, with a response rate of 31%. The hypoglycaemic episodes were recent events and perhaps therefore fresh in the memory. 45% of respondents were on insulin. Respondents might have been more likely to have been concerned about hypoglycaemia than non-respondents.

Around one third of respondents had T1DM with around two thirds of respondents having T2DM. Quite what covariates were considered and quite how the paper arrived at the final regressions is not entirely explicit. Patient data from the first survey was removed if the patient also responded to the second survey reducing the sample to 57% of the original, though the reasons for this and impacts of doing so are not clear. Similarly, the grouping of complications was also possible subjective.

The 5.881 coefficient for severe hypoglycaemia episodes was also based on whether patients had had any severe hypoglycaemia events during the recall period. If within this group the mean number of severe hypoglycaemic episodes was more than one, it seems likely that the coefficient somewhat overestimates the impact of having one severe hypoglycaemia events within a quarter.

The patient number and demographics reported by Currie et al[195] for the first survey are based upon the full 408 patients of this survey. But for the analysis 175 of these patients were excluded due to also being in the second survey. As a consequence the demographics and events rates that were used when analysing the data subset of the first survey cannot be determined.

For the full 408 patients of the first survey only 2.3% (n=9) reported experiencing at least one severe hypoglycaemic event during the previous 3 months. This was somewhat less than the 8.6% (n=77) proportion who reported experiencing at least one severe hypoglycaemic event during the previous three months in the second survey.

For severe hypoglycaemic event rates, Currie et al state that within the surveys "*very few people >1 event*" and they report a mean rate of "*1.47 events per patient year*". It seems likely that this mean rate was the average across the two surveys. It would have been useful to have known the mean rate for each survey, and for the small subset of the first survey that was actually analysed.

The relationship between having experienced at least one severe hypoglycaemic event in the last three months and the HFS index i.e. the 5.881 coefficient consequently appears to have been based upon at most 9 patients reporting. The restriction of the subset analysed to 57% of the total sample of the first survey suggests that this number is likely to have been somewhat less than 9 patients. This gives rise to the possibility of an outlier patient within this small subset having an unreasonable impact upon results. The construction of the subset was at investigator discretion.

The AG cannot further interrogate the data underlying the estimates of Currie et al, and it is possible that they may be over-estimates. Note that in common with previous analyses, the method of the table above in effect assumes that a patient experiences at most one severe hypoglycaemic event per quarter. There may be an argument for dividing the QALY decrement associated with severe hypoglycaemic events by 1.47, the mean event rate reported in Currie et al.

Costs: Direct drug costs

Treatment costs are based upon the NHS drug tariff, and upon list prices where there are no entries in the NHS drug tariff. Daily doses are assumed to be 60mg for gliclazide modified release, 45mg for

pioglitazone, 6.0mg for repaglinide, 100mg for sitagliptin, 10mg for dapagliflozin, 25mg for empagliflozin and 300mg for canagliflozin. Insulins costs are based upon a requirement of 0.3IU/kg when starting NPH, with this rising to 0.55IU/kg when adding bolus which itself is required at 0.2IU/kg.

AG expert opinion also suggests that those receiving pioglitazone should have their BNP measured, perhaps initially six-monthly but annually thereafter. A marginal cost of £21has been taken from Craig et al[41] and inflated to 2014 prices using a 1.25 multiplier from the PSSRU HCSC index. This has also been assumed to require a dedicated GP appointment, costed at £46 using the 2014 PSSRU Unit Costs of Health and Social Care.

This results in the following treatment costs for the oral therapies (see Table **59**).

Table 59 AG sequences drug and administration costs

Strategy	Mono	Cost	1st intens.	Cost	2nd intens.	Cost	3rd intens.	Cost
S1	Empa.	£476.98	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Empa.	£476.98	Empa.	£476.98	Empa.	£476.98
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S1 Total Cost		£476.98		£539.16		£730.63		£947.88
S2	Cana.	£476.93	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Cana.	£476.93	Cana.	£476.93	Cana.	£476.93
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S2 Total Cost		£476.93		£539.11		£730.58		£947.83
S3	Dapa.	£476.98	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Dapa.	£476.98	Dapa.	£476.98	Dapa.	£476.98
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S3 Total Cost		£476.98		£539.16		£730.63		£947.88
S4	Sita.	£433.57	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Sita.	£433.57	Sita.	£433.57	Sita.	£433.57
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S4 Total Cost		£433.57		£495.75		£687.22		£904.47
S5	Pio.	£93.25	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Pio.	£93.25	Pio.	£93.25	Pio.	£93.25
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S5 Total Cost		£93.25		£155.43		£346.90		£564.15
S6	Glicl. MR	£62.18	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Pio.	£93.25	Pio.	£93.25	Pio.	£93.25
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S6 Total Cost		£62.18		£155.43		£346.90		£564.15
S7	Repag.	£71.91	Glicl. MR	£62.18	Glicl. MR	£62.18		
			Pio.	£93.25	Pio.	£93.25	Pio.	£93.25
					INS	£140.38	Int. INS	£351.36
					SMBG	£51.09	SMBG	£119.54
S7 Total Cost		£71.91		£155.43		£346.90		£564.15

The AG modelled sequences differ from those of the company submissions in that patients add NPH insulin rather than switch to it and as a consequence the cost differences between the sequences are maintained over the horizon of the modelling. In the light of this, a scenario analysis is undertaken which withdraws the initial monotherapies when patients switch to NPH insulin. Note that this only affects the direct drug costs and not the clinical effectiveness estimates.

Costs: Treatment intensifications and switches

Treatment intensifications due to breaching the 7.5% HbA1c threshold and treatment switches due to intolerance are assumed to involve one 12 minute GP appointment. This is costed using the 2014 PSSRU Unit Costs of Health and Social Care at £46.

Costs: Adverse events

The AG treatment assumptions are in broadly line with those of the Janssen submission as below, with this resource use being confirmed by AG expert opinion. Medication for UTIs is assumed to be seven days of trimethropim 200mg twice daily, for male GTIs fluconazole 200mg and for female GTIs 3 200mg clotrizamole pessaries (see Table **60**).

Table 60 AG resource use and costs of UTIs and GTIs

UTI	GP visits	Unit cost	Cost	Drug Tariff	Cost/day	Days	Cost	Total Cost
Male	2	£46	£92	£1.87	£0.62	7	£4.36	£96
Female	1	£46	£46	£1.87	£0.62	7	£4.36	£50
Total UTI cost								£73
GTI	GP visits	Unit cost	Cost	Drug Tariff	Cost/day	Days	Cost	Total Cost
Male	1	£46	£46	£6.23	£0.89	7	£6.23	£52
Female	1	£46	£46	£3.10	..	..	£3.10	£49
Total GTI cost								£51

These costs are largely based upon assumption and have consequently been treated deterministically within the probabilistic modelling.

Costs: Hypoglycaemic events

The AG have followed the current draft NICE CG when costing severe hypoglycaemic events.

Hammer et al[209] in an industry sponsored study surveyed 147 UK patients with T2DM using insulin with 19 reporting at least one severe hypoglycaemic episode in the previous year with 10 of these being treated by the NHS. Hammer et al acknowledge the non-random selection of their patient sample, but provide few details about it other than to note that it was predominantly through health

care professionals. Patients were surveyed using a structured questionnaire about the resource use associated with their events.

Patients were divided into three groups: those who had their severe hypoglycaemic event treated by family members; by medical practitioners in the community; and, in hospital. The mean direct costs by type in 2007 prices were £33 for those treated by family members, due to NHS follow up costs, £231 for those treated by the NHS in the community and £862 for those treated in hospital. Due to the non-random sample selection there is no definitive means to translate these into a weighted average cost. But the GDG of the draft NICE CG were reportedly happy to use the sample proportion treated by family members (9/19) coupled with an assumption that of the remainder 65% would be treated in hospital.

This results in a mean cost per severe hypoglycaemic event of £353 in 2007 prices which when uplifted by a 1.16 multiplier from the 2014 PSSRU Unit Costs of Health and Social Care results in an estimate of £411.

Costs: Diabetes and the complications of diabetes

The costs of diabetes and the complications of diabetes are taken from the UKPDS84 tables, and uprated for inflation using a multiplier of 1.03 from the PSSRU HCHS index (see Table **61**).

Table 61 Costs of diabetes and its complications

	Inpatient costs			Outpatient costs			Total
	Mean	S.E.	Dist	Mean	S.E.	Dist	Mean
No event	£472	£33	Gamma	£547	£23	Gamma	£1,019
Event year							
Fatal myocardial infarction	£1,564	£531	Gamma				£1,564
Fatal ischaemic heart disease	£3,873	£1,250	Gamma				£3,873
Fatal stroke	£4,066	£1,158	Gamma				£4,066
Myocardial infarction	£6,560	£1,062	Gamma	£990	£95	Gamma	£7,550
Ischaemic heart disease	£10,044	£1,484	Gamma	£888	£78	Gamma	£10,932
Stroke	£6,998	£1,685	Gamma	£1,122	£191	Gamma	£8,120
Heart failure	£3,281	£846	Gamma	£1,007	£167	Gamma	£4,288
Amputation	£9,816	£1,849	Gamma	£2,775	£713	Gamma	£12,592
Blindness in one eye	£1,393	£588	Gamma	£1,841	£571	Gamma	£3,234
Subsequent years							
Myocardial infarction	£1,187	£158	Gamma	£690	£49	Gamma	£1,877
Ischaemic heart disease	£1,249	£153	Gamma	£673	£42	Gamma	£1,922
Stroke	£1,157	£234	Gamma	£777	£89	Gamma	£1,934
Heart failure	£1,515	£347	Gamma	£1,001	£98	Gamma	£2,515
Amputation	£1,843	£494	Gamma	£1,657	£242	Gamma	£3,499
Blindness in one eye	£466	£99	Gamma	£759	£89	Gamma	£1,225

It should be noted that these costs are for a representative 60 year old male patient, and are for a patient with only one complication. Costs are to a degree a function of age. There are interactions between complications within the UKPDS82 which mean that those with more than one complication do not necessarily incur a simple sum of the individual complication costs. Only one set of the costs of complications can be fed into the OM1. As a consequence, it has not been possible to take these effects into account, but they are not particularly marked.

The UKPDS84 does not provide a costing for renal disease. In common with the draft NICE CG for diabetes, these have been drawn from Lamping et al[210] with the inpatient cost in 1996 prices of £20,802 (s.e. £613) being uprated for inflation using a multiplier of 1.75 from the PSSRU HCSC index.

Assessment group sensitivity analyses

All scenario analyses have been run deterministically with a cohort of 50,000 patients and 1,000 inner loops to reduce Monte-Carlo error. The sensitivity analyses around the -0.0061 quality of life decrement per BMI point above 25kgm^{-2} and the rebound of treatments' effect upon weight are presented for all analyses:

- BMI 1: natural history progression with no rebound
- BMI 2: natural history progression with weight losses rebounding after one year
- BMI 3: natural history progression with weight losses rebounding at treatment change
- BMI 4: natural history progression with weight rebounding after one year
- BMI 5: natural history progression with weight rebounding at treatment change

The AG has also undertaken the following sensitivity analyses.

- SA01: At the third intensification patients switch to insulin plus gliclazide, and cease their other treatments
- SA02: Applying the UTI and GTI rates to all cycles of the model
- SA03: Assuming that all patients when starting monotherapy have an HbA1c of 7.5%
- SA04: Adjusting the HbA1c treatment effect for patients' baseline HbA1c values as in the NICE CG
- SA05: Not applying the discontinuation rates
- SA06: Applying the NICE CG baseline TC:HDL values and the UKPDS68 TC:HDL progression
- SA07: Applying the UKPDS68 year 2 parameter for the evolution of HbA1c
- SA08: Intensifying when adding gliclazide having a -0.47% HbA1c effect
- SA09: Applying the Janssen linear evolutions of HbA1c for all treatments
- SA10: Assuming that those discontinuing from a treatment omit any subsequent intensification step that reapplies this treatment
- SA11: SA01 and SA08 combined

Assessment group base case results

The disaggregate costs of the base case are as below (Table **62**).

Table 62 AG base case: Disaggregate costs

Quantity	Empa. 25	Cana. 300	Dapa. 10	Sita. 100	Pio.	Glicl.	Repag.
OM1 Costs	£22,880	£22,925	£22,926	£23,039	£22,905	£22,876	£22,871
Tx Costs	£9,768	£9,624	£9,811	£9,199	£4,521	£4,323	£4,401
Tx change	£95	£92	£96	£96	£94	£91	£92
Hypos	£20	£20	£21	£21	£19	£20	£46
UTI	£8	£10	£8	£3	£3	£3	£3
GTI	£4	£5	£5	£1	£1	£1	£1
Total costs	£32,775	£32,676	£32,866	£32,358	£27,543	£27,314	£27,413

The UKPDS OM1 costs are slightly lower for empagliflozin than for canagliflozin despite its smaller effect upon HbA1c. This seems likely to have arisen due to the larger SBP effect of empagliflozin, but

the differences are slight. All the flozins are similar, with slightly lower costs than sitagliptin due in part to the latter having little impact upon SBP whereas the flozins reduce it.

Pioglitazone, gliclazide and repaglinide are estimated to have similar or slightly lower UMPDS OM1 costs than the flozins which is in line with the estimates of them having slightly larger effects upon HbA1c.

Treatment costs are the main source of the differences in costs, as would be anticipated. The flozins are of similar cost, but canagliflozin is a reasonable amount cheaper. This arises due to the greater HbA1c effect of canagliflozin meaning that patients will tend to intensify to the more expensive subsequent lines of treatment slightly later.

For the base case, with the exception of repaglinide and to a lesser extent gliclazide, patients remain on their initial monotherapy throughout, adding treatments to it when they intensify. As a consequence, the annual treatment costs difference between sitagliptin and the flozins is maintained over the time horizon of the model and the sitagliptin treatment costs are noticeably lower than those of the flozins. This outweighs the slightly higher UKPDS OM1 costs for sitagliptin, and its total costs are a reasonable amount less than those of the flozins.

Pioglitazone, gliclazide and repaglinide treatment costs are considerably lower than those of the flozins and sitagliptin. Treatment costs cause the total costs of pioglitazone, gliclazide and repaglinide to be considerably less than those of the flozins and sitagliptin.

The disaggregate quality of life impacts of the base case are as below. Within this the total QALYs estimated under the UKPDS OM1 model and those associated with treatment switching, hypoglycaemic events and UTIs and GTIs are summed to give a subtotal. This subtotal corresponds to the sensitivity analysis of assuming that a patent's BMI has no impact upon the patient's quality of life. The QALY impacts from assuming a -0.0061 quality of life decrement for each BMI point above 25kgm^{-2} are then presented for each of the five weight progression scenarios that are modelled (see Table **63**).

Table 63 AG base case: Disaggregate QALYs

Quantity	Empa. 25	Cana. 300	Dapa. 10	Sita. 100	Pio.	Glicl.	Repag.
OM1 QALYs	10.380	10.382	10.369	10.355	10.385	10.393	10.390
Tx Switch	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Hypos	-0.001	-0.000	-0.000	-0.000	-0.000	-0.000	-0.001
UTI and GTI	-0.001	-0.002	-0.002	-0.000	-0.000	-0.000	-0.000
SubTotal	10.378	10.380	10.367	10.355	10.384	10.392	10.389
BMI 1	-0.631	-0.600	-0.633	-0.697	-0.772	-0.759	-0.726
BMI 2	-0.694	-0.689	-0.696	-0.700	-0.772	-0.759	-0.726
BMI 3	-0.684	-0.673	-0.686	-0.699	-0.772	-0.759	-0.726
BMI 4	-0.612	-0.610	-0.612	-0.616	-0.622	-0.622	-0.619
BMI 5	-0.622	-0.613	-0.623	-0.636	-0.656	-0.653	-0.645

The QALY estimates are driven by the UKPDS OM1 outputs, and the BMI quality of life decrements if these are applied. The other elements have little impact, though it should be borne in mind that the base case only applies the UTI rates and GTI rates during the first year.

The QALY losses associated with the -0.0061 quality of life decrement for each BMI point above 25kgm^{-2} may appear large at around 6% of the total QALYs. But the baseline QoL of 0.801 in the absence of complications, the quality of life impacts of complications and the baseline mean BMI of 31.9kgm^{-2} should be borne in mind. The baseline mean BMI of 31.9kgm^{-2} when coupled with the -0.0061 quality of life decrement per BMI point above 25kgm^{-2} reduces the baseline QoL of 0.801 in the absence of complications by around 4.5% by itself.

A summary of the total costs and QALYs with treatments ranked from the least expensive to the most expensive is presented below (Table **64**).

Table 64 AG base case: Lifetime total costs and QALYs

		Total QALYs					
Treatment	Total costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,314	10.392	9.633	9.633	9.633	9.771	9.739
Repag.	£27,413	10.389	9.663	9.663	9.663	9.770	9.744
Pio.	£27,543	10.384	9.612	9.612	9.612	9.762	9.728
Sita. 100	£32,358	10.355	9.657	9.655	9.655	9.739	9.719
Cana. 300	£32,676	10.380	9.780	9.691	9.707	9.770	9.767
Empa. 25	£32,775	10.378	9.747	9.683	9.694	9.766	9.756
Dapa. 10	£32,866	10.367	9.734	9.671	9.681	9.756	9.745

These quantities can be subtracted from one another to present how much more costly and effective each treatment is compared with the least costly treatment as below (Table **65**).

Table 65 AG base case: Lifetime net costs and QALYs versus the least costly treatment

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..	..
Repag.	£100	-0.003	0.030	0.030	0.030	-0.001	0.005
Pio.	£230	-0.008	-0.021	-0.021	-0.021	-0.008	-0.011
Sita. 100	£5,045	-0.037	0.024	0.022	0.022	-0.031	-0.020
Cana. 300	£5,362	-0.012	0.147	0.057	0.074	0.000	0.028
Empa. 25	£5,461	-0.015	0.113	0.050	0.061	-0.005	0.017
Dapa. 10	£5,553	-0.025	0.101	0.038	0.048	-0.015	0.006

There is a large step in total costs when moving from pioglitazone to sitagliptin driven by treatment costs. There is a reasonable step in total costs when moving from sitagliptin to canagliflozin.

Pioglitazone is estimated to be both more costly and less effective than repaglinide under all the BMI scenarios. Similarly, empagliflozin and dapagliflozin are estimated to be more costly and less effective than canagliflozin under all BMI scenarios, though the differences are not particularly large. This dominance is reflected in the estimates of cost effectiveness as tabulated below (Table **66**). Note that the following ICERs are not relative to the least costly treatment, but are relative to the next least costly treatment which is not dominated. In other words for BMI 1 the cost effectiveness of repaglinide compared to gliclazide is £3,331 per QALY and the cost effectiveness of canagliflozin relative to repaglinide is £44,994 per QALY.

Table 66 AG base case: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,331	£3,331	£3,331	Dom	£18,507
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£44,994	£192k	£119k	Dom	£235k
Empa. 25	Dom	Dom	Dom	Dom	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Dom = Dominated: i.e. more costly and less effective than another treatment						

If the effects of BMI upon quality of life are ignored or assumed not to apply gliclazide is estimated to be both the cheapest and the most effective treatment. It is cheaper than sitagliptin and the flozins by quite a large amount, though the differences in the total lifetime QALYs are less marked.

For the scenarios of BMI progressing with natural history and the -0.0061 BMI quality of life impact applying, if there is no rebound of treatment weight effects or only weight losses rebound the weight gain associated with gliclazide reduces its relative effectiveness. The smaller weight gain associated with repaglinide means that it is estimated to have a cost effectiveness of £3,331 per QALY compared to repaglinide under these scenarios.

The scenarios of both weight gains and weight losses rebounding may be felt to be unrealistic. But these are better seen as scenarios that explore when weight might tend to converge between the alternative treatments. If this happens after only one year the differences in weight between gliclazide and repaglinide are not maintained long enough for the BMI QALY effects to outweigh the QALYs estimated under the UKPDS OM1 and repaglinide remains dominated. Maintaining the difference for a longer period up until treatment change is sufficient for repaglinide to confer more QALYs and yields a cost effectiveness estimate of £18,507 per QALY.

Pioglitazone is estimated to yield slightly fewer QALYs under the UKPDS OM1 than gliclazide, and its larger weight gain than gliclazide further hampers it. It remains dominated by gliclazide under all scenarios. But this should not obscure the fact that the UKPDS OM1 estimates pioglitazone to be more effective than sitagliptin and marginally more effective than the flozins. Pioglitazone is also considerably cheaper than sitagliptin and the flozins. Without the quality of life impacts of weight changes pioglitazone is formally estimated to dominate sitagliptin and the flozins. Even with the quality of life impacts of weight changes the cost effectiveness estimates for sitagliptin and the flozins

compared to pioglitazone are poor and well above conventional thresholds. Only canagliflozin and empagliflozin show any reasonable cost effectiveness estimates compared to pioglitazone, and these only occur if treatment weight changes and the resulting differences in weight between treatments are assumed to be maintained over the patient lifetime. The BMI 1 scenario results in cost effectiveness estimates for canagliflozin and empagliflozin compared to pioglitazone of £30,537 per QALY and £38,889 per QALY respectively.

The UKPDS OM1 estimates sitagliptin to be slightly less effective than gliclazide. Being weight neutral its weight profile is superior to gliclazide, but this is insufficient to render it cost effective at conventional thresholds under any of the BMI scenarios when compared to gliclazide. Sitagliptin is dominated by gliclazide if there are no direct quality of life impacts from weight, and for the BMI scenario 4 and 5. For the BMI scenarios 1, 2 and 3 the cost effectiveness estimates for sitagliptin compared to gliclazide are £207k, £231k and £227k per QALY.

The UKPDS OM1 estimates canagliflozin to be slightly less effective than both gliclazide and repaglinide. Its superior weight profile means that applying the -0.0061 quality of life impact per BMI point canagliflozin is estimated to provide more benefits than both gliclazide and repaglinide, except for the scenario of all weight changes rebounding after one year. The cost effectiveness of canagliflozin compared to repaglinide is £44,994 per QALY if weight changes are maintained indefinitely. But for the other scenarios the cost effectiveness estimates are well into six figures.

If the flozins main comparator is sitagliptin, this eliminates the much less costly alternatives. The net quantities relative to sitagliptin are as follows (Table **67**).

Table 67 AG base case: Flozin cost effectiveness estimates relative to sitagliptin

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Sita. 100	..	..	..	..	..	..	..
Cana. 300	£318	0.025	0.123	0.036	0.052	0.031	0.048
Empa. 25	£416	0.023	0.089	0.028	0.038	0.026	0.037
Dapa. 10	£508	0.013	0.077	0.017	0.026	0.017	0.026

The cost effectiveness estimates for the flozins compared to sitagliptin is outlined below (Table **68**).

Table 68 AG base case: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,623	£2,590	£8,913	£6,111	£10,256	£6,627
Empa. 25	£18,341	£4,676	£14,716	£10,841	£15,734	£11,300
Dapa. 10	£40,383	£6,632	£30,710	£19,787	£30,487	£19,679

Even without their superior weight profiles, canagliflozin and empagliflozin are estimated to have reasonable cost effectiveness estimates compared to sitagliptin of £12,623 per QALY and £18,341 per QALY respectively. Factoring in the weight profiles and assuming that the -0.0061 quality of life decrement applies improves these cost effectiveness estimates. The picture for dapagliflozin is more mixed, in part due to the estimate of its impact upon HbA1c being similar to that of sitagliptin.

Assessment group sensitivity analyses results

SA01: Patients switch to insulin plus gliclazide and drop other therapies

Applying the same cost for the insulin containing regimes across the treatment arms results in the flozins changing their ordering when ranked by increasing total cost. Canagliflozin 300mg is now slightly more expensive than the other flozins. This is probably due to the larger HbA1c effect of canagliflozin meaning that patients on average switch to insulin slightly later compared to the other flozins (see Table **69**).

Table 69 AG SA01: Total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£26,628	10.392	9.633	9.633	9.633	9.771	9.739
Repag.	£26,719	10.389	9.663	9.663	9.663	9.770	9.744
Pio.	£26,835	10.384	9.612	9.612	9.612	9.762	9.728
Sita. 100	£28,875	10.355	9.657	9.655	9.655	9.739	9.719
Empa. 25	£28,990	10.378	9.747	9.683	9.694	9.766	9.756
Dapa. 10	£29,010	10.367	9.734	9.671	9.681	9.756	9.745
Cana. 300	£29,040	10.380	9.780	9.691	9.707	9.770	9.767

Total costs have fallen. As would be expected they have fallen furthest for the flozins and by almost as much for sitagliptin when compared to the base case (see Table **70**). Since only the treatment costs are changing there is not difference in QALYs.

Table 70 AG SA01: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	-£685	0.000	0.000	0.000	0.000	0.000	0.000
Repag.	-£694	0.000	0.000	0.000	0.000	0.000	0.000
Pio.	-£709	0.000	0.000	0.000	0.000	0.000	0.000
Sita. 100	-£3,483	0.000	0.000	0.000	0.000	0.000	0.000
Empa. 25	-£3,785	0.000	0.000	0.000	0.000	0.000	0.000
Dapa. 10	-£3,856	0.000	0.000	0.000	0.000	0.000	0.000
Cana. 300	-£3,635	0.000	0.000	0.000	0.000	0.000	0.000

Due to the reordering of the treatments by total costs, empagliflozin is no longer dominated (see Table **71**).

Table 71 AG SA01: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,026	£3,026	£3,026	Dom	£16,814
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Empa. 25	Dom	£27,230	£112,991	£74,209	Dom	£201k
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£1,504	£6,882	£3,722	Dom	£4,559
Dom = Dominated: i.e. more costly and less effective than another treatment						

The cost effectiveness of repaglinide compared to gliclazide improves slightly for the BMI 1, 2 and 3 scenarios to £3,026 per QALY and for the BMI 5 scenario to £16,814 per QALY.

The flozins remain dominated if there are no direct quality of life impacts from weight changes. For the BMI scenarios 1, 2 and 3 the cost effectiveness of empagliflozin compared to repaglinide is £27,230 per QALY, £113k per QALY and £74,209 per QALY, while for the BMI scenario 5 it is £201k per QALY. But these cost effectiveness estimates for empagliflozin are extendedly dominated by canagliflozin, which has cost effectiveness estimates compared to repaglinide of £19,850 per QALY, £84,634 per QALY and £52,571 per QALY for the BMI scenarios 1, 2 and 3, and £104k per QALY for the BMI scenario 5.

For the cost effectiveness of the flozins compared to sitagliptin the estimates improve quite considerably due to the greater cost reductions for the flozins (see Table **72**).

Table 72 AG SA01: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£6,567	£1,347	£4,637	£3,179	£5,335	£3,447
Empa. 25	£5,054	£1,288	£4,055	£2,987	£4,335	£3,114
Dapa. 10	£10,739	£1,764	£8,166	£5,262	£8,107	£5,233

SA02: UTI and GTI rates applied to all model cycles

If the UTI and GTI rates are applied to all model cycles this has a slightly larger impact upon the flozins than the other treatments. Compared to the values of the base case the following changes occur (see Table **73**).

Table 73 AG SA02: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£65	-0.007	-0.007	-0.007	-0.007	-0.007	-0.007
Repag.	£65	-0.007	-0.007	-0.007	-0.007	-0.007	-0.007
Pio.	£66	-0.007	-0.007	-0.007	-0.007	-0.007	-0.007
Sita. 100	£68	-0.007	-0.007	-0.007	-0.007	-0.007	-0.007
Cana. 300	£93	-0.010	-0.010	-0.010	-0.010	-0.010	-0.010
Empa. 25	£84	-0.009	-0.009	-0.009	-0.009	-0.009	-0.009
Dapa. 10	£86	-0.009	-0.009	-0.009	-0.009	-0.009	-0.009

The pattern of dominated strategies is as for the base case. Given the similarity of changes for both gliclazide and repaglinide the costs effectiveness estimates for repaglinide compared to gliclazide are little different from those of the base case.

Due to the flozins being slightly worse affected by this, the cost effectiveness estimates for canagliflozin compared to repaglinide for BMI scenarios 1, 2, 3 and 5 worsen slightly to £46,721 per QALY, £223k per QALY, £131k per QALY and £283k per QALY. There is also some worsening in the cost effectiveness estimates for the flozins compared to sitagliptin (see Table **74**).

Table 74 AG SA02: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£15,805	£2,875	£10,656	£7,065	£12,465	£7,709
Empa. 25	£21,167	£4,987	£16,622	£11,973	£17,878	£12,513

Dapa. 10	£52,010	£7,093	£37,364	£22,660	£37,046	£22,523

SA03: A common baseline HbA1c of 7.5%

The common baseline HbA1c of 7.5% does not changes the ordering of treatments by their total costs, with the aggregate outcomes being as below (Table **75**).

Table 75 AG SA03: Total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£26,593	10.432	9.687	9.687	9.687	9.810	9.776
Repag.	£26,710	10.429	9.717	9.717	9.717	9.810	9.784
Pio.	£26,814	10.425	9.665	9.665	9.665	9.802	9.763
Sita. 100	£31,501	10.404	9.716	9.714	9.714	9.787	9.767
Cana. 300	£31,925	10.421	9.831	9.742	9.766	9.810	9.815
Empa. 25	£32,003	10.420	9.800	9.737	9.752	9.808	9.803
Dapa. 10	£32,044	10.414	9.789	9.728	9.742	9.801	9.794

Total costs have fallen and the total QALYs have increased compared to the base case as outlined below (below (

Table **76**).

Table 76 AG SA03: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	-£721	0.040	0.054	0.054	0.054	0.039	0.037
Repag.	-£703	0.041	0.054	0.054	0.054	0.040	0.040
Pio.	-£730	0.041	0.053	0.053	0.053	0.040	0.035
Sita. 100	-£858	0.049	0.059	0.059	0.059	0.048	0.048
Cana. 300	-£751	0.041	0.050	0.052	0.059	0.040	0.048
Empa. 25	-£772	0.043	0.053	0.054	0.058	0.042	0.047
Dapa. 10	-£822	0.046	0.055	0.057	0.061	0.045	0.049

While the effects are reasonably similar across all the treatments, they appear to be larger for sitagliptin and in some instances for the flozins too. While the differences in total QALYs are sometimes slight for sitagliptin compared to the cheaper alternatives, there is always a cheaper alternative that offers slightly more QALYs. The cost differences remain large and as a consequence sitagliptin remains dominated.

For BMI scenarios 1, 2 and 3 the cost effectiveness of repaglinide compared to gliclazide rises slightly to £3,911 per QALY. For BMI scenarios 1, 2, 3 and 5 the cost effectiveness of canagliflozin worsen slightly to £45,968, £207k, £107k and £173k respectively.

For the cost effectiveness of the flozins compared to sitagliptin the estimates worsen due to the relative improvement of sitagliptin (see Table **77**).

Table 77 AG SA03: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£24,939	£3,717	£14,961	£8,237	£18,309	£8,880
Empa. 25	£30,150	£6,042	£21,643	£13,310	£24,300	£13,972
Dapa. 10	£54,863	£7,442	£38,256	£19,902	£38,725	£20,011

SA04: Initial HbA1c treatment effect a function of baseline HbA1c

If the monotherapies' treatment effects upon HbA1c are made a function of patients' baseline HbA1c, as derived from the NICE CG modelling which implies a larger effect for those with a higher baseline value, the following applies (see Table **78**).

Table 78 AG SA04: Total costs and QALYs

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,410	10.393	9.629	9.629	9.629	9.771	9.738
Repag.	£27,518	10.389	9.658	9.658	9.658	9.770	9.741
Pio.	£27,650	10.384	9.608	9.608	9.608	9.762	9.729
Sita. 100	£32,588	10.358	9.654	9.651	9.652	9.742	9.718
Cana. 300	£32,782	10.381	9.777	9.687	9.700	9.771	9.760
Empa. 25	£32,953	10.380	9.744	9.680	9.687	9.768	9.751
Dapa. 10	£33,100	10.371	9.732	9.669	9.674	9.759	9.740

And the following changes from the baseline values (see Table **79**).

Table 79 AG SA04: Total costs and QALYs compared to the base case

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£97	0.001	-0.004	-0.004	-0.004	0.001	-0.001
Repag.	£105	0.000	-0.005	-0.005	-0.005	0.000	-0.003
Pio.	£106	0.000	-0.004	-0.004	-0.004	0.000	0.001
Sita. 100	£230	0.003	-0.003	-0.004	-0.004	0.002	-0.001
Cana. 300	£106	0.001	-0.003	-0.003	-0.008	0.001	-0.006
Empa. 25	£179	0.003	-0.003	-0.003	-0.007	0.002	-0.005
Dapa. 10	£234	0.004	-0.002	-0.003	-0.007	0.003	-0.004

This does not change the treatments that are modelled as being dominated. The cost effectiveness estimates for repaglinide compared to gliclazide are little changed at £3,747 per QALY for the BMI scenarios 1, 2 and 3 and but the cost effectiveness estimate for the BMI scenario 5 worsens to £34,225 per QALY due to the similarity in effectiveness between the two treatments.

For the BMI scenarios 1, 2, 3 and 5 the cost effectiveness estimate for canagliflozin compared to repaglinide are broadly similar to those of the base case at £44,115 per QALY, £179k per QALY, £127k per QALY, and £272k per QALY.

The cost effectiveness estimates for the flozins compared to sitagliptin are typically slightly better than those of the base case (see Table **80**).

Table 80 AG SA04: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£8,314	£1,570	£5,367	£4,037	£6,636	£4,570
Empa. 25	£16,222	£4,063	£12,671	£10,411	£13,894	£11,064
Dapa. 10	£37,733	£6,582	£29,767	£23,093	£29,242	£22,808

SA05: No discontinuation rates

Not applying the treatment discontinuation rates results in the following (see Table **81** and Table 82).

Table 81 AG SA05: Total costs and QALYs

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,320	10.393	9.634	9.634	9.634	9.771	9.739
Repag.	£27,421	10.389	9.665	9.665	9.665	9.770	9.745
Pio.	£27,571	10.383	9.610	9.610	9.610	9.761	9.727
Sita. 100	£32,456	10.354	9.658	9.655	9.656	9.739	9.718
Cana. 300	£32,735	10.379	9.781	9.690	9.707	9.769	9.766
Empa. 25	£32,826	10.377	9.747	9.683	9.694	9.765	9.755
Dapa. 10	£32,944	10.367	9.735	9.671	9.681	9.755	9.744

Table 82 AG SA05: Total costs and QALYs compared to the base case

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£6	0.000	0.001	0.001	0.001	0.000	0.000
Repag.	£7	0.000	0.002	0.002	0.002	0.000	0.001
Pio.	£28	-0.001	-0.002	-0.002	-0.002	-0.001	-0.001
Sita. 100	£98	-0.001	0.000	0.000	0.000	-0.001	0.000
Cana. 300	£59	-0.001	0.001	0.000	0.000	-0.001	0.000
Empa. 25	£52	0.000	0.001	0.000	0.000	0.000	0.000
Dapa. 10	£78	-0.001	0.001	0.000	0.000	-0.001	0.000

Repaglinide increases in cost slightly but the small increases in the total QALYs are proportionally slightly greater and there is a minor improvement in the cost effectiveness estimates for repaglinide compared to gliclazide compared to those of the base case for the BMI scenarios 1, 2, 3 and 5.

The costs for sitagliptin and the flozins increase slightly with minimal impact upon the total QALYs associated with them. Compared to the cost effectiveness estimate of the base case the cost effectiveness estimates for canagliflozin compared to repaglinide for the BMI scenarios 1, 2, 3 and 5 worsen slightly, but the effect is small.

SA06: NICE CG baseline TC:HDL values and UKPDS68 progression

If the NICE CG baseline TC:HDL values are applied and the TC:HDL ratio is evolved as per the UKPDS68 equation 13 the patient outcomes worsen and costs rise as below (see Table **83** and Table **84**).

Table 83 AG SA06: Total costs and QALYs

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,783	10.006	9.273	9.273	9.273	9.404	9.373
Repag.	£27,884	10.003	9.302	9.302	9.302	9.404	9.379
Pio.	£27,996	9.997	9.251	9.251	9.251	9.394	9.361
Sita. 100	£32,676	9.963	9.289	9.287	9.287	9.367	9.348
Cana. 300	£32,968	9.990	9.411	9.325	9.341	9.400	9.398
Empa. 25	£33,057	9.989	9.379	9.318	9.329	9.397	9.387
Dapa. 10	£33,154	9.977	9.366	9.305	9.315	9.385	9.375

Table 84 AG SA06: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£469	-0.386	-0.361	-0.361	-0.361	-0.367	-0.366
Repag.	£470	-0.386	-0.361	-0.361	-0.361	-0.366	-0.365
Pio.	£452	-0.388	-0.362	-0.362	-0.362	-0.368	-0.367
Sita. 100	£318	-0.392	-0.368	-0.368	-0.368	-0.372	-0.371
Cana. 300	£292	-0.390	-0.369	-0.366	-0.366	-0.370	-0.369
Empa. 25	£283	-0.389	-0.367	-0.365	-0.365	-0.369	-0.368
Dapa. 10	£288	-0.390	-0.369	-0.366	-0.366	-0.370	-0.370

The costs effectiveness estimates for repaglinide compared to gliclazide are little different from those of the base case.

The cost effectiveness estimates for canagliflozin compared to repaglinide for the BMI scenarios 1, 2, 3 and 5 of £46,562 per QALY, £129k per QALY, £223k per QALY and £272k per QALY are broadly similar to those of the base case.

The cost effectiveness estimates of the flozins compared to sitagliptin show some improvements compared to the base case estimates (see Table **85**).

Table 85 AG SA06: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£10,601	£2,403	£7,748	£5,420	£8,807	£5,845
Empa. 25	£14,657	£4,237	£12,152	£9,208	£12,873	£9,552
Dapa. 10	£33,394	£6,284	£26,373	£17,585	£26,173	£17,486

SA07: Applying the UKPDS68 year 2 parameter for the evolution of HbA1c

Applying the UKPDS68 year 2 parameter of equation 11 for the evolution of HbA1c has little impact upon results compared to the base case in absolute terms (see Table **86**).

Table 86 AG SA07: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	-£7	0.001	0.001	0.001	0.001	0.001	0.001
Repag.	£3	0.001	0.001	0.001	0.001	0.001	0.001
Pio.	-£4	0.000	0.000	0.000	0.000	0.000	0.000
Sita. 100	-£5	0.001	0.001	0.001	0.001	0.001	0.001
Cana. 300	-£16	0.000	0.000	0.000	0.000	0.000	0.000
Empa. 25	-£12	0.000	0.000	0.000	0.001	0.000	0.000
Dapa. 10	-£8	0.001	0.001	0.001	0.001	0.001	0.001

The costs effectiveness estimates for the treatments that are not dominated are little different from those of the base case. The cost effectiveness estimates compared to sitagliptin are similar to those of the base case (see Table **87**).

Table 87 AG SA07: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,919	£2,527	£8,936	£6,036	£10,356	£6,563
Empa. 25	£18,616	£4,635	£14,818	£10,825	£15,879	£11,294
Dapa. 10	£41,268	£6,630	£31,255	£19,911	£31,026	£19,801

SA08: Intensifying by adding gliclazide has a -0.47% HbA1c reduction

If the intensification of adding gliclazide to a monotherapy only results in a -0.47% reduction in HbA1c this has very little impact upon those who had gliclazide and repaglinide monotherapy due to this only affecting the small percentage that discontinue due to adverse events. But the impact upon the other treatments is quite marked. For these the change affects the vast majority of patients. They have an overall smaller clinical effect applied which is in itself harmful, and will also tend to progress through to insulin more quickly than compared to the base case (see Table **88**).

Table 88 AG SA08: Total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,320	10.393	9.634	9.634	9.634	9.771	9.739
Repag.	£27,421	10.389	9.665	9.665	9.665	9.770	9.745
Pio.	£27,571	10.383	9.610	9.610	9.610	9.761	9.727
Sita. 100	£32,456	10.354	9.658	9.655	9.656	9.739	9.718
Cana. 300	£32,735	10.379	9.781	9.690	9.707	9.769	9.766
Empa. 25	£32,826	10.377	9.747	9.683	9.694	9.765	9.755
Dapa. 10	£32,944	10.367	9.735	9.671	9.681	9.755	9.744

This results in the following differences in costs and QALYs compared to the base case (see Table 89).

Table 89 AG SA08: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£5	0.000	0.000	0.000	0.000	0.000	0.000
Repag.	£13	0.000	0.000	0.000	0.000	0.000	0.000
Pio.	£273	-0.016	-0.020	-0.020	-0.020	-0.016	-0.016
Sita. 100	£299	-0.019	-0.023	-0.023	-0.023	-0.018	-0.018
Cana. 300	£266	-0.018	-0.023	-0.023	-0.023	-0.018	-0.018
Empa. 25	£281	-0.018	-0.022	-0.022	-0.022	-0.018	-0.017
Dapa. 10	£286	-0.020	-0.024	-0.024	-0.024	-0.020	-0.019

And the following cost effectiveness estimates (see Table **90**).

Table 90 AG SA08: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,604	£3,604	£3,604	Dom	£19,784
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£58,292	£1.1mn	£254k	Dom	£1.1mn
Empa. 25	Dom	Dom	Dom	Dom	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Dom = Dominated: i.e. more costly and less effective than another treatment						

If 2nd line gliclazide is less effective, and crucially is less effective than the 2nd line pioglitazone in the gliclazide and repaglinide arms, this considerably worsens the cost effectiveness estimates for the flozins compared to gliclazide and repaglinide. It also worsens their cost effectiveness estimates compared to pioglitazone.

For the comparisons with sitagliptin the costs effectiveness estimates for the flozins is as below (Table **91**).

Table 91 AG SA08: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£11,125	£2,311	£7,903	£5,435	£9,065	£5,909
Empa. 25	£17,003	£4,442	£13,784	£10,214	£14,676	£10,638
Dapa. 10	£43,173	£6,551	£32,025	£20,133	£31,759	£19,999

The flozins continue to show reasonable cost effectiveness estimates compared to sitagliptin, though again the picture is more mixed for dapagliflozin.

SA09: Applying the Janssen linear evolutions of HbA1c

Applying the Janssen linear evolutions for treatments causes pioglitazone to become the cheapest as below (see Table **92**).

Table 92 AG SA09: Total costs and QALYs

		QALYs					
Treatment	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Pio.	£25,818	10.486	9.740	9.740	9.740	9.861	9.811
Glicl.	£25,986	10.476	9.734	9.734	9.734	9.852	9.807
Repag.	£26,139	10.470	9.761	9.761	9.761	9.849	9.812
Sita. 100	£31,303	10.426	9.741	9.738	9.739	9.808	9.782
Cana. 300	£31,385	10.465	9.882	9.793	9.821	9.853	9.857
Empa. 25	£31,643	10.453	9.836	9.773	9.790	9.840	9.831
Dapa. 10	£31,836	10.438	9.817	9.754	9.769	9.825	9.813

Compared to the base case costs have fallen considerably in for all treatments, and total QALYs have risen (see Table **93**).

Table 93 AG SA09: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Pio.	-£1,725	0.101	0.128	0.128	0.128	0.099	0.082
Glicl.	-£1,328	0.084	0.101	0.101	0.101	0.082	0.069
Repag.	-£1,275	0.081	0.098	0.098	0.098	0.079	0.067
Sita. 100	-£1,055	0.071	0.083	0.083	0.083	0.069	0.063
Cana. 300	-£1,291	0.085	0.102	0.102	0.114	0.083	0.091
Empa. 25	-£1,131	0.076	0.090	0.090	0.096	0.074	0.075
Dapa. 10	-£1,030	0.071	0.083	0.083	0.088	0.069	0.068

Gliclazide is now dominated by pioglitazone, though the pattern of dominance of the base case has not otherwise changed.

Table 94 AG SA09: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Pio.	..	..	..	..	..	..
Glicl.	Dom	Dom	Dom	Dom	Dom	Dom
Repag.	Dom	£15,633	£15,633	£15,633	Dom	£343k
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£43,246	£163k	£86,862	Dom	£115k
Empa. 25	Dom	Dom	Dom	Dom	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Dom = Dominated: i.e. more costly and less effective than another treatment						

The cost effectiveness estimates for repaglinide compared to pioglitazone are somewhat worse than the corollaries for repaglinide compared to gliclazide of the base case. The cost effectiveness estimates for canagliflozin compared to repaglinide are surprisingly similar, though that for BMI scenario 5 and to a lesser extent scenario 3 have improved (see Table **94**).

Despite the quite radical change in the evolution of HbA1c the cost effectiveness estimates for the flozins compared to sitagliptin are not radically different from those of the base case, but have improved somewhat for canagliflozin and empagliflozin (see Table **95**). The picture for dapagliflozin remains mixed.

Table 95 AG SA09: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£11,125	£2,311	£7,903	£5,435	£9,065	£5,909
Empa. 25	£17,003	£4,442	£13,784	£10,214	£14,676	£10,638
Dapa. 10	£43,173	£6,551	£32,025	£20,133	£31,759	£19,999

SA10: Those discontinuing a treatment omit the intensification step that applies this treatment

This sensitivity analysis has little impact upon results and does not affect the ordering of treatments by their total costs. The pattern of dominated treatments is also not affected.

The cost effectiveness of repaglinide compared to gliclazide is estimated to improve for the BMI scenarios 1, 2 and 3 to £2,744 per QALY and for BMI scenario 5 to £14,190 per QALY.

The cost effectiveness estimates of canagliflozin compared to repaglinide are little affected, being £45,679 per QALY, £206k per QALY, £124k per QALY and £257 per QALY for the BMI scenarios 1, 2, 3 and 5 respectively.

The cost effectiveness estimates for the flozins compared to sitagliptin are essentially those of the base case.

SA11: SA01 and SA08 combined

If intensifying from monotherapy by adding gliclazide only results in a -0.47% reduction in patients HbA1c and when switching to insulin patients receive only insulin and gliclazide the combined effects of this are as below. As for SA01, canagliflozin is now estimated to be the most expensive treatment (see Table **96**).

Table 96 AG SA11: Total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£26,631	10.392	9.633	9.633	9.633	9.770	9.739
Repag.	£26,730	10.389	9.663	9.663	9.663	9.770	9.744
Pio.	£27,054	10.368	9.592	9.592	9.592	9.746	9.713
Sita. 100	£28,922	10.336	9.634	9.632	9.632	9.721	9.701
Empa. 25	£28,988	10.359	9.724	9.661	9.671	9.748	9.738
Dapa. 10	£29,018	10.347	9.710	9.647	9.657	9.736	9.726
Cana. 300	£29,022	10.361	9.758	9.668	9.685	9.752	9.749

The pattern of changes in cost is much as per SA01, while the pattern of changes in QALYs is as per SA08 (see Table 97).

Table 97 AG SA11: Total costs and QALYs compared to the base case

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	-£682	0.000	0.000	0.000	0.000	0.000	0.000
Repag.	-£684	0.000	0.000	0.000	0.000	0.000	0.000
Pio.	-£489	-0.016	-0.020	-0.020	-0.020	-0.016	-0.016
Sita. 100	-£3,437	-0.019	-0.023	-0.023	-0.023	-0.018	-0.018
Empa. 25	-£3,787	-0.018	-0.022	-0.022	-0.022	-0.018	-0.017
Dapa. 10	-£3,848	-0.020	-0.024	-0.024	-0.024	-0.020	-0.019
Cana. 300	-£3,654	-0.018	-0.023	-0.023	-0.023	-0.018	-0.018

Due to the reordering of the treatments by total costs, empagliflozin is no longer dominated.

Table 98 AG SA11: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,278	£3,278	£3,278	Dom	£17,994
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Empa. 25	Dom	£36,837	Dom	£268k	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£1,030	£460k	£2,581	Dom	£470k
Dom = Dominated: i.e. more costly and less effective than another treatment						

Note that the erratic pattern for canagliflozin as the BMI scenarios are worked across is due to it being compared to empagliflozin for the BMI scenarios 1, 3 and 5 but to repaglinide for the BMI scenarios 2 and 4 (see Table 98).

The flozins remain dominated if there are no direct quality of life impacts from weight changes. For the BMI scenarios 1 and 3 the cost effectiveness of empagliflozin compared to repaglinide is £36,837 per QALY and £268k per QALY. But these cost effectiveness estimates for empagliflozin are extendedly dominated by canagliflozin, which has cost effectiveness estimates compared to repaglinide of £24,226 per QALY and £105k per QALY for the BMI scenarios 1 and 3.

For the cost effectiveness of the flozins compared to sitagliptin the estimates improve quite considerably due to the greater cost reductions for the flozins and sitagliptin seeing similar falls in total QALYs as the flozins (see Table **99**).

Table 99 AG SA11: Flozin cost effectiveness estimates relative to sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£3,927	£816	£2,789	£1,918	£3,199	£2,085
Empa. 25	£2,818	£736	£2,285	£1,693	£2,432	£1,763
Dapa. 10	£8,399	£1,274	£6,230	£3,917	£6,178	£3,891

Summary of the assessment group modelling

The AG modelling base case estimates that the lifetime QALYs arising from diabetes, its complications and adverse events are highest for gliclazide at 10.392 QALYs, with repaglinide having a similar estimate of 10.389 QALYs. Pioglitazone accrues slightly fewer at 10.384 QALYs. The flozins lie a little below this with canagliflozin being estimated to yield 10.380 QALYs, empagliflozin 10.378 QALYs and dapagliflozin 10.367 QALYS. Sitagliptin fares worse at 10.355 QALYs. Gliclazide is estimated to be superior to the flozins by 0.012 QALYs compared to canagliflozin, 0.015 QALYs compared to empagliflozin and 0.025 QALYs compared to dapagliflozin. Adverse events contribute relatively little to these estimates, and even less to the estimates of the differences between treatments. To place these amounts in context, at the baseline quality of life of 0.801 they would be equivalent to survival gains of around 6 days compared to canagliflozin, 7 days compared to empagliflozin and 11 days compared to dapagliflozin.

But these amounts ignore the direct quality of life effects of weight changes. The flozins have a superior weight profile, with canagliflozin providing the largest weight losses. If the monotherapy weight changes are retained over the patient lifetime canagliflozin is estimated to yield an additional 0.147 QALYs compared to gliclazide: equivalent to 67 days additional survival at the baseline quality of life of 0.801. These gains are reduced if it is assumed that weight losses rebound after one year to only 0.057 QALYs, and if it is assumed that weight losses rebound at treatment change to 0.074 QALYs.

The flozins and to a slightly lesser extent sitagliptin are estimated to be considerably more expensive than gliclazide, repaglinide and pioglitazone, the increases in lifetime costs ranging between £5,000 and £5,500.

In the light of the above, if there are no direct quality of life effects from weight changes, the flozins are estimated to be dominated. But if there are direct quality of life impacts from weight changes and the monotherapy weight changes persist throughout the patient life time the flozins are no longer dominated. Repaglinide remains more expensive than gliclazide but now yields slightly more QALYs and has a cost effectiveness estimate compared to gliclazide of £3,331 per QALY. Canagliflozin has a cost effectiveness estimate of £44,994 per QALY compared to repaglinide. While canagliflozin formally dominates the other flozins, the cost effectiveness estimates for empagliflozin and for dapagliflozin compared to gliclazide are £48,169 per QALY and £55,000 per QALY respectively.

It may be unrealistic to expect the monotherapies' weight changes and the differences they imply between treatments to persist indefinitely. If weight losses rebound after one year the cost effectiveness of canagliflozin compared to repaglinide worsens considerably to £192k per QALY. If they persist until treatment intensification the cost effectiveness estimate for canagliflozin compared to repaglinide worsens to £119k per QALY.

The companies argue that the main comparator for the flozins is sitagliptin. The flozins are estimated to provide slightly greater total QALYs from the modelling of diabetes, its complications and the adverse events associated with treatments. The flozins are also associated with somewhat larger weight losses than sitagliptin, which is broadly weight neutral. Total costs are higher than sitagliptin by £318 for canagliflozin, £ 416 for empagliflozin and £508 for dapagliflozin. Even without the direct quality of life effects of weight changes, canagliflozin has a reasonable cost effectiveness compared to sitagliptin of £12,623 per QALY as does empagliflozin at £18,341 per QALY. Dapagliflozin fares worse with a cost effectiveness estimate of £40,383 per QALY.

With the direct quality of life effects of weight changes and weight changes being assumed to persist over the patient lifetime the cost effectiveness of the flozins compared to sitagliptin improves considerably. Canagliflozin has an estimate of £2,590 per QALY, empagliflozin has an estimate of £4,676 per QALY and dapagliflozin has an estimate of £6,632 per QALY. If weight changes are assumed to rebound either after one year or at treatment change, the cost effectiveness estimates for the flozins generally remain within conventional thresholds. The exception to this is dapagliflozin for which if weight rebounds after one year the cost effectiveness estimates go slightly above the £30,000 threshold.

A key difference between the AG modelling and that of the companies is that the AG has assumed that patients remain on their monotherapy and add treatments to it. When patients intensify to insulin, they do so by adding it to their existing regime e.g. they intensify from canagliflozin plus gliclazide to canagliflozin plus gliclazide plus insulin. Retaining the original monotherapy increases the total costs,

and in particular increases the total cost for the flozins and to a slightly lesser extent sitagliptin. If it is assumed that the monotherapies are discontinued when the patients intensify to insulin the net costs fall to be within the range £2,362 to £2,412 for the flozins and to £2,247 for sitagliptin.

The flozins remain dominated if the direct quality of life impact of weight changes are not included, but applying them and assuming weight changes persist indefinitely improves the costs effectiveness estimates for the flozins compared to repaglinide to £19,850 per QALY for canagliflozin, £27,230 per QALY for empagliflozin and £32,288 per QALY for dapagliflozin. Weight losses rebounding after one year cause these estimates to worsen to £84,634 per QALY, £112k per QALY and £274k per QALY respectively, while weight losses rebounding at change of treatment cause these estimates to worsen to £52,571 per QALY, £74,209 per QALY and £128k per QALY respectively.

This sensitivity analysis also sees the flozins being estimated to be cost effective relative to sitagliptin under all the weight change scenarios including that of no direct quality of life impact from weight changes.

The base case applied the baseline HbA1c values for those starting a monotherapy of the NICE CG which had a mean of 8.4% (s.d. 1.8%). This differs from some of the companies' modelling, which assumed a common baseline HbA1c of 7.5%. As would be expected this both improved patient outcomes and lowered total costs. It did not alter the patterns of dominance, and while the cost effectiveness estimates for the flozins compared to repaglinide worsened the effect was not major.

Of more interest was that the cost effectiveness estimates of the flozins compared to sitagliptin worsened. With no direct quality of life impacts from weight these worsened to £24,939 per QALY for canagliflozin, £30,150 per QALY for empagliflozin and £54,863 per QALY for dapagliflozin. With the monotherapy BMI effects persisting for the patient lifetime these cost effectiveness estimates improve to £3,717 per QALY, £6,042 per QALY and £7,442 per QALY respectively. Weight loss rebound after one year reduces the improvements to £14,961 per QALY, £21,643 per QALY and £38,256 per QALY, while weight loss rebound at treatment change reduces the improvements to £8,237 per QALY, £13,310 per QALY, and £19,902 per QALY respectively.

Making the HbA1c treatment effect a function of patients' baseline HbA1c had little practical impact upon the cost effectiveness estimates for the flozins compared to gliclazide, repaglinide and pioglitazone. But it improved the cost effectiveness estimates for canagliflozin compared to sitagliptin by around one third. The impact for empagliflozin is less, and there was little impact for dapagliflozin. This is as would be expected given the greater HbA1c effect for canagliflozin compared to sitagliptin,

the slightly greater effect for empagliflozin and broad equivalence between dapagliflozin and sitagliptin.

Janssen applied linear evolutions of HbA1c with the annual rate of change being treatment specific. Applying the same annual rates of change within the AG modelling reduced total costs and increased total QALYs quite considerably. It also caused pioglitazone to be estimated as the cheapest treatment, with it dominating gliclazide. Pioglitazone also dominated repaglinide if there were no direct quality of life impacts from weight changes. Including these with no rebound for weight gains caused the cost effectiveness of repaglinide compared to pioglitazone to improve to £15,633 per QALY. The pattern of dominance was not otherwise altered.

The linear HbA1c evolutions still saw the flozins dominated unless there were direct quality of life impacts from weight changes. Given these, the cost effectiveness estimates for canagliflozin compared to repaglinide were surprisingly similar to those of the base case, though the higher cost effectiveness estimates varied more due to the divisions by small net QALY gains.

Assuming that adding gliclazide at the 1st intensification causes only a -0.47% reduction in HbA1c compared to the -1.01% reduction of the base case has little to no impact for gliclazide and repaglinide as patients will not use this intensification. But it increases costs and reduces QALYs in the other arms, so worsening the cost effectiveness estimates for the flozins. The cost effectiveness estimates for the flozins compared to sitagliptin are not particularly affected, though those for dapagliflozin do worsen slightly.

Assuming that the UTI and GTI rates apply throughout the modelling rather than just for the first cycle has little practical impact upon results.

Summary: A comparison of the modelling exercises' assumptions and inputs

NICE checklist

The modelling exercises and their data sources can be assessed against the NICE reference case checklist (see Table **100**).

Table 100 NICE reference case checklist: Companies and AG

	Janssen	AZ	BI	AG
Comparator(s) :	The individual flozins were assessed alongside Sita. 100mg, Pio and SU.	The flozins were grouped into a class effect, as are the gliptins, with Pio and SU also being considered.	The main analysis compared Empa. 10mg, Empa. 25mg, Sita. 100mg, Pio, SU and repaglinide.	Cana. 100mg, Dapa. 10mg, Empa. 10mg, Empa. 25mg, Sita. 100mg, Pio and SU.
Patient group	Adult patients with T2DM unable to take metformin starting monotherapy			
Perspective: Costs	NHS & PSS			
Perspective: Benefits	Patient			
Analysis	Cost utility			
Time horizon	40 years			
Clinical evidence	Own NMA	Own NMA	Own NMA	Own NMA
Outcome measure	QALYs			
Health states generic QoL: Other than UTIs & GTIs UTIs and GTIs	 Yes, EQ-5D No	 Yes, EQ-5D IWB	 Yes, EQ-5D IWB	 Yes, EQ-5D No
Benefit valuation: Other than UTIs & GTIs UTIs and GTIs	 TTO Janssen TTO	 TTO Ranking scale	 TTO Ranking scale	 TTO Janssen TTO
HRQL pref. data.: Other than UTIs & GTIs UTIs and GTIs	 UK Tariff 100 UK Public	 UK Tariff 62 US Med/Pub	 UK Tariff 62 US Med/Pub	 UK Tariff 100 UK Public
Discount rates	3.5% for both costs and benefits			
Equity	Equal QALY regardless of patient characteristics			
Probabilistic modelling	Yes	Yes	No (Model B)	Yes
Sensitivity analyses	Yes	Yes	No	Yes

Modelling assumptions

In terms of the main assumptions and data sources the companies and the AG have used the following (see Table **101**).

Table 101 Main assumptions: Companies and AG

	Janssen	Astrazeneca	BI	AG
HbA1c	Linear	UKPDS68	UKPDS68	UKPDS68
SBP	Linear	UKPDS68	UKPDS68	UKPDS68
TC:HDL	Linear	UKPDS68	UKPDS68	UKPDS68
Weight	Linear	Linear	Linear	Linear
Complications modelling	Variety	UKPDS82	UKPDS68	UKPDS68
QoL main source	CODE-2	UKPDS62	Alva 2014	UKPDS62
Costs main source	UKPDS84	UKPDS65/84	UKPDS84	UKPDS84

The above is a simplification. For instance, the Janssen submission has a large number of health states associated with eGFR levels which also have ongoing costs associated with them. These are not sourced from the UKPDS84. The ECHO-T2DM model used by Janssen has been submitted to the Mt. Hood challenges. But the Janssen implementation of the ECHO-T2DM and base case assumptions is likely to have differed quite considerably from that submitted to the Mt. Hood challenges.

But the above does help highlight the main differences between the submissions and the AG modelling. Janssen is the outlier in terms of its approach, both in terms of the modelling of its complications and its assumptions about the linearity of the evolution of HbA1c and SBP. Astrazeneca, and Boehringer Ingelheim use the UKPDS68 to model the evolution of HbA1c, SBP and the TC:HDL ratio. The AG does as well with the exception of the TC:HDL ratio which is assumed to be constant for the base case, but is evolved using the UKPDS68 in a sensitivity analysis. Janssen argues that the evolutions of the UKPDS include the effects of treatment intensifications so cannot be used when the modelling is separately accounting for the treatment intensifications. There is some force to this argument. But it then has to be asked whether the alternative of linear evolutions is preferable. The treatment specific linear evolutions of HbA1c within the Janssen submission are not obviously related to the treatments under consideration. There are also concerns with linear evolutions maintaining absolute differences indefinitely when the UKPDS clearly suggests convergence.

As already discussed, the UKPDS OM2 which is based upon the UKPDS82 was not available to the AG. As a consequence, in line with the modelling of Boehringer Ingelheim the older OM1 was used to model the complications of diabetes, this being based upon the UKPDS68. The Astrazeneca modelling was based upon the UKPDS68 for the evolution of the risk factors and the UKPDS82 for the calculation of event probabilities, as implemented within the CDM. As far as the AG is aware this version of the CDM has not been previous used, has not been submitted to the Mt. Hood challenge and has not been independently interrogated or validated.

A concern with the Janssen and the Astrazeneca models is that there has been little presented on model convergence. The AG has relied upon the work of the draft NICE CG for diabetes, which resulted in deterministic model runs having 50,000 patients simulated with 1,000 inner loops for each patient to reduce the Monte-Carlo error. The draft NICE CG for diabetes could be read as suggesting that only 100 inner loops are necessary for convergence, but even this seems to be somewhat more model runs that any of the company submissions. As a consequence, the AG is uncertain whether the company models have reliably converged. Boehringer Ingelheim did present some work on convergence and concluded that results of the OM1 stabilised after 1,000 inner loops for each patient had been run, choosing to run the model with 10,000 inner loops though only for 9,211 patients so around 92mn model runs: approximately double the 50mn of the AG.

Monotherapies modelled and sequences compared

The companies and the AG considered the following monotherapies (see Table **102**).

Table 102 Base case comparators considered: Companies and AG

	Janssen	AZ	BI		AG
Analysis	Base	Base	24 week	52 week	Base
		Flozin			
	Cana. 100mg		Cana. 100mg		
	Cana. 300mg		Cana. 300mg		Cana 300mg
			Dapa. 5mg		
	Dapa. 10mg		Dapa. 10mg		Dapa. 10mg
	Empa. 10mg		Empa. 10mg	Empa. 10mg	
	Empa. 25mg		Empa. 25mg	Empa. 25mg	Empa. 25mg
		Gliptin			
	Sita. 100mg			Sita. 100mg	Sita. 100mg
	Pioglitazone	Pioglitazone		Pioglitazone	Pioglitazone
	Sulfonylurea	Sulfonylurea		Sulfonylurea	Gliclazide
				Repaglinide	Repaglinide

Note that Janssen considered repaglinide in a scenario analysis.

Astrazeneca pooled the flozins into a single treatment group, with pooled treatment effect estimates and weighted average direct drug costs. The gliptins were similarly pooled.

The following treatment intensifications were assumed for the base cases, with treatment intensifications occurring when a patient's HbA1c was modelled as breaching the 7.5% intensification threshold (see Table **103**).

Table 103 Base case intensifications: Companies and AG

	Janssen	AZ	BI	AG
1st intensification	+ Glicl.	Switch to NPH	+SU; or +Sita.	-Repag. +Pio; and/or +Glicl.
2nd intensification	Switch to NPH	Intensify NPH	Switch to NPH	+ NPH
3rd intensification	+ Aspart	None	None	-Glicl., +Bolus

Within the Boehringer Ingelheim submission all but gliclazide had a 1st intensification of adding gliclazide to the existing monotherapy. Those on gliclazide monotherapy had a 1st intensification of adding sitagliptin.

Similarly, for the 1st intensification within the AG modelling all but gliclazide added gliclazide to the existing monotherapy. Those on gliclazide monotherapy has a 1st intensification of adding pioglitazone. The repaglinide monotherapy arm stands out, having repaglinide withdrawn and both pioglitazone and gliclazide added. For the 2nd intensification all strategies intensify by adding NPH insulin. The 3rd intensification adds bolus insulin and withdraws gliclazide.

The AG modelled sequences differ from those of the company submissions in that patients add NPH insulin rather than switch to it. The retention of the monotherapies in the AG triple therapy combinations with gliclazide and NPH means that the differences in costs between the monotherapies are retained throughout the AG base case modelling. In the light of this, a scenario analysis was undertaken which withdraws the initial monotherapies when patients now in effect switch to NPH insulin though this only affected the direct drug costs and not the clinical effectiveness estimates.

Patient characteristics and complications prevalences at baseline

The patient baseline characteristics were as below (Table **104**).

Table 104 Main baseline risk factors: Companies and AG

	Janssen	AZ	BI	AG
Source	Cana. trials	NMA	CPRD	THIN/EHS
Age	56.2	55.0	63.1	59.8
Duration diabetes	0.0	3.6	2.9	2.0
Male	53%	55%	57%	57%
BMI	29.7	28.9	31.1	31.9
Male	..		31.0	..
Female	..		32.0	..
HbA1c	8.02%	7.50%	8.49%	8.40%
SBP	127.7	128.3	134.7	137.5
TC	5.17	5.07	..	4.96
HDL	1.25	1.20	1.20	1.18
LDL	3.06	3.32	4.02	..
Current smoker	9.0%	36.90%	16.7%	18.1%
Past smoker	..	..	36.5%	34.0%

Note that the baseline HbA1c of 7.5% of Astrazeneca is based upon the treatment intensification threshold rather than the Astrazeneca NMA, which had a mean of 8.2%. The Astrazeneca proportion who smoke has been taken from the electronic model, where it is ambiguous whether this is the proportion at diagnosis, the proportion at baseline, or both.

The mean baseline age differs quite a lot across the companies' and AG's estimates, with the AG's estimate lying somewhere in the middle. Baseline age is likely to affect results as this determines the amount of time left for the longer term impacts of clinical effects to be realised. Perhaps more pertinently, it will also affect the amount of time the direct quality of life impacts of weight changes apply if weight changes are modelled as being maintained into the long term.

The proportion modelled as smoking is unclear within the Janssen submission but it seems likely to have been somewhat lower than the other exercises. Within the Astrazeneca submission it is somewhat higher, though there is some ambiguity about this. The AG assumption, given the electronic copy of the CDM that was submitted, is that the 36.9% is the proportion at both diagnosis and at baseline as only one value for smoking could be found.

The prevalences of the complications of diabetes at baseline were as below (Table **105**).

Table 105 Prevalence of main complications at baseline: Companies and AG

	Janssen	AZ	BI	AG
Atrial fibrillation	..	0.00%	6.63%	0.81%
PVD	0.00%	0.00%	3.18%	0.51%
MI	0.80%	0.00%	2.21%	0.80%
CHF	0.00%	0.00%	1.92%	0.50%
Stroke	0.10%	0.00%	1.62%	0.50%
IHD	1.20%	0.00%	6.13%	2.70%
Amputation	0.10%	0.00%	0.29%	0.10%
Blindness	0.00%	0.00%	0.23%	0.40%
Renal failure	0.00%	0.00%	0.05%	0.20%

Given the recentness of the diagnosis of diabetes, the companies and the AG all suggest low prevalences of complications at baseline. But Astrazeneca assumes these to be zero. Since the CDM models the instances of initial events, and some secondary events, this will slightly bias the analysis of Astrazeneca towards the more effective treatment.

Again, the above does some disservice to the Janssen submission which modelled a range of other microvascular conditions.

Clinical effectiveness estimates

The main clinical effect estimates are as follows (see Table **106**). The Janssen NMA is for BMI rather than for weight in kg. To aid comparison with the other estimates the Janssen estimates have been converted to kg at assuming a patient weight of 85kg and a patient BMI of 30kgm^{-2}. The Janssen BMI estimates are presented in brackets.

Table 106 Central clinical effectiveness estimates: Companies and AG: HbA1c %

	Janssen	AZ	BI		AG
Treatment	Base	Base	24 week	52 week	Base
Flozins pooled		-0.74			
Cana. 100mg	-0.97		[redacted]		
Cana. 300mg	-1.20		[redacted]		-1.153
Dapa. 5mg			[redacted]		
Dapa. 10mg	-0.64		[redacted]		-0.704
Empa. 10mg	-0.73		[redacted]	[redacted]	
Empa. 25mg	-0.85		[redacted]	[redacted]	-0.870
Gliptins pooled		-0.64		[redacted]	
Sita. 100mg	-0.72			[redacted]	-0.723
Pioglitazone	-0.78	-0.90		[redacted]	-1.200
Sulfonylurea	-0.59	-0.95		[redacted]	-1.301
Repaglinide	-1.28			[redacted]	-1.200*
* Assumed as no estimate within NMA					

The estimates for the HbA1c changes are broadly in line for the flozins and sitagliptin. Among the flozins all sources that provide individual estimates suggest that canagliflozin 300mg provides that largest reduction, though the practical clinical differences between these estimates is a moot point. The AG estimates for pioglitazone and sulfonylurea are larger than those of the companies to the extent that these are estimated to be more effective than canagliflozin 300mg (see Table **107**).

Table 107 Central clinical effectiveness estimates: Companies and AG: SBP mmHg

	Janssen	AZ	BI		AG
Treatment	Base	Base	24 week	52 week	Base
Flozins pooled		-5.87			
Cana. 100mg	-3.71		[redacted]		
Cana. 300mg	-5.41		[redacted]		-1.338
Dapa. 5mg			[redacted]		
Dapa. 10mg	-3.21		[redacted]		-2.931
Empa. 10mg	-2.60		[redacted]	[redacted]	
Empa. 25mg	-3.40		[redacted]	[redacted]	-3.743
Gliptins pooled		-1.53		[redacted]	
Sita. 100mg	+0.80			[redacted]	+0.394
Pioglitazone	+0.88	-1.31		[redacted]	-1.400*
Sulfonylurea	+0.19	-0.65		[redacted]*	-0.600*

Repaglinide	+0.19*			[redacted] *	-1.000*
* Assumed as no estimate within NMA					

There is a greater variety between the sources when SBP is considered. The AG estimate for canagliflozin 300mg is slightly below that of the other sources, the latter suggesting that canagliflozin 300mg again has the largest effect (see Table **108**).

Table 108 Central clinical effectiveness estimates: Companies and AG: Weight kg

	Janssen	AZ	BI		AG
Treatment	Base (BMI)	Base	24 week	52 week	Base
Flozins pooled		-2.81			
Cana. 100mg	-2.40 (-0.85)		[redacted]		
Cana. 300mg	-3.42 (-1.21)		[redacted]		-3.577
Dapa. 5mg			[redacted]		
Dapa. 10mg	-1.61 (-0.57)		[redacted]		-2.457
Empa. 10mg	-1.72 (-0.61)		[redacted]	[redacted]	
Empa. 25mg	-1.84 (-0.65)		[redacted]	[redacted]	-2.471
Gliptins pooled		-0.13		[redacted]	
Sita. 100mg	+0.82 (+0.29)			[redacted]	-0.003
Pioglitazone	+2.35 (+0.83)	+2.61		[redacted]	+2.962
Sulfonylurea	+0.62 (+0.22)	+0.07		[redacted]	+1.397
Repaglinide	+0.62 (+0.22)			[redacted]	+0.100*
* Assumed as no estimate within NMA					

While not perfectly aligned, the estimates of weight changes are similar across the sources. The AG suggests slightly larger reductions in weight than the companies' estimates for dapagliflozin 10mg and empagliflozin 25mg, with the AG also suggesting that sitagliptin is broadly weight neutral. The Boehringer Ingelheim estimate for pioglitazone, sulfonylurea and repaglinide lie a reasonable amount above those of the other sources.

Quality of life values

Turning to the main quality of life values these are as follows, though again the presentation is slightly biased against the Janssen submission due to the number of health states within the ECHO-T2DM model and these not being particularly aligned with those of the other modelling (see Table **109**).

Table 109 Main health state QoL values: Companies and AG

	Janssen	Astrazeneca	BI	AG
No complications	0.843	0.882	0.720	0.801
MI year	-0.028	-0.055	-0.065	-0.055
MI history	-0.028	-0.055	0.008	-0.055
IHD	-0.028	-0.090	-0.028	-0.090
Stroke	-0.115	-0.164	-0.165	-0.164
CHF	-0.028	-0.108	-0.101	-0.108
Amputation	-0.272	-0.280	-0.172	-0.280
Blindness	-0.057	-0.074	0.033	-0.074
ESRD	-0.175	-0.263	-0.263	-0.263
per BMI > 25	-0.0061	-0.0061	-0.0061	-0.0061
Severe hypo	-0.0470	-0.0470	-0.0470	-0.0470
Non-severe hypo	-0.0142	-0.0142	-0.0142	-0.0142
UTI (QALY)	-0.0043	-0.0028	-0.0028	-0.0073
GTI (QALY)	-0.0046	-0.0028	..	-0.0096

Janssen is unusual in selecting the CODE-2 dataset as its main source of quality of life estimates. But this is a respected publication and since Janssen is using the ECHO-T2DM model, the health states of their model are not so obviously aligned with the health states of the UKPDS OM1 and OM2 for which UKPDS quality of life estimates are available for. Astrazeneca, Boehringer Ingelheim and the AG all use models based upon the UKPDS, and as a consequence quality of life estimates from the UKPDS are a natural choice.

For quality of life, Boehringer Ingelheim draws most of its values from the fixed effects estimates of Alva et al (2014), which is an analysis of the updated UKPDS dataset with Alva et al expressing a clear preference for the fixed effects estimates over their OLS estimates. This explicitly analyses the data longitudinally in order to estimate the quality of life pre and post and event and the impact of events upon an individual, rather than comparing patients cross-sectionally. This has obvious attractions, but there may be some difficulty when applying these estimates in that the coefficients for blindness and a history of MI are positive. Within Alva et al, these coefficients and that for IHD are not statistically significant so it could be argued that these could or should be set to zero. But if these are set to zero, it would obviously be preferable for the coefficients to have been further explored or excluded within the analysis of Alva et al, in order to explore the impact that this would have upon the estimates of the other coefficients. But given its choice of Alva et al as the source of its quality of life estimates, this option was not available to Boehringer Ingelheim.

The AG is not as familiar with the Alva et al estimates as with those from the UKPDS62. It seems likely that there is an age effect within the estimates of Alva et al as well, due to the mean age at completion of the 1st questionnaire being 62 compared to a mean age of 71 for the 7th, coupled with negative and statistically significant coefficients for the questionnaires. Whether it is reasonable to apply the mean value of the EQ-5D in the absence of complications of 0.72 or whether it would be better to estimate it from the fixed effect model is a moot point, but it can be noted that the constant for the fixed effects model was somewhat higher at 0.807. But the values of Alva et al are reasonable to apply.

All the analyses have used the CODE-2 quality of life decrement for BMI above 25kgm^{-2}. Astrazeneca may not have restricted this to when the patient BMI is above 25kgm^{-2}, but given baseline BMIs the impact of this will not have been large. All analyses also rely upon the estimates of Currie et al (2005) for the quality of life impacts of hypoglycaemic events, though again it appears that Astrazeneca may have applied the coefficient for non-severe hypoglycaemia to the event rate rather than to its logarithm.

And all analyses apply fairly similar absolute QALY decrements per UTI and per GTI: they are small. Those of the AG are slightly higher, this probably being due to the assumption of 2 weeks duration as drawn from Nicholle et al (2014) who estimated median durations of UTIs of between 11.0 days and 12.5 days.

Costs

Turning to the main costs these are as follows, though again the presentation is slightly biased against the Janssen submission. The Janssen submission has a number of health states associated with a patient's eGFR and the cost in the absence of complications will not have been zero. But it is difficult to identify quite what the cost in the absence of complications was. In the opinion of the AG, it is likely to have been quite small (see Table **110**).

Table 110 Monotherapy direct drug costs: Companies and AG

	Janssen	AZ	BI	AG
Empagliflozin 10mg	£477.30	£476.98	£477.98	£476.98
Empagliflozin 25mg	£477.30	£476.98	£477.98	£476.98
Dapagliflozin 5mg	..	..	£477.98	..
Dapagliflozin 10mg	£477.30	£476.92	£477.98	£476.98
Canagliflozin 100mg	£477.26	£476.93	£477.98	£476.93
Canagliflozin 300mg	£608.63		£608.21	£476.93
Flozin average	..	£481.79	..	..
SU (Gliclazide MR)	£25.81	£65.70	£68.36	£62.18
Pioglitazone	£20.48	£19.03	£24.25	£20.99
Repaglinide 6mg	£71.10	..	£93.40	£71.91
Sitagliptin 100mg	£433.86	£433.57	£433.86	£433.57
Glitpin average	..	£429.13	..	..

It seems likely that Janssen assumed the costs for gliclazide rather than the costs for gliclazide modified release. The company submissions also predated the recent change to the canagliflozin 300mg cost.

Note that the AG adds an additional £72.26 to the cost of pioglitazone for BNP monitoring: £26.26 for the test itself and £46.00 for a dedicated GP appointment (see Table **111** and Table **112**).

Table 111 Main health state costs: year of event: Companies and AG

	Janssen	Astrazeneca	BI	AG
No complications	£0	£0	£459	£1,019
Complications 1st year				
Fatal MI	£1,566	£2,605	£1,521	£1,564
Fatal IHD	£3,818	£0	£3,766	£3,873
Fatal stroke	£4,255	£5,188	£3,954	£4,066
Fatal CHF	£3,366	£0	£3,191	n.a.
Non-fatal MI	£6,665	£7,938	£6,379	£7,550
Non-fatal IHD	£10,116	£12,762	£9,767	£10,932
Non-fatal stroke	£7,247	£11,450	£6,805	£8,120
Non-fatal CHF	£3,337	£5,180	£3,191	£4,288
Amputation	£11,810	£13,499	£9,546	£12,592
Blindness	£2,260	£6,502	£1,355	£3,234
ESRD	£26,297	£18,776	£35,715	£36,801

Table 112 Main health state costs: history of event: Companies and AG

	Janssen	Astrazeneca	BI	AG
MI	£875	£2,177	£1,154	£1,877
IHD	£920	£1,395	£1,215	£1,922
Stroke	£934	£1,378	£1,125	£1,934
CHF	£1,527	£1,656	£1,473	£2,515
Amputation	£2,531	£4,618	£1,792	£3,499
Blindness	£215	£2,307	£453	£1,225
ESRD	£26,152	£18,776	£35,631	£36,801

For Janssen the first year costs of events appear to be broadly in line with those of the AG. But the costs for those with a history of events are somewhat lower. It appears that these costs may not have included the outpatient costs.

For Astrazeneca the costs of all events are somewhat higher than those of the AG. The AG cannot definitively identify the source of these discrepancies, and any error may well be on the side of the AG. But it seems possible that Astrazeneca may have indexed the UKPDS84 costs from 2007 rather than from 2012. Astrazeneca also assumed zero costs in the absence of complications which is not in line with the UKPDS84. This will have tended to exaggerate the differences between treatments' total costs.

Boehringer Ingelheim appears to have only applied the inpatient costs of the UKPDS84, and to have ignored the outpatient costs (see Table **113**).

Table 113 Main health state costs: adverse events: Companies and AG

	Janssen	Astrazeneca	BI	AG
Severe hypo	£380	£424	£380	£411
Non-severe hypo	£0	£0	£0	£0
UTI	£82	£46	£36	£73
GTI	£51	£46	n.a.	£51

In the above presentation the Janssen costs for UTIs are a simple mean of the Janssen costs of upper UTIs and lower UTIs, but the Janssen modelling explicitly accounts for this.

Summary and conclusions: A comparison of the modelling exercises' results

All the company submissions apply the old £608 annual cost for canagliflozin300mg, rather than the recently revised list price that equalises this with the £477 annual canagliflozin 100mg. As a

consequence, the summary of cost effectiveness results of the companies concentrates upon the canagliflozin 100mg results.

Due in part to the assumed slow rate of HbA1c drift for pioglitazone, Janssen estimates that it has the lowest total costs of £20,264 and yields and average 9.998 QALYs. Gliclazide is estimated to be somewhat more expensive than pioglitazone with total costs of £2,956 and to yield 9.949 QALYs so is dominated by pioglitazone. Sitagliptin is also more expensive with a total cost of £23,442 and yields a total of 9.981 per QALY so is dominated by pioglitazone, though has a cost effectiveness estimate compared to gliclazide of £6,969 per QALY.

Janssen estimates that canagliflozin 100mg has total costs of £23,525 and yields 10.039 QALYs which implies a cost effectiveness estimate of £79,537 per QALY compared to pioglitazone. The cost effectiveness estimate compared to gliclazide is £3,377 per QALY, this being largely due to the higher costs in the gliclazide arm compared to pioglitazone. Canagliflozin 100mg is estimated to dominate empagliflozin 10mg, empagliflozin 25mg and dapagliflozin 10mg.

The Janssen cost effectiveness estimates for the flozins compared to sitagliptin are £1,414 per QALY for canagliflozin 100mg, £1,977 per QALY for empagliflozin 25mg, £4,724 per QALY for empagliflozin 10mg and £6,040 per QALY for sitagliptin.

If that annual rate of increase in HbA1c is equalised between the treatments and repaglinide is included as a comparator it appears that this worsens the cost effectiveness estimate for canagliflozin compared to repaglinide to £189k per QALY. The cost effectiveness estimates for canagliflozin 100mg compared to gliclazide and sitagliptin worsen to £21,580 per QALY and £21,470 per QALY respectively. Applying the UKPDS68 evolution of HbA1c results in broad clinical equivalence between canagliflozin 100mg and gliclazide, but the costs of canagliflozin 100mg are £744 greater.

Astrazeneca pooled the flozins into a class effect. Given this pioglitazone was estimated to be the least costly with total costs of £26,067 and to yield 13.111 QALYs. The sulfonylureas were estimated to have a total cost of £26,582 so £515 higher than pioglitazone, and to yield 13.179 QALYs so have a cost effectiveness estimate of £7,574 per QALY compared to pioglitazone. The gliptins were estimated to have a total cost of £27,873 and to yield 13.188 QALYs or only 0.009 QALYs more than the sulfonylureas, hence have a cost effectiveness compared to the sulfonylureas of £143k per QALY. The flozins were only £106 more expensive than the glitpins and yielded an additional 0.018 QALYs so had a cost effectiveness compared to the gliptins of £5,904 per QALY. But the flozins cost effectiveness compared to the sulfonylureas was poor at £52,047 per QALY.

Astrazeneca sensitivity analyses showed results were sensitive to the HbA1c intensification threshold and to the assumptions around the evolution of weight.

Boehringer Ingelheim presented four modelling exercises, with all four having been previously summarised above. The following summary concentrated upon the lifetime OM1 modelling which compares empagliflozin 10mg and 25mg with pioglitazone, repaglinide, gliclazide and sitagliptin. This estimates that pioglitazone is the least expensive treatment with a total cost of [redacted] and yields [redacted] QALYs. Only repaglinide is close to being cost effective compared to pioglitazone, yielding an additional 0.025 QALYs at an additional cost of £635 hence a cost effectiveness estimate of £25,349 per QALY. Empagliflozin 25mg and empagliflozin 10mg are estimated to be £2,834 and £2,834 more expensive than pioglitazone to yield an additional 0.061 and 0.056 QALYs, so have cost effectiveness estimates of £46,480 per QALY and £50,892 per QALY compared to pioglitazone. The cost effectiveness estimates for empagliflozin 25mg and 10mg compared to sitagliptin were somewhat better. The net costs are estimated to be £330 and £333 with additional patient gains of [redacted] and [redacted], resulting in cost effectiveness estimates of around [redacted] per QALY and [redacted] per QALY respectively.

The AG modelling suggests that gliclazide is the least expensive with total costs of £27,314. Repaglinide and pioglitazone have similar total costs of £27,413 and £27,543 respectively. The increased costs for pioglitazone are due in part to the AG including a £72 allowance for annual BNP monitoring. Costs increase quite markedly with sitagliptin at a total cost of £32,358, and increase further with the flozins being clustered between £32,676 and £32,866. Sitagliptin is estimated to be £5,045 more expensive than gliclazide, and the flozins between £5,362 and £5,553 more expensive than gliclazide.

If there are no direct quality of life impacts from weight changes gliclazide is estimated to yield 10.392 QALYs. This is the highest total QALYs for this scenario and as a consequence gliclazide dominates all the other treatments.

Including direct quality of life impacts from weight changes and assuming that the weight changes associated with the monotherapies persist indefinitely results in repaglinide now being superior to gliclazide by 0.030 QALYs and so having a cost effectiveness estimate of £3,331 per QALY. Repaglinide formally dominates pioglitazone and sitagliptin, but canagliflozin yields an additional 0.177 QALYs at an additional cost of £5,262 so has a cost effectiveness estimate of £44,994 per QALY compared to repaglinide. If weight losses associated with treatment tend to rebound at either one year or at treatment intensification the cost effectiveness estimate for canagliflozin compared to repaglinide worsens to £192k per QALY and £119k per QALY respectively.

Canagliflozin is estimated to be around £100 less expensive than empagliflozin and £200 less expensive than dapagliflozin. With no direct quality of life effects from weight changes it is estimated to be marginally more effective than empagliflozin by 0.002 QALYs and 0.013 QALYs more effective than dapagliflozin. Including the effects of weight upon quality of life increases these net gains to 0.034 QALYs and 0.046 QALYs if weight changes persist indefinitely. If they rebound after one year these gains fall to 0.007 QALYs and 0.019 QALYs, while if they rebound at treatment change they fall to 0.014 QALYs and 0.026 QALYs.

Both canagliflozin and empagliflozin have reasonable cost effectiveness estimates compared to sitagliptin of £12,623 per QALY and £18,341 per QALY even if there are no quality of life impacts from weight changes. Including these effects improves their cost effectiveness estimates compared to sitagliptin.

Dapagliflozin fares slightly worse compared to sitagliptin. It costs an additional £508 but only yields an additional 0.013 QALYs if there are no direct quality of life impacts from weight changes, so has a cost effectiveness estimate of £40,383 per QALY compared to sitagliptin. This improves to £6,632 per QALY if weight changes have a quality of life impact and are assumed to persist indefinitely. If they only persist for one year the cost effectiveness estimate worsens to a little over £30,000 per QALY, but if they persist until treatment change the cost effectiveness estimate worsens but only to a little under £20,000 per QALY.

The AG results showed some sensitivity to whether patients add insulin to their existing treatments or switch to it, the application of a common 7.5% HbA1c baseline and applying a reduced -0.47% HbA1c effect for gliclazide as recently reviewed above.

Chapter 6 Discussion and Research Needs

Principal findings

The key findings are;

- Canagliflozin, dapagliflozin and empagliflozin are clinically effective in improving glycaemic control when used in monotherapy
- They also provide modest reductions in systolic blood pressure, and promote weight loss
- The main adverse effects are urinary tract and genital area infections
- There are concerns following reports of DKA and bone loss. DKA appears rare – about 1 per 3000 patient years. Fractures were not increased after 3 years of empagliflozin treatment in the empagliflozin outcomes trial.

Other options

The NICE scope did not include all possible comparators. Four not included were;

- Bariatric surgery which is covered by other guidance
- Early intensive treatment
- Very low calorie diets
- Intensive lifestyle interventions[211, 212]

Bariatric surgery

The NICE guidance on bariatric surgery[213] includes a section specific to type 2 diabetes, reproduced in Box 3 below

Box 3. NICE guidance on bariatric surgery for type 2 diabetes

1.11 Bariatric surgery for people with recent-onset type 2 diabetes

1.11.1 Offer an expedited assessment for bariatric surgery to people with a BMI of 35 or over who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent).

1.11.2 Consider an assessment for bariatric surgery for people with a BMI of 30–34.9 who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent).

1.11.3 Consider an assessment for bariatric surgery for people of Asian family origin who have recent-onset type 2 diabetes at a lower BMI than other populations (see recommendation 1.2.8) as

long as they are also receiving or will receive assessment in a tier 3 service (or equivalent).

Early intensive treatment

The use of intensive treatment at diagnosis was first reported by a Chinese study in 2004.[214] Two weeks of intensive insulin treatment (with CSII) improved beta cell function, after which 47% remained well controlled on diet alone for 12 months and 42% for two years. A later trial randomised 410 Chinese patients to intensive insulin, or oral agents (metformin or gliclazide or both). Once patients had been normoglycaemic for two weeks, the drugs were stopped. After insulin, 51% of the CSII group and 45% of the MDI group remained in good glycaemic control a year later, compared to 27% of those on oral agents, suggesting that how the normoglycaemia is achieved is important(Yang and Weng[215]).

A systematic review[216] published in 2013 by Kramer and colleagues found seven studies of short-term intensive insulin therapy at diagnosis of type 2 diabetes. Two were RCTs and five were case series from China. When considering data from China, we need to bear in mind that Chinese people with type 2 diabetes have a more insulin-deficient and less insulin-resistant pattern.

Two small studies in white populations were not included in the Kramer review. Ilkova and colleagues[217]from Turkey and Israel treated 13 patients with newly-diagnosed type 2 diabetes not responding to 3-6 weeks of diet and physical activity with CSII for 2 weeks. Most (9/13) responded and three had three to five years remission of diabetes. In 5 patients control deteriorated after 9 to 36 months but good control was restored after a second fortnight of CSII.

Ryan[218] in Canada treated 16 people newly diagnosed with type 2 diabetes with MDI for 2-3 weeks, and a year later 7 were on no glucose lowering agents.

Introducing metformin earlier after diagnosis has been advocated by Brown and colleagues.[219] They noted that in a cohort of 1,799 patients that had metformin as first ever glucose lowering drug, those who started it less than 3 months after diagnosis of diabetes had a lower failure rate (12.2% a year) than those who started metformin 12 or more months after diagnosis (about 20% a year).

Another form of early intensive treatment is triple therapy from diagnosis, Abdul-Ghani and colleagues[220] report the results of the EDICT (Efficacy and durability of initial combination therapy for type 2 diabetes) in which patients were treated from diagnosis with metformin, pioglitazone and exenatide, and compared to a control arm that had a more standard approach of starting with

metformin followed by addition of sulfonylurea then glargine as required. The hypothesis behind the trial combination was to have a combination of drugs to improve both insulin secretion and sensitivity. The triple therapy group had lower HbA1c (by 0.55%), far less hypoglycaemia, and 1.2kg weight loss compared to 4kg gain on the standard sequence.

Very low calorie diets

Tyalor and colleagues from Newcastle have challenged the consensus that diabetes is a progressive irreversible disease, by showing that very low calorie diets (600kcal.day) for 8 weeks) can reverse type 2 diabetes by restoring beta-cell function and hepatic insulin sensitivity. They did this first for relatively recent onset cases in the Counterpoint Study[221], but then showed that about half of people with long-standing diabetes could return to normal glucose levels and stop their glucose-lowering medications.[222] This was achieved by weight loss averaging 14-15 kgs. The 8-week time period was too short to show full effect on HbA1c but even by then it fell by 1.15 in the short duration group and by an average of 0.6% in the long-duration group. Stevens and Taylor report (2015) that email feedback from people who lost weight and kept it off, have continued to have normal glucose levels for up to 3 years, so far. So it appears that as long as weight loss is maintained, they remain non-diabetic.

Non-pharmacological interventions

A very large number of trials reporting effects of different drugs are mentioned in this report and the industry submissions. Research into the management of type 2 diabetes is very pharmaco-centric, partly because the manufacturers of the drug have to carry out such trials for licensing purposes. There is no such pressure on developers of lifestyle interventions, nor guaranteed funding. However, lifestyle interventions should also be considered. Type 2 diabetes is strongly associated with overweight and obesity, and physical inactivity, and lifestyle change can be effective.
The work of Aas and colleagues[211] has been reported in previous reviews for NICE. Aas et al carried out a trial in 38 diabetic subjects poorly controlled (HbA1c 8 to 10.5%; mean 9.0%) on oral drugs and being considered for insulin treatment. They were randomised to insulin treatment or to an intensive lifestyle intervention based on exercise and diet, or both. After 12 months, HbA1c improved by 1.2% in the lifestyle arm and by 1.5% in the insulin (NPH twice daily with short-acting at mealtimes if required) arm. Weight fell by 3 kg in the lifestyle arm but rose 4.9kg in the insulin arm. The lifestyle intervention comprised 14 sessions of dietary advice, two individual sessions and one hour of exercise of moderate intensity twice a week, including group aerobics, walking and swimming. Unfortunately a year after the intervention had finished, HbA1c and weight rose again in the lifestyle group.

The problem with lifestyle interventions is adherence. A previous health technology assessment on prevention of diabetes in people with impaired glucose tolerance noted the tendency for gains after lifestyle interventions to be lost once the intervention was stopped, with the exception of the Finnish Diabetes Prevention Study in which the intervention continued for four years.[223]

However ways of improving adherence have been researched. Perri and colleagues[224] randomised 379 adults to walking at different speeds, and found that increasing the frequency of exercise achieved better adherence than increasing the intensity. Their study was prompted by awareness of a public perception that health benefits would only be achieved by frequent high intensity exercise.

Hansen and colleagues[225] from the Belgium and the Netherlands also reported that prolonged low-to-moderate exercise was almost as effective as more intense exercise. Their participants had three sessions a week of supervised walking, cycling or cross-country ski-type exercise for six months. In the moderate intensity group, HbA1c fell from 7.4% at baseline to 7.2% at 6 months. There were modest improvements in weight (91.1kg) and total cholesterol. The higher intensity group did better, with HbA1c reduction of 0.5% and weight loss of 1.8kg. The authors note that participants are more likely to drop out of high intensity physical activity, partly because people with long-standing type diabetes often have comorbidities that restrict such exercise.

Walking supported by pedometer use has been reported to be effective in a 12-month trial from Leicester.[226] However arguments to the contrary have appeared in recent years, suggesting that short duration high intensity exercise may be effective with the brevity improving adherence.[227]

Snowling and Hopkins[228] carried out a meta-analysis of the effects of different forms of exercise (aerobic, resistance mixed) in type 2 diabetes. They reported an improvement in HbA1c of 0.8% which is as great as many drugs achieve.

A full review of the benefits of physical activity in type 2 diabetes is beyond the scope of this report. Reviews of exercise therapy in type 2 diabetes and the mechanisms are provided by Praet and van Loon[229] and Zanuso et al.[230]
The NICE Public Health Guidance on weight management[231] noted that even modest weight loss could be cost-effective if sufficient and maintained. An Australian review of six interventions to promote physical activity also concluded that most would be cost-effective.[232]

A review by Fujioka[233] also concluded that in type 2 diabetes, weight loss of 1-4kg improved metabolic control and cardiovascular risk, though greater weight loss achieved greater benefit. Wing and colleagues[234] reported from the Look AHEAD trial (Action for Health in Diabetes) that modest

weight loss (5-10% body weight, 7.25 kg) improved glycaemic control (HbA1c reduced by 0.5%), blood pressure (6 mmHg) and HDL cholesterol. but even minor weight loss (2-5%) showed some benefit (HbA1c reduced by about 0.25%, SBP by about 4mm Hg).

Coppell and colleagues from Otago[212] carried out a randomised trial of an intensive nutritional intervention (seven individual sessions with a dietitian, one group session and telephone calls) compared to standard care (general practitioner or hospital clinic). After six months, the intensive group recorded reductions in HbA1c (0.5%), weight (2.1kg), waist circumferences (3.5cm), SBP (4.1mm Hg) and total cholesterol (0.24mmol/l) while HDL-cholesterol was unchanged. The control group showed little change and none in HbA1c.

A full review of the benefits of weight loss in type 2 diabetes is outwith the scope of the this report, and others have reviewed the subject.[235] The cost-effectiveness of lifestyle interventions was reviewed by Jacobs-van der Bruggen et al[236] who concluded that short-term results showed that they were cost-effective. However they noted a lack of long-term maintenance of benefit.

In summary, there is a range of effective lifestyle interventions, but the main problems are adherence and long-term maintenance.

Research needs

The clinical effectiveness of the SGLT2 inhibitors for at least 2 years is not in doubt, and the main need now is for data on long-term effectiveness and safety. The empagliflozin cardiovascular outcomes trial[131] has reported, though some clarifications are required. The equivalent studies for canagliflozin (CANVAS[124] and dapagliflozin DECLARE[125] are underway. Continued monitoring for diabetic ketoacidosis (DKA) and fractures is required. FDA and EMA reports are expected in autumn of 2015.

The first trials of the SGLT2 in type 1 diabetes are emerging, and because of their insulin-independent mode of action, they would be expected to be useful there. However the DKA risk would be more of a concern than in type 2 diabetes.

Conclusions

The SGLT2 inhibitors are effective in improving glycaemic control, promoting weight loss and reducing blood pressure – the first oral drugs for diabetes to do so. Their safety record remains to be established, but the only common adverse effects are small increases in the frequency of urinary and genital tract infections, seldom serious.However they are much more expensive than older drugs such as gliclazide and pioglitazone.

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Appendix 1 Search strategy

Clinical effectiveness searches

1. *Searches for journal articles*

   Search strategy for Ovid Medline (1946- February 16, 2015) and Ovid Embase (1974-February 16th, 2015)

   1. (empagliflozin or canagliflozin or dapagliflozin or sodium glucose cotransporter 2 inhibitor* or sodium glucose co-transporter 2 inhibitor* or SGLT2 inhibitor* or SGLT-2 inhibitor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
   2. randomized controlled trial.pt.
   3. random*.tw.
   4. 2 or 3
   5. 1 and 4

164 retrieved in Medline and 239 in Embase

There were no restrictions by language.

Weekly auto-alerts of both searches were then run from February 2015 until the end of August 2015 in Medline, Embase and PubMed to check for newly emerging studies.

A total of 403 records were downloaded into EndNote, and after removal of duplicates 246 unique records remained, of which 195 were excluded on the basis of title and abstract on the first screening. The full text of the 51 records remaining was obtained and a second screening was performed. Seven trials (8 full text articles) were included in clinical effectiveness.

Table x gives reasons for exclusion for full text studies.

2. *Search for meeting abstracts*

   2.1 Search strategy for Ovid Embase (1947 to 2015 Week 12)

   1. (empagliflozin or canagliflozin or dapagliflozin).m_titl.
   2. conference.pt.
   3. 1 and 2

   400 retrieved

   2.2 Search strategy for Web of Science Core Collection (from inception to February 2015)

   TITLE field: (empagliflozin or canagliflozin or dapagliflozin); Refined by: Document Types: (MEETING ABSTRACT)

239 retrieved

636 meeting abstracts were downloaded into Endnote, and after removing duplicates there were 372 unique records. These were screened on the basis of title (and abstract if available) and the completel abstracts of 46 were selected for further scrutiny, of which one was selected for inclusion.

Cost effectiveness searches

Ovid MEDLINE (1946 to July Week 1 2015, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations July 13, 2015)

1. exp Economics/
2. exp "Costs and Cost Analysis"/
3. Health Status/
4. exp "Quality of Life"/
5. exp Quality-Adjusted Life Years/
6. (pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.
7. (health state* or health status).tw.
8. (qaly* or ICER* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF-6D or SF6D or HUI).tw.
9. (markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit*).tw.
10. (quality adj2 life).tw.
11. (decision adj2 model).tw.
12. (visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.
13. "resource use".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. (empagliflozin or canagliflozin or dapagliflozin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
16. (sodium glucose cotransporter 2 or sodium glucose co-transporter 2 or SGLT2* or SGLT-2*).m_titl.
17. 15 or 16
18. 14 and 17

29 retrieved

Ovid Embase 1974 to 2015 July 13

1. exp health economics/
2. exp health status/
3. exp "quality of life"/
4. exp quality adjusted life year/
5. (pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.
6. (health state* or health status).tw.
7. (qaly* or ICER* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or short-form or SF-12 or SF12 or SF-36 or SF36 or SF-6D or SF6D or HUI).tw.
8. (markov or time trade off or TTO or standard gamble or hrql or hrqol or disabilit* or disutilit* or net benefit or contingent valuation).tw.
9. (quality adj2 life).tw.
10. (decision adj2 model).tw.
11. (visual analog* scale* or discrete choice experiment* or health* year* equivalen* or (willing* adj2 pay)).tw.
12. (resource* or quality of well-being or qwb).tw.
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. (empagliflozin or canagliflozin or dapagliflozin).mp.
15. (sodium glucose cotransporter 2 or sodium glucose co-transporter 2 or SGLT2* or SGLT-2*).m_titl.
16. 14 or 15
17. 13 and 16
18. (monotherap* or placebo).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
19. 17 and 18

136 retrieved

Cochrane Library – NHS Economic Evaluation Database in July 2015

(empagliflozin or canagliflozin or dapagliflozin) in Title, Abstract or Keywords

2 retrieved

The Endnote database had 167 references. Retained 43 for a second viewing; the full text of 6 were retrieved.

Searches for trials of gliclazide in monotherapy lasting 24-26 weeks, versus placebo

Search strategy in Ovid Medline (1946-April 7 2005)
1. gliclazide.mp. or exp Gliclazide/
2. randomized controlled trial.pt.
3. 1 and 2
142 retrieved

Search strategy in Ovid Embase
1. gliclazide.mp. or gliclazide/
2. (placebo or monotherapy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. 1 and 2
4. random*.mp.
5. 3 and 4
6. randomized controlled trial/
7. 5 and 6
153 retrieved

295 in total in Endnote; 230 after removing duplicates; 138 selected in first screening, and 58 in the second screening of 11 full text requested

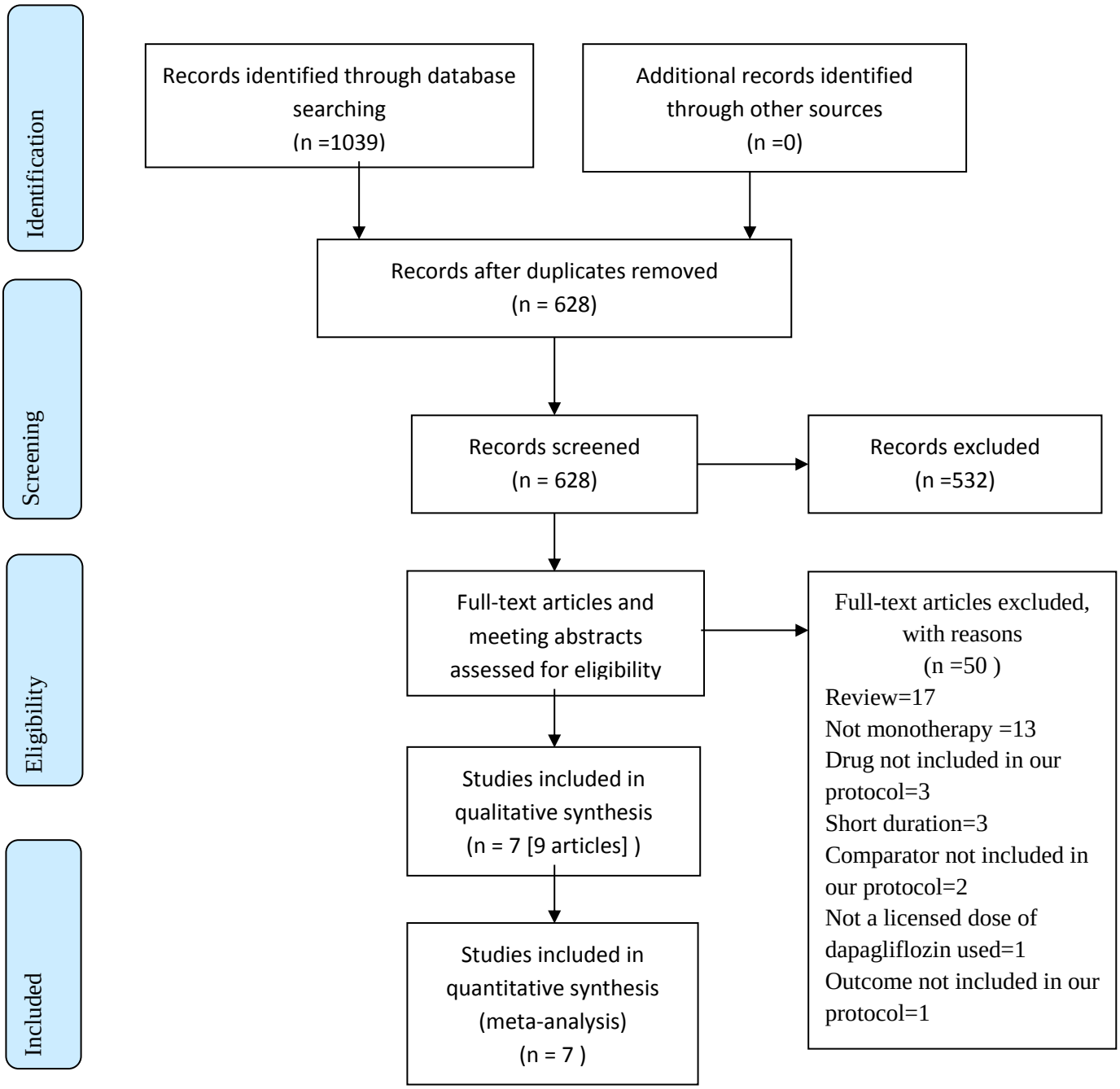
Searches for systematic reviews of sulphonylureas and gliclazide

Search strategy for Ovid Medline 1946 – April 7th – then updated September week 1, 2015
1. (sulfonylurea* or sulphonylurea* or gliclazide).tw.
2. meta-analysis.pt.
3. (systematic review or meta-analysis).tw.
4. 2 or 3
5. 1 and 4
143 retrieved

Ovid Embase 1974 – September 14, 2015
1. (sulfonylurea* or sulphonylurea* or gliclazide).tw.
2. (systematic review or meta-analysis).tw.
3. 1 and 2
263 retrieved

Total of 406 combined; after removal of duplicates it was 301. After a first screening 34 selected for a second screening and 15 full text were selected.

PRISMA Flow Diagram



Appendix 2 Reasons for Exclusions

Study ID	Reason for Exclusion
Bailey 2012[237]	Not a licensed dose of dapagliflozin used
Berhan 2013[238]	Review
Bluher 2014[239]	Review
Brand 2012[240]	Patients did not have diabetes
Escudero Vilaplana 2014[241]	Review
Ferrannini 2013[242]	Not monotherapy
Goring 2014[243]	Not monotherapy
Henry 2012[244]	Comparator not included in our protocol
Hussey 2013[245]	Short duration
Johnsson 2013a[96]	Review
Johnsson 2013b[246]	Review
Kadowaki 2014[247]	Short duration
Kaku 2014[248]	Comparator not included in our protocol
Lavalle-Gonzalez 2013[88]	Not monotherapy
Lutz 2014[249]	Review
Matthaei 2014[250]	Review
Nauck 2013[251]	Not monotherapy
Nauck 2011[114]	Not monotherapy
Orme 2014[252]	Not monotherapy
Pafili 2014[253]	Review
Phung 2014[254]	Review
Plosker 2012[255]	Review
Plosker 2014[256]	Review
Polidori 2014[257]	Outcome not included in our protocol
Raskin 2013[258]	Review
Rosenstock 2012a[259]	Not monotherapy
Rosenstock 2012b[260]	Not monotherapy
Rosenstock 2013[261]	Not monotherapy
Scheen 2015[262]	Review
Seino 2014a[263]	Drug not included in our protocol
Seino 2014b[264]	Drug not included in our protocol
Seino 2014c[265]	Drug not included in our protocol
Strojek 2011[266]	Not monotherapy
Strojek 2013[267]	Not monotherapy
Strojek 2014[268]	Not monotherapy
Tahrani 2013[126]	Review
Usiskin 2014[269]	Review
Wilding 2013[270]	Not monotherapy
Yang 2014[271]	Review
Zambrowicz 2013[272]	Short duration
Zhang 2014[273]	Review
Zinman 2014[132]	Protocol only

Appendix 3 Study characteristics

Study	Participants and baseline data	Intervention / Outcomes
CANAGLIFLOZIN		
CANTATA-M (Stenlöf 2013) **Setting:** multicentre (n=NR); 17 countries (United States, Austria, Colombia, Estonia, Guatemala, Iceland, India, Korea, Republic of, Lithuania, Malaysia, Mexico, Philippines, Poland, Puerto Rico, Romania, South Africa, Spain, Sweden) **Design:** phase 3 RCT, double blind, placebo controlled **Duration:** 26 weeks **Extension:** 26 week extension, replacing placebo with sitagliptin **Sponsor:** Janssen Research & Development, LLC	**N:** 584 (172/195 completers in the cana100 group, 175/197 in the cana300 group, 160/192 in the placebo group; 152/170 completed extension in cana100 group, 165/170 in cana300 group, 135/155 in placebo group); 91 in the high glycaemic substudy (40/47 completers in the cana100 group, 40/44 in the cana300 group) **Inclusion criteria:** age 18 to 80 years, type 2 diabetes inadequately controlled with diet and exercise or on anti-hyperglycaemic agents (AHA) who underwent washout of the agent; HbA1c for participants not on AHAs ≥7.0 to ≤10.0%; HbA1c for participants on AHA monotherapy or SU plus metformin ≥6.5 and ≤9.5% at screening and ≥7.0 and ≤10% and FPG <15 mmol/L at -2 weeks; substudy conducted for participants with HbA1c >10.0 and ≤12.0% at screening or -1 weeks and FPG ≤19.4 mmol/L at -1 weeks **Exclusion criteria:** repeated FPG repeatedly >15.0 mmol/L during pre-treatment (or >19.4 mmol/L for the high glycaemic substudy); history of type 1 diabetes, hereditary glucose-galactose malabsorption, primary renal glucosuria or cardiovascular disease; treatment with a PPARγ agonist, insulin, another SGLT2 inhibitor or any other AHA except as specified in the inclusion criteria within 12 weeks before screening; estimated glomerular filtration rate (eGFR) <50 ml/min/1.73m^2 at screening **Age (years):** *cana100:* 55.1 SD10.8; *cana300:* 55.3 SD10.2; *placebo:* 55.7 SD10.9; *cana100 high HbA1c:* 49.7 SD11.1; *cana300 high HbA1c:* 48.8 SD10.8 **Sex (%women):** *cana100:* 58.5%; *cana300:* 54.8%; *placebo:* 54.2%; *cana100 high HbA1c:* 51.1%; *cana300 high HbA1c:* 56% **Ethnicity:** *cana100:* 63.6% White, 9.2% Black, 13.8% Asian, 13.3% other; *cana300:* 69.5% White, 7.1% Black, 14.7% Asian, 8.6% other; *placebo:* 69.8% White, 4.7% Black, 15.1% Asian, 10.4% other; *cana100 high HbA1c:* 53.2% White, 6.4% Black, 23.4% Asian, 17.0% other; *cana300 high HbA1c:* 68.2% White, 2.3% Black, 15.9% Asian, 13.6% other **Diabetes duration (years):** *cana100:* 4.5 SD4.4; *cana300:* 4.3 SD4.7; *placebo:* 4.2 SD4.1; *cana100 high HbA1c:* 4.6 SD4.6; *cana300 high HbA1c:* 5.2 SD4.8 **HbA1c (%):** *cana100:* 8.1 SD1.0; *cana300:* 8.0 SD1.0; *placebo:* 8.0 SD1.0; *cana100 high HbA1c:* 10.6 SD0.9; *cana300 high HbA1c:* 10.6 SD0.6 **BMI (kg/m^2):** *cana100:* 31.3 SD6.6; *cana300:* 31.7 SD6.0; *placebo:* 31.8 SD6.2; *cana100 high HbA1c:* 30.4 SD7.1; *cana300 high HbA1c:* 30.5 SD5.5 **Baseline medication:** patients on AHA at screening: *cana100:* 48.2%; *cana300:*	**<u>Intervention</u>** **cana100 (n=195):** 100 mg/day canagliflozin **cana300 (n=197):** 300 mg/day canagliflozin **cana100 high HbA1c (n=47):** 100 mg/day canagliflozin in participants with HbA1c >10.0 and ≤12.0% **cana300 high HbA1c (n=44):** 300 mg/day canagliflozin in participants with HbA1c >10.0 and ≤12.0% **Control (n=192):** placebo **Run-in:** 8 weeks and diet and exercise and washout period for participants on AHA, followed by a 2 week single blind placebo run-in period; participants not on AHA directly entered the 2 week placebo run-in period; participants in the high glycaemic substudy entered a 1 week single blind placebo run-in period **Extension:** after 26 weeks, the placebo group received double blind sitagliptin (100 mg/day) **All groups:** rescue therapy with metformin was initiated if FPG was >15.0 mmol/L after day 1 to week 6, >13.3 mmol/L after week 6 to week 12 and >11.1 mmol/L after week 12 to week 26; HbA1c >8% after week 26 **<u>Outcomes</u>** **Primary outcome:** change in HbA1c from baseline to week 26 **Secondary outcomes:** proportion achieving HbA1c <7.0%, FPG, 2h postprandial glucose, HOMA, systolic blood pressure, HDL-cholesterol, triglycerides, body weight **Other outcomes:** LDL-cholesterol, non-HDL-cholesterol, apolipoprotein B, diastolic blood pressure, safety assessments (incl. laboratory, vital signs, hypoglycaemia) **Note:** the main outcomes for the extension period were only reported for the canagliflozin groups [not considered in the data extraction]; safety parameters for all groups

Study	Participants and baseline data	Intervention / Outcomes
	48.2%; *placebo:* 47.9%; *cana100 high HbA1c:* 23.4%; *cana300 high HbA1c:* 22.7%	
Inagaki 2014 **Setting:** multicentre (n=31); Japan **Design:** phase 3 RCT, double blind, parallel group, placebo controlled **Duration:** 24 weeks **Follow-up:** 2 weeks post-intervention follow-up **Sponsor:** Mitsubishi Tanabe Pharma Corp	**N:** 183 in relevant comparison groups (84/90 completers in the cana100 group, 74/93 in the placebo group) **Inclusion criteria:** age ≥20 years, type 2 diabetes mellitus diagnosed ≥3 months before run-in, HbA1c 7.0 to 10%, on diet and exercise therapy for ≥55 days; patients on antihyperglycaemic treatment had to start a washout period of ≥55 days before starting run-in **Exclusion criteria:** non type 2 diabetes, current or history of severe diabetic complications, FPG >270 mg/dl, indication for insulin therapy, hereditary glucose-galactose malabsorption or renal glycosuria, inadequately controlled thyroid abnormality, anorexia or bulimia, current or history of urinary tract/genital infection <1 year before run-in, triglyceride ≥6.72 mmol/L, BP ≥160/≥100 mmHg during run-in or patients with known hypertension immediately requiring the addition/ modification of antihypertensive therapy, heart disease, serious liver disease, serious kidney disease, estimated glomerular filtration rate <50 ml/min/1.73 m^2; urinary albumin creatinine ratio ≥300 mg/g creatinine, history of malignancy, neuropsychiatric disorder likely to hinder study evaluations; history of drug-related shock or anaphylactic symptoms; unwilling to use contraception; pregnant or breast feeding women, prior use of canagliflozin **Age (years):** *cana100:* 58.4 SD10.4; *placebo:* 58.2 SD11.0 **Sex (%women):** *cana100:* 34.4%; *placebo:* 35.5% **Ethnicity:** 100% Japanese **Diabetes duration (years):** *cana100:* 4.72 SD4.59; *placebo:* 5.63 SD5.76 **HbA1c (%):** *cana100:* 7.98 SD0.73; *placebo:* 8.04 SD0.70 **BMI (kg/m^2):** *cana100:* 25.59 SD4.20; *placebo:* 25.85 SD4.39 **Comorbidities:** NR **Baseline medication:** *cana100:* 22.2% previously on OADs; *placebo:* 25.8% previously on OADs	**<u>Intervention</u>** **cana100 (n=90):** 100 mg/day canagliflozin, once daily before breakfast **Control (n=93):** placebo, once daily **Note:** the trial also included a 200 mg group, this was not considered here **Run-in:** 4 week single blind placebo lead-in **All groups:** patients were instructed to continue diet and exercise therapy as before **<u>Outcomes</u>** **Primary outcome:** change in HbA1c from baseline to week 24 **Secondary outcomes:** FPG, body weight, proportion achieving HbA1c <7%, 2h postprandial glucose, waist circumference, lipids, blood pressure, HOMA, proinsulin, C-peptide **Other outcomes:** safety assessments (incl. laboratory, vital signs, hypoglycaemia)

Study	Participants and baseline data	Intervention / Outcomes
DAPAGLIFLOZIN		
Ferrannini 2010 / Bailey 2014 **Setting:** multicentre (n=85); USA, Canada, Mexico, Russia **Design:** phase 3 RCT, double blind, parallel group, placebo controlled **Duration:** 24 weeks **Extension:** 78 weeks (Bailey 2014), double blind **Sponsor:** Bristol-Myers Squibb; AstraZeneca	**N:** 260 in relevant comparison groups (156/185 completers in the dapa10 groups, 63/75 in the placebo group; 42/56 completed extension in dapa10 AM group, 42/62 in placebo group) **Inclusion criteria:** age 18 to 77 years, type 2 diabetes mellitus inadequately controlled with diet and exercise, naïve to treatment, BMI ≤45 kg/m^2, fasting C-peptide ≥1.0 ng/ml **Exclusion criteria:** type 1 diabetes, serum creatinine ≥133 µmol/L (men) or ≥124 µmol/L (women), urine albumin-to-creatinine ratio >200 mg/mmol, aspartate transaminase and/or alanine transaminase >3 times the upper limits of normal, creatine kinase ≥3 times the upper limit of normal, symptoms of severely uncontrolled diabetes (incl. marked polyuria and polydipsia with >10% weight loss during last 3 months before enrolment); significant renal, hepatic, haematological, oncological, endocrine, psychiatric, or rheumatic diseases, cardiovascular event within 6 months of enrolment, severe uncontrolled BP (systolic ≥180 mmHg and/or diastolic ≥110 mmHg) **Age (years):** *dapa10 AM:* 50.6 SD10.0; *dapa10 PM:* 50.7 SD9.7; *dapa10 high HbA1c:* 47.9 SD12.1; *placebo:* 52.7 SD10.3 **Sex (%women):** *dapa10 AM:* 51.4%; *dapa10 PM:* 48.7%; *dapa10 high HbA1c:* 41.0%; *placebo:* 58.7% **Ethnicity:** *dapa10 AM:* 90% White, 2.9% Black, 4.3% Asian, 2.9% other; *placebo:* 94.7% White, 2.7% Black, 2.7% Asian **Diabetes duration (years, median, IQR):** *dapa10 AM:* 0.45 (0.1, 3.4); *dapa10 PM:* 0.40 (0.1, 2.45); *dapa10 high HbA1c:* 1.4 (0.2, 3.5); *placebo:* 0.5 (0.1, 3.4) **HbA1c (%):** *dapa10 AM:* 8.01 SD0.96; *dapa10 PM:* 7.99 SD1.05; *dapa10 high HbA1c:* 10.73 SD0.85; *placebo:* 7.84 SD0.87 **BMI (kg/m^2):** *dapa10 AM:* 33.6 SD5.4; *dapa10 PM:* 33.3 SD5.6; *dapa10 high HbA1c:* 31.1 SD5.9; *placebo:* 32.3 SD5.5 **Comorbidities:** *dapa10 AM:* 1.4% diabetic neuropathy, 1.4% microalbuminuria, 41.4% hypertension; *placebo:* 8% diabetic neuropathy, 1.3% diabetic neuropathy, 1.3% microalbuminuria, 52% hypertension **Baseline medication:** no OAD; *dapa10 AM:* 41.4% on anti-hypertensives; *placebo:* 41.3% on anti-hypertensives	**Intervention** **dapa10 AM (n=70):** 10 mg/day dapagliflozin, administered once daily in the morning in people with HbA1c 7 to 10% **dapa10 PM (n=76):** 10 mg/day dapagliflozin, administered once daily in the evening in people with HbA1c 7 to 10% **dapa10 high HbA1c (n=39):** 10 mg/day dapagliflozin, administered once daily in the morning in people with HbA1c 10.1 to 12% **Control (n=75):** placebo, once daily in people with HbA1c 7 to 10% **Note:** the trial also included 2.5 mg and 5 mg groups, these were not considered here **Run-in:** 2 week diet/exercise placebo lead-in (1 week for patients with HbA1c 10.1 to 12.0%) **Extension:** after 24 weeks, the placebo group received low dose metformin (500 mg/day) and the dapa groups received matching placebo; results only reported for main dapa AM groups versus placebo **All groups:** if fasting FPG was >270 mg/dl at week 4, >240 mg/dl at week 8, or >200 mg/dl at weeks 12 to 24, patients were eligible for open-label rescue medication (500 mg metformin, titrated as needed up to 2000 mg); patients with HbA1c >8.0% for 12 weeks despite maximum tolerated metformin dose were discontinued; the strategy for rescue medication based on HbA1c was continued during the extension period. Patients received diet/exercise counselling according to American Diabetes Association recommendations throughout the study **Outcomes** **Primary outcome:** change from baseline in HbA1c at week 24 in the dapa10 AM group **Secondary outcomes:** FPG, body weight **Other outcomes:** safety assessments and adverse events (incl.

Study	Participants and baseline data	Intervention / Outcomes
		laboratory, vital signs, urinary tract and genital infections, hypoglycaemia)
Ji 2014 **Setting:** multicentre (n=40); China, Korea, Taiwan, India **Design:** phase 3 RCT, double blind, parallel group, placebo controlled **Duration:** 24 weeks **Follow-up:** 28 days post intervention (not reported) **Sponsor:** Bristol-Myers Squibb; AstraZeneca	**N:** 265 in relevant comparison groups (117/133 completers in the dapa10 group, 113/132 in the placebo group) **Inclusion criteria:** age ≥18 years, inadequately controlled type 2 diabetes mellitus (HbA1c ≥7.5 and ≤10.5% at enrolment and ≥7.0% and ≤10.5% during lead-in), drug naïve, BMI ≤45 kg/m^2, C-peptide ≥1.0 ng/ml **Exclusion criteria:** aspartate aminotransferase and/or alanine aminotransferase levels >3 times upper limit of normal, serum total bilirubin >34.2 µmol/L, serum creatinine ≥132.6 µmol/L for men or ≥123.8 µmol/L for women, haemoglobin ≤110 g/L for men and ≤100 g/L for women, creatine kinase ≥3 times the upper limit of normal, urine albumin to creatinine ratio >1800 mg/g, severe hypertriglyceridaemia (triglyceride >9.3 mmol/L), urinary excretion of N-acetyl-β-D-glucosaminidase >84 µmol/h per mmol creatinine, urinary excretion of α1 microglobulin >28 mg/g creatinine, parathyroid hormone value >1.5 times the upper limit of normal, calcium or serum phosphate values outside the normal reference range, abnormal free T4 values, positive hepatitis B surface antigen or positive anti-hepatitis C antibodies; currently unstable or serious vascular, renal, hepatic, haematologic, oncologic, endocrine, psychiatric, or rheumatic diseases **Age (years):** *dapa10:* 51.2 SD9.9; *placebo:* 49.9 SD10.9 **Sex (%women):** *dapa10:* 35.3%; *placebo:* 34.1% **Ethnicity:** *dapa10:* 88.7% Chinese, 6.8% Asian Indian, 3.8% Korean, 0.8% other Asian; *placebo:* 88.6% Chinese, 6.1% Asian Indian, 3.8% Korean, 0.8% Japanese, 0.8% other Asian **Diabetes duration (years):** *dapa10:* 1.67 SD2.8 (range 0 to 13); *placebo:* 1.3 SD2.0 (range 0 to 9.9) **HbA1c (%):** *dapa10:* 8.28 SD0.95; *placebo:* 8.35 SD0.95 **BMI (kg/m^2):** *dapa10:* 25.76 SD3.43; *placebo:* 25.93 SD3.64 **Comorbidities:** *dapa10:* 42.9% history of dyslipidaemia, 37.6% history of hypertension; *placebo:* 40.2% history of dyslipidaemia, 40.9% history of hypertension **Baseline medication:** no OAD; others not reported	**<u>Intervention</u>** **dapa10 (n=133):** 10 mg/day dapagliflozin, taken once daily before the first meal of the day **Control (n=132):** placebo, once daily **Note:** the trial also included a 5 mg group, this was not considered here **Run-in:** 6 week single blind placebo run-in with diet and exercise counselling consistent with China Diabetes Society recommendations **All groups:** open-label rescue therapy with metformin (500 mg daily, titrated to 2000 mg if necessary) could be given if glycaemic control was inadequate (during weeks 4 to 12, FPG >13.3mmol/L; during weeks 12 to 24, FPG level >11.1mmol/L); patients with FPG values consistently greater than protocol-specified values for 12 weeks despite a maximum tolerated dose of metformin were discontinued from the study **<u>Outcomes</u>** **Primary outcome:** change in HbA1c from baseline to week 24 **Secondary outcomes:** FPG, 2 h post-prandial glucose, proportion achieving HbA1c<7%, body weight **Other outcomes:** β-cell function and insulin resistance, waist circumference, lipids, proportion of patients with ≥3% or ≥5% reduction in total weight, fasting urinary glucose to creatinine ratio, safety and tolerability (incl. laboratory, vital signs, hypoglycaemia)

Study	Participants and baseline data	Intervention / Outcomes
Kaku 2014 **Setting:** multicentre (n=NR); Japan **Design:** phase 3 RCT, double blind, parallel group, placebo controlled **Duration:** 24 weeks **Follow-up:** 3 week post-intervention follow-up **Sponsor:** Bristol-Myers Squibb; AstraZeneca	**N:** 175 in relevant comparison groups (79/88 completers in the dapa10 group, 79/87 in the placebo group) **Inclusion criteria:** age ≥20 years, type 2 diabetes mellitus inadequately controlled with diet and exercise, naïve to drug treatment or on antihyperglycaemic treatment (the latter underwent a washout period before study begin), HbA1c ≥6.5% and ≤10% for drug-naïve patients and ≤8% for patients on ongoing treatment **Exclusion criteria:** type 1 diabetes, FPG >13.3 mmol/L, creatinine kinase >3 times upper limit of normal, estimated glomerular filtration rate <45 ml/min or serum creatinine >133 µmol/L for men and >124 µmol/L for women; severe hepatic insufficiency and/or significant abnormal liver function (aspartate aminotransferase >3 times upper limit of normal and/or alanine aminotransferase >3 times upper limit of normal; New York Heart Association class IV congestive heart failure; unstable or acute congestive heart failure; treatment with thiazolidinediones <6 months before enrolment; pregnant or breastfeeding women **Age (years):** *dapa10:* 57.5 SD9.3; *placebo:* 60.4 SD9.7 **Sex (%women):** *dapa10:* 39.8%; *placebo:* 40.2% **Ethnicity:** 100% Japanese **Diabetes duration (years):** *dapa10:* 4.93 SD4.52; *placebo:* 5.29 SD6.17 **HbA1c (%):** *dapa10:* 7.46 SD0.61 (21.6% <7%); *placebo:* 7.50 SD0.63 (24.1% <7%) **BMI (kg/m^2):** *dapa10:* 26.06 SD4.52; *placebo:* 25.22 SD4.39 **Comorbidities:** *dapa10:* 50% history of cardiovascular disease, 40.9% hypertension only; *placebo:* 42.5% history of cardiovascular disease, 35.6% hypertension only, 2.3% congestive heart failure; most patients in both groups had mild to moderate renal impairment (69% stage 1 or mild chronic kidney disease, 28% stage 2 or moderate chronic kidney disease) **Baseline medication:** not reported	**Intervention** **dapa10 (n=88):** 10 mg/day dapagliflozin, administered once daily **Control (n=87):** placebo, once daily **Note:** the trial also included a 5 mg group, this was not considered here **Run-in:** 2 week screening period and 4 week single blind placebo lead-in **Follow-up:** post-intervention follow-up mainly used for safety monitoring – no further results reported **All groups:** no further information **Outcomes** **Primary outcome:** change in HbA1c from baseline to week 24 **Secondary outcomes:** FPG, body weight **Other outcomes:** body weight in patients with BMI ≥25 kg/m^2, fasting insulin and C-peptide, systolic blood pressure, blood lipids, proportion achieving HbA1c <7%; safety assessments (incl. laboratory, vital signs, hypoglycaemia)

Study	Participants and baseline data	Intervention / Outcomes
EMPAGLIFLOZIN		
Lewin 2015 **Setting:** multicentre (n=197); 22 countries (no UK sites) **Design:** phase 3 RCT, double blind, parallel group **Duration:** 52 weeks**,** primary endpoint at 24 weeks **Follow-up:** follow-up visit 4 weeks after the last dose of study drug **Sponsor:** Boehringer Ingelheim; Eli Lilly	**N:** 404 in relevant comparison groups (398 with on treatment measurements) (114/133 completers in the empa25 group, 110/132 in the empa10 group, 116/133 in the lina5 group) **Inclusion criteria:** age ≥18 years, type 2 diabetes mellitus inadequately controlled with diet and exercise, no therapy with OAD, GLP1-analogue or insulin for ≥12 weeks prior to randomisation, BMI ≤45 kg/m^2, HbA1c >7% and ≤10.5% **Exclusion criteria:** uncontrolled hyperglycaemia (FPG >13.3. mmol/L); estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2; acute coronary syndrome, stroke, or transient ischaemic attack within 3 months prior to consent; bariatric surgery in the past 2 years; treatment with anti-obesity drugs within 3 months prior to consent **Age (years):** *empa25:* 56.0 SD9.3; *empa10:* 53.9 SD10.5; *lina5:* 53.8 SD11.5 **Sex (%women):** *empa25:* 42.1%; *empa10:* 51.5%; *lina5:* 43.6% **Ethnicity:** *empa25:* 69.9% White, 14.3% Asian, 15.8% other; *empa10:* 75.0% White, 9.8% Asian, 15.2% other; *lina5:* 77.4% White, 12.8% Asian, 9.8% other; Asians were from Malaysia, the Philippines, Taiwan; no South Asian recruits; other mainly Hispanic **Diabetes duration (time since diagnosis):** *empa25:* 36.1% ≤1 yr, 36.1% >1 to 5 yrs, 18.8% >5 to 10 yrs, 9.0% >10 yrs; *empa10:* 32.6% ≤1 yr, 45.5% >1 to 5 yrs, 11.4% >5 to 10 yrs, 10.6% >10 yrs; *lina5:* 37.6% ≤1 yr, 42.9% >1 to 5 yrs, 16.5% >5 to 10 yrs, 3.0% >10 yrs **HbA1c (%):** *empa25:* 7.99 SD0.97 (27.1% ≥8.5%); *empa10:* 8.05 SD1.03 (28.8% ≥8.5%); *lina5:* 8.05 SD0.89 (25.6% ≥8.5%) **BMI (kg/m^2):** *empa25:* 31.2 SD5.7; *empa10:* 31.5 SD5.7; *lina5:* 31.9 SD5.9 **Comorbidities:** *empa25:* n=20 (15%) microalbuminuria, n=0 macroalbuminuria; *empa10:* n=21 (16%) microalbuminuria, n=3 (2%) macroalbuminuria; *lina5:* n=16 (12%) microalbuminuria, n=2 (1.5%) macroalbuminuria **Baseline medication:** no anti-hyperglycaemic medication	**<u>Intervention</u>** **empa25 (n=133):** 25 mg/day empagliflozin, taken once daily in the morning **empa10 (n=132):** 10 mg/day empagliflozin, taken once daily in the morning **lina5 (n=133):** 5 mg/day linagliptin, taken once daily in the morning **Note:** the trial also included fixed combination empagliflozin 25 mg / linagliptin 5 mg and empagliflozin 10 mg / linagliptin 5 mg groups, these were not considered here **Run-in:** 2 week placebo run-in **All groups:** rescue medication initiated if blood glucose >240 mg/dL after overnight fast between weeks 1 and 12, blood glucose >200 mg/dL after overnight fast between weeks 12 and 24, or blood glucose >180 mg/dL or HbA1c >8% after overnight fast between weeks 24 and 52 (initiation, choice, and dosage of rescue medication at the discretion of the investigator but use of DPP-4 inhibitors, GLP-1 analogues, SGLT2 inhibitors not permitted); in cases of hypoglycaemia, rescue medication was to be reduced in dose or discontinued; if hyper- or hypoglycaemia could not be controlled, participants was discontinued from the trial **<u>Outcomes</u>** **Primary outcome:** change in HbA1c from baseline to week 24 **Secondary outcomes:** FPG, body weight, proportion achieving HbA1c <7% (of participants with HbA1c ≥7%) **Other outcomes:** systolic blood pressure, diastolic blood pressure, blood lipids, safety assessments (incl. laboratory, vital signs, hypoglycaemia)
Roden 2013/4 **Setting:** multicentre (n=124); nine countries	**N:** 986 (899 randomised, 87 in open-label empagliflozin) in relevant comparison groups (187/228 completed control, 206/224 completed empa10, 204/224 completed empa25, 206/223 completed sita100, 78/87 completed empa25open) **Inclusion criteria:** previously untreated type 2 diabetes (no oral or injected anti-	**<u>Intervention</u>** **Empa10 (n=224):** empagliflozin 10 mg/day in people with HbA1c 7 to 10% **Empa25 (n=224):** empagliflozin 25 mg/day in people with HbA1c

Study	Participants and baseline data	Intervention / Outcomes
(Belgium, Canada, China, Germany, India, Ireland, Japan, Switzerland, USA) **Design:** phase 3 RCT, placebo-controlled, double blind , parallel group **Duration:** 24 weeks **Extension:** 76 week extension trial **Sponsor:** Boehringer Ingelheim and Eli Lilly	diabetes treatment for 12 weeks before randomisation or start of open-label treatment), age ≥ 18 years (≥20 years in Japan, 18 to 65 in India), BMI ≤45 kg/m^2, and insufficient glycaemic control despite diet/exercise regimen (HbA1c 7.0-10.0% (or 7.0 to 9.0% in Germany)) at screening for patients eligible for randomised treatment, or >10.0% for those eligible for the open-label treatment group (this arm not included in Germany or Ireland) **Exclusion criteria:** uncontrolled hyperglycaemia (plasma glucose >13.3mmol/L after overnight fast during placebo run-in phase and confirmed by 2nd measurement), eGFR (estimated using modification of diet in renal disease equation) <50 ml/min/1.73m^2 (or <60ml/min/1.73 m^2 in China), any contraindications to sitagliptin according to local label, treatment with anti-obesity drugs within 3 months before informed consent, treatment with systemic steroids at time of informed consent, change in thyroid hormone dose within 6 weeks before informed consent, any uncontrolled endocrine disorder apart from type 2 diabetes **Age (years):** *empa10:* 56.2 SD11.6, *empa25:* 53.8 SD11.6, *sita100:* 55.1 SD9.9, *empa25open:* 50.2 SD11.3, *placebo:* 54.9 SD10.9 **Sex (%women):** *empa10: 37%*, *empa25:* 35%, *sita100:* 37%, *empa25open:* 26%, *placebo:* 46% **Ethnicity:** *empa10:* 64% Asian, 34% White, 1% Black/African American, <1% Hawaiian/Pacific Islander; *empa25:* 64% Asian, 33% White, 3% Black/African American; *sita100:* 64% Asian, 34% White, 1% Black/African American, <1% American-Indian/Alaska Native; *empa25open:* 61% Asian, 33% White, 2% Black/African American, 2% American-Indian/Alaska Native, 1% information not available, *placebo:* 64% Asian, 33% White, 3% Black/African American **Diabetes duration:** *empa10:* 39% ≤1 year, 41% 1 to 5 yrs, 13% 5 to 10 yrs, 7% >10 yrs; *empa25:* 41% ≤1 yr, 37% 1 to 5 yrs, 17% 5 to 10 yrs, 6% >10 years; *sita100:* 42% ≤1 yr, 39% 1 to 5 yrs, 14% 5 to 10 yrs, 5% >10 yrs; *empa25open:* 52% ≤1 yr, 25% 1 to 5 yrs, 14% 5 to 10 yrs, 8% >10 yrs; *placebo:* 32% ≤1 yr, 46% 1 to 5 yrs, 15% 5 to 10 yrs, 8% >10 yrs **HbA1c (%):** *empa10:* 7.87 SD0.88, *empa25:* 7.86 SD0.85, *sita100:* 7.85 SD0.79, *empa25open:* 11.50 SD1.39, *placebo:* 7.91 SD0.78 **BMI (kg/m^2):** *empa10:* 28.3 SD5.5, *empa25:* 28.2 SD5.5, *sita100:* 28.2 SD5.2, *empa25open:* 28.2 SD5.5, *placebo:* 28.7 SD6.2 **Baseline medication:** no oral/injectable anti-diabetic drug	7 to 10% **Sita100 (n=223):** sitagliptin 100 mg/day in people with HbA1c 7 to 10% **Empa25open (n=87):** empagliflozin 25 mg/day in people with HbA1c >10% **Control (n=228):** placebo once a day in people with HbA1c 7 to 10% **Run-in:** 2 week open-label placebo run-in **Extension:** 68.4% of the 899 patients continued in a double-blind extension (numbers in each group not given) for ≥52 weeks **All groups:** All received diet/exercise counselling according to local recommendations; rescue medication was started at FPG >13.3mmol/L between week 1 and 12 or FPG >11.1mmol/L between week 12 and 24 (drug of choice at the discretion of the investigator, but GLP1 agonists and DPP4 inhibitors were not permitted) **<u>Outcomes</u>** **Primary outcome:** change from baseline HbA1c at week 24 **Secondary outcomes:** weight, systolic and diastolic blood pressure **Other outcomes:** percentage achieving HbA1c <7.0% (of those with HbA1c >7.0% at baseline), FPG, percentage with >5.0% reduction in body weight, waist circumference, percentage of patients with previously uncontrolled hypertension who achieved controlled blood pressure (<130 mmHg systolic, <80 mmHg diastolic); use of rescue therapy, safety endpoints (vital signs, clinical laboratory parameters, adverse events e.g. hypoglycaemic episodes, urinary tract and genital infections

Abbreviations: AHA – anti-hyperglycaemic agent; BMI – body mass index; BP – blood pressure; FPG – fasting plasma glucose; HOMA – homeostatic model assessment (for insulin sensitivity); IQR – interquartile range; NR – not reported; OAD – oral antidiabetic drug; SU – sulphonylurea

Appendix 4 Quality assessment

Rate as: adequate, inadequate, unclear, not reported

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Canagliflozin										
CANTATA-M (Stenlöf 2013)	**unclear** method not reported; randomisation stratified by previous AHA use	**NR**	**adequate** double-blind	**NR**	**adequate** (main analysis) 11.8% discontinuation in cana100 group, 11.2% in cana300 group, 16.7% in placebo group	**adequate** intention-to-treat for all patients receiving at least one dose of study drug; last observation carried forward for missing data	**partial** some data only shown in graphs with no numeric values given	**adequate** for main study	**adequate** 90% power to detect a difference in HbA1c with 85 participants per group	5/9 adequate

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Inagaki 2014	**adequate** block randomisation (block size of 6 and 97 blocks); randomisation code list prepared by investigational product allocation manager and maintained until code was broken	**adequate** randomisation code not broken until data entry had been completed or unless needed in an emergency	**adequate** double-blind	**adequate** code not broken until data entry completed	**imbalance** 6.7% discontinuation in cana100 group, 20.4% in placebo group; reasons given	**adequate** efficacy analyses performed in the full analysis set of patients receiving at least one dose of study drug, except patients who did not have any efficacy data after administration of drug; last observation carried forward for missing data	**adequate** all outcomes reported as indicated in the methods section	**adequate** some difference between groups were noted regarding sex and glomerular filtration rate, but this seemed to apply mainly to the 200 mg canagliflozin group	**adequate** 95% power to detect a difference in HbA1c with 80 participants per group	8/9 adequate

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Dapagliflozin										
Ferrannini 2010 / Bailey 2014	**adequate** "computer-generated randomisation by an interactive voice response system, stratified by site in blocks of 7"	**adequate** "randomisation codes kept centrally at Bristol-Myers Squibb"	**adequate** "investigators, other clinical staff and participants blinded to treatment allocation during the 24 week initial and 78 week extension periods"	**adequate** see previous	**adequate** 15.7% discontinuation in dapa10 groups, 16% in placebo group; 60% completed extension in dapa10 AM group, 56% in placebo group; reasons given	**unclear** states that analyses were based on all participants taking at least one dose of medication, but main follow-up data appear to be based on fewer participants?	**adequate** all outcomes reported as indicated in the methods section	**adequate** between dapa10 AM/PM groups and placebo, the dapa10 high HbA1c group had a longer diabetes duration (other than a higher HbA1c)	**adequate** 90% power to detect a difference in HbA1c with 67 participants per group (primary endpoint)	8/9 adequate (main analysis)

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Ji 2014	**adequate** participants were "randomised sequentially by using an interactive voice response system in a blinded manner"	**adequate** see previous	**adequate** "patients, investigators and the sponsors were blinded to the treatment group"	**adequate** see previous	**adequate** 12.0% discontinuation in dapa10 group, 14.4% in placebo group; reasons given	**adequate** "patients randomised to treatment who received at least 1 dose of double-blind study medication and had both a baseline and post-baseline measurement were included in the efficacy analyses; patients who received at least 1 dose of double-blind study medication were included in the safety analyses"	**adequate** all outcomes reported as indicated in the methods section	**adequate** stated that demographic and baseline characteristics were similar between groups	**adequate** 97% power to detect a difference in HbA1c with 120 participants per group	9/9 adequate

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Kaku 2014	**NR**	**NR**	**adequate** "double-blind"	**NR**	**adequate** 10.2% discontinuation in dapa10 group, 9.2% in placebo group; reasons given	**adequate** "efficacy data were analysed with a full analysis set of individuals who took at least one dose of study medication"	**adequate** all outcomes reported as indicated in the methods section	**adequate** stated that demographic and baseline characteristics were similar between groups	**adequate** 90% power to detect a difference in HbA1c with 85 participants per group	6/9 adequate
Empagliflozin										
Lewin 2015	**adequate** third-party interactive voice and web response system; stratified by baseline HbA1c, eGFR and region	**NR**	**adequate** "double-blind"	**NR**	**adequate** 17% discontinuation in the empa25 group, 19.4% in the empa10 group, 15.6% in the lina5 group)	**adequate** efficacy data were analysed with a full analysis set of individuals who took at least one dose of study medication and had at least one on treatment HbA1c value; missing values imputed using last observation carried forward	**adequate** some data only shown one graph with no numeric values given	**adequate** stated that baseline characteristics were balanced between groups	**unclear** 89% power to detect a difference in HbA1c with 133 participants per group; slightly underpowered after drop-outs	6/9 adequate

Trial	Method of randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Intention-to-treat analysis	Selective reporting	Similarity at baseline	Other (e.g. power analysis)	Overall
Roden 2013	**adequate** computer-generated random sequence in block sizes of four, stratified by region (Asia, Europe, North America), HbA1c at screening (< 8.5%, ≥ 8.5%) and eGFR (≥ 90, 60-89, 50-59)	**adequate** study sponsor allocated participants using an interactive voice and internet-based response system	**adequate** "patients, investigator and individuals involved in the analysis of trial data were masked to treatment assignment"	**adequate** see previous	**adequate** (all <20%) discontinuation rates: 18% control, 8% empa10, 9% empa25, 8% sita100, 10% empa25open; reasons given	**adequate** efficacy data were analysed with a full analysis set of individuals who took at least one dose of study medication; missing values imputed using last observation carried forward	**adequate** all outcomes reported as indicated in the methods section	**adequate** between empa10, empa25, sita100 and control groups; empa25open had greater proportion of participants at ≤1 year	**adequate** 95% power to detect a difference in HbA1c with 180 participants per group (primary endpoint)	9/9 adequate

Abbreviations: NR – not reported

Appendix 5 Cochrane risk of bias table: EMPAGLIFLOZIN-REG OUTCOME

Overall, the trial scores well, and it is likely that the unclear items are just failure to report the processes rather than causing a high risk of bias.

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low risk.	Computerised randomisation
Allocation concealment (selection bias)	Low risk	Paper reports that a computerised randomisation system was used
Blinding of participants and personnel (performance bias)	Unclear	No information on appearance of placebo and empagliflozin tablets.
Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Unclear	Paper says "All CV outcome events and deaths are being prospectively adjudicated by the Clinical Events Committee (one for cardiac events and one for neurological events), as recommended in FDA guidelines" but gives no detail as to whether the assessors are blinded to allocation.
Blinding of outcome assessment (detection bias) (Mortality)	Unclear	As above. But death from any cause 8.3% in placebo group and 5.7% in empagliflozin group.
Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	N/A	Outcomes long-term
Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Low risk.	Very good retention of participants with around 97% completing the study.
Selective reporting (reporting bias)	Low risk.	

Appendix 6 Trials excluded in NMA

Trial	Drug	Comparator	Notes
Abbatecola 2006[141]	repaglinide	glibenclamide	Baseline Hba1c 7.2%
Aronoff 2000[274]	Pioglitazone	Placebo	High drop-out rate and mean baseline HbA1c high
Barnett 2012[275]	linagliptin	Placebo then glimepiride	18 weeks versus placebo
Barzilai 2011[276]	Sitagliptin 50 or 100	placebo	High drop-out rate. Some not new to drug treatment. Mixed doses according to renal function
Chou 2012[277]	pioglitazone	placebo	Drop-out rate
Goldstein 2007[278]	Sitagliptin	placebo	High drop-out rate and entry HbA1c up to 11%
Jovanovic 2000[142]	repaglinide	Placebo	High drop out rate
Kamel 1997[279]	Glibenclamide, gliclazide,metformin, acarbose	placebo	Abstract only and only 43 patients across 5 arms.
Mohan 2009[280]	sitagliptin	placebo	Only 18 weeks
Moses 1999[281]	Repaglinide with/without metformin	metformin	All failed on metformin monotherapy and 25% Hba1c >9%. Duration
Moses 2001[282]	repaglinide	placebo	16 weeks
Raz 2006[283]	sitagliptin	placebo	Only 18 weeks
Saleem 2011[143], Shah 2011[144], Jibran 2006.[145]	Repaglinide	Glibenclamide	Wrong comparator and quality issues. The Jibran 2006and Saleem 2011 papers are very similar but have no authors in common. They are reported to be from different time periods but almost all figures are identical.
Scherbaum 2002[284]	pioglitazone	Placebo	Drop-out rate

Warwick Medical School

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Addendum to Assessment Report on Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes

Flozins for T2DM monotherapy: Probabilistic sensitivity analysis

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Flozins for T2DM monotherapy: Probabilistic sensitivity analysis

1. Introduction

The model was run probabilistically over 996 iterations for each of the BMI scenarios:

- No BMI direct effect upon quality of life
- BMI 1: natural history progression with no rebound
- BMI 2: natural history progression with weight losses rebounding after one year
- BMI 3: natural history progression with weight losses rebounding at treatment change
- BMI 4: natural history progression with weight rebounding after one year
- BMI 5: natural history progression with weight rebounding at treatment change

The central estimates for these are as below.

Table 1. Probabilistic central estimates of total costs and total QALYs

	Costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£28,222	10.649	9.850	9.850	9.850	9.996	9.963
Repag.	£28,338	10.645	9.880	9.873	9.875	9.995	9.968
Pio.	£28,456	10.640	9.827	9.827	9.827	9.987	9.952
Sita.	£33,472	10.612	9.878	9.874	9.874	9.966	9.944
Cana.	£33,813	10.635	10.005	9.909	9.927	9.995	9.991
Empa.	£33,922	10.634	9.972	9.903	9.915	9.992	9.982
Dapa.	£34,023	10.624	9.956	9.891	9.900	9.981	9.969

This suggests the following cost effectiveness estimates.

Table 2. Probabilistic central cost effectiveness estimates

	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom.	£3,858	£4,949	£4,708	Dom.	£22,679
Pio.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Sita.	Dom.	Dom.	£34mn	Dom.	Dom.	Dom.
Cana.	Dom.	£43,952	£9,583	£105k	Dom.	£242k
Empa.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dapa.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.

The patterns of dominance are the same across the deterministic results with the exception of the BMI scenario 2 where sitagliptin is no longer inferior to repaglinide but is now slightly superior to it. This

results in a cost effectiveness estimate for sitagliptin compared to repaglinide of £34mn per QALY. But given a cost effectiveness estimate for canagliflozin compared to repaglinide of £153k per QALY, sitagliptin is extendedly dominated.

Extended dominance.
Simple dominance is when another treatment offers more QALYs at a lower cost; e.g. in BMI scenario 2 repaglinide is both cheaper and more effective than pioglitazone.

Extended dominance occurs when it is possible to arrive at more QALYs at a lower cost by treating a proportion of patients with one treatment and the remainder with another treatment compared to the treatment under consideration. For instance, for the BMI scenario 2 treating 50% of patients with repaglinide and 50% of patients with canagliflozin would yield 9.891 QALYs at a cost of £31,075. This combination dominates sitagliptin.

Less formally but perhaps more intuitively, extended dominance can also be thought of along the following lines. If under BMI scenario 2 I am willing to pay £4,949 per QALY for repaglinide but to also then move to sitagliptin at a marginal cost of £34mn per QALY compared to repaglinide, I am certainly going to be willing to take the next step of paying £9,583 per QALY by moving up to canagliflozin. Sitagliptin cannot logically be the most cost effective treatment regardless of my willingness to pay.

The cost effectiveness estimates for repaglinide compared to gliclazide of £3,858 per QALY, £4,949 per QALY and £4,708 per QALY for BMI scenarios 1, 2 and 3 and £22,679 per QALY for the BMI scenario 5 are reasonably similar to the £3,331 per QALY for BMI scenarios 1, 2 and 3 and £18,507 per QALY for BMI scenario 5 of the deterministic analysis. In the opinion of the AG, the differences between the probabilistic analyses and the deterministic analyses are unlikely to be the result differences in the simulated complications of diabetes, hypoglycaemic events and adverse events. The most likely explanation is that the sampling of weight changes results in around 40% of the PSA iterations for repaglinide having a weight loss, but 0% of the PSA iterations for gliclazide. Apart from the scenario of weight changes having no impact upon quality of life, these repaglinide weight losses rebound under the various BMI scenarios. For the 40% of iterations with a repaglinide weight loss the cost effectiveness estimate for repaglinide compared to gliclazide worsens. As a consequence, the central estimate for the cost effectiveness estimate for repaglinide compared to gliclazide worsens.

The cost effectiveness estimates for canagliflozin compared to repaglinide are similar to those of the deterministic model, though for the BMI 2 scenario it has improved from the £192k per QALY of the

deterministic modelling to £153k per QALY. The issue around 40% of repaglinide iterations being associated with weight losses appears to have less of an impact due to the larger absolute QALY differences between canagliflozin and repaglinide compared to the differences between repaglinide and gliclazide.

The probabilistic cost effectiveness estimates of the individual flozins compared to sitagliptin are as below.

Table 3. Probabilistic ICERs for the flozins compared to sitagliptin

	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Sita.	..	..	..	..	..	..
Cana.	£14,714	£2,704	£9,583	£6,532	£11,685	£7,305
Empa.	£20,040	£4,795	£15,051	£11,168	£17,021	£12,048
Dapa.	£47,766	£7,110	£32,372	£21,194	£35,379	£22,208

The probabilistic central estimates for the cost effectiveness of the flozins compared to sitagliptin are much as per the deterministic estimates. While those for dapagliflozin have worsened slightly, they are qualitatively the same.

In the figures that follow the ordering of the legends helps to identify the curves. The topmost curve in the legend is the curve of the treatment which is the most likely to be cost effective at a willingness to pay of £0 per QALY; i.e. at the vertical axis. Since the willingness to pay is £0 per QALY only costs are of interest, so this point depict which treatment has the highest likelihood of being cost saving. The curve below this in the legend is the curve for the treatment which as the willingness to pay is increased next becomes the most likely to be cost effective. And so on down the legend until the frontier is specified. The curves within the legend that lie below the entry for the frontier in the legend are those that do not achieve the frontier at any willingness to pay in the range £0 to £50k per QALY. Where a curve is mentioned in the legend but is not visible in the figure it coincides with the horizontal axis: i.e. is estimated to have no probability of being cost effective over the willingness to pay range of £0 to £50k per QALY.

Also note that the frontier has been arbitrarily lifted by 0.5% in all figures so that it does not overlay the treatment curve to which it corresponds in order to ease identification of the relevant treatment curve.

2. Scenario analysis

2.1 BMI scenario of no direct effects from weight upon quality of life.

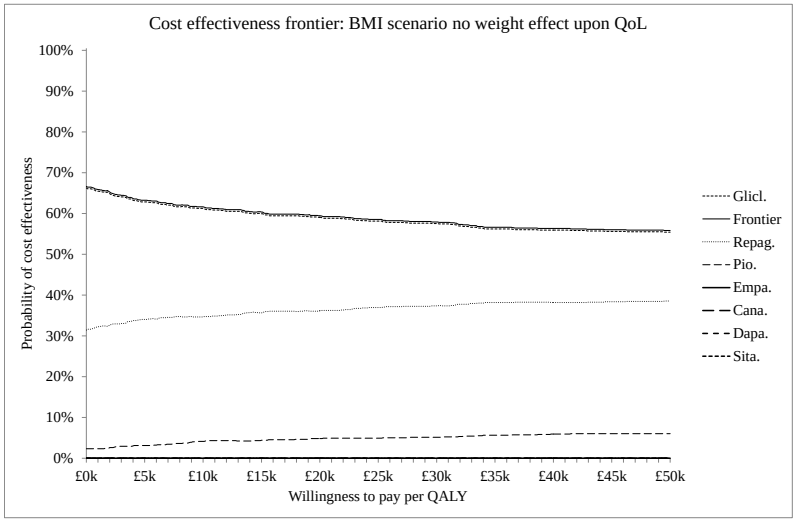

Figure 1. BMI no QoL effect: CEAF across all comparators

Table 4. BMI no QoL effect: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	4%	61%	35%
£20k	0%	0%	0%	0%	5%	59%	36%
£30k	0%	0%	0%	0%	5%	58%	37%
£40k	0%	0%	0%	0%	6%	56%	38%
£50k	0%	0%	0%	0%	6%	55%	39%

The probabilistic analysis suggests that the flozins and sitagliptin have no real probability of being cost effective. The main uncertainty is around whether glicalazide or repaglinide is the most cost effective, with it becoming more finely balanced between the two as the willingness to pay approaches £50k per QALY.

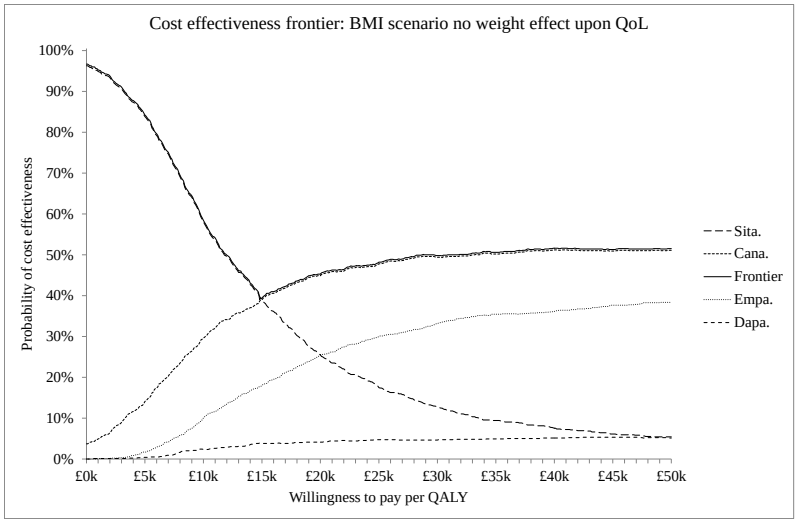

Figure 2. BMI no QoL effect: CEAF for flozins and sitagliptin

Table 5. BMI no QoL effect: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	10%	30%	2%	58%
£20k	26%	45%	4%	26%
£30k	33%	49%	5%	13%
£40k	36%	51%	5%	8%
£50k	38%	51%	5%	5%

At low values of willingness to pay the additional cost of the flozins is not warranted. Sitagliptin is estimated to be the most likely to be cost effective up to a willingness to pay of around £15k. Thereafter canagliflozin becomes the most likely to be cost effective, though the probability of empagliflozin being the most cost effective is not that far behind. Dapagliflozin fares worse, with there being little likelihood of it being the most cost effective at any willingness to pay value.

2.2 BMI scenario of weight changes retained indefinitely.

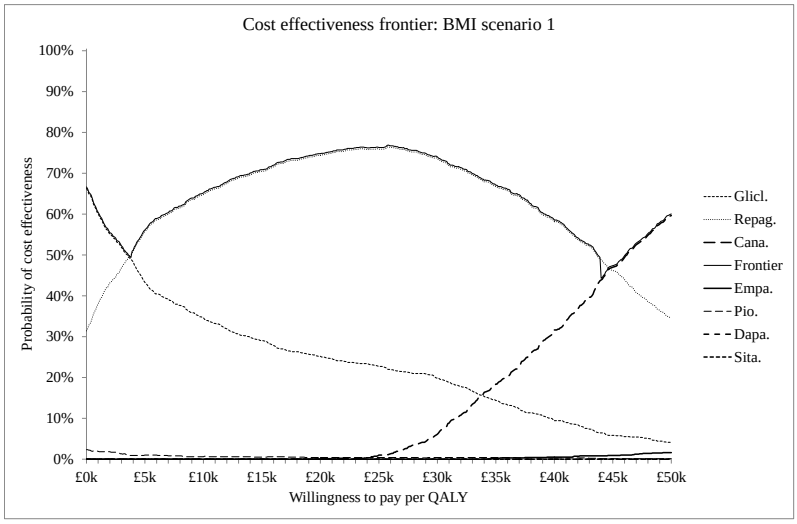

Figure 3. BMI scenario 1: CEAF across all comparators

Table 6. BMI scenario 1: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	1%	35%	65%
£20k	0%	0%	0%	0%	0%	25%	74%
£30k	0%	6%	0%	0%	0%	20%	74%
£40k	1%	32%	0%	0%	0%	9%	58%
£50k	2%	60%	0%	0%	0%	4%	35%

With weight changes being retained indefinitely gliclazide is soon overtaken by repaglinide due to the greater weight gain with gliclazide. But canagliflozin is associated with the largest weight losses of the treatments. As the willingness to pay rises to around £45k per QALY canagliflozin has the highest likelihood of being cost effective. This £45k per QALY is broadly in line with the cost effectiveness estimate for canagliflozin of both the deterministic and the probabilistic modelling.

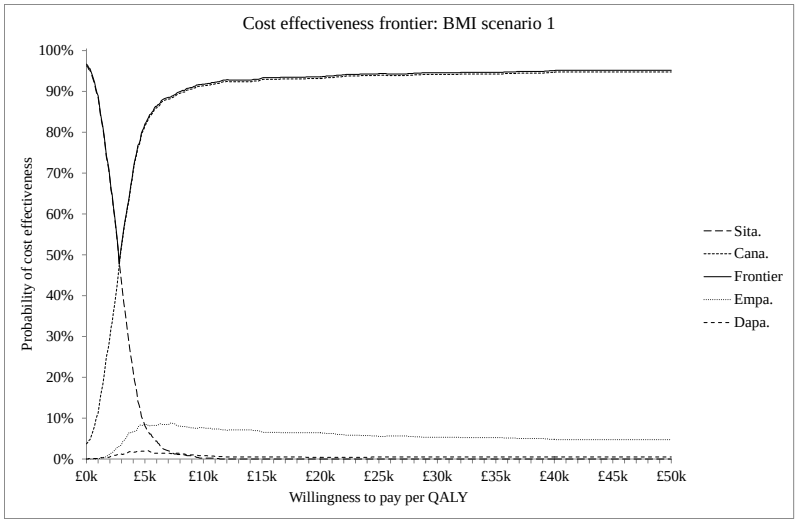

Figure 4. BMI scenario 1: CEAF for flozins and sitagliptin

Table 7. BMI scenario 1: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	8%	91%	1%	0%
£20k	6%	93%	0%	0%
£30k	5%	94%	1%	0%
£40k	5%	95%	1%	0%
£50k	5%	95%	1%	0%

Given the greater weight changes associated with canagliflozin, if weight changes are retained indefinitely canagliflozin is estimated to have the greatest likelihood of being cost effective at all but low willingness to pay values and there is little uncertainty around this.

2.3 BMI scenario of weight losses rebounding after one year.

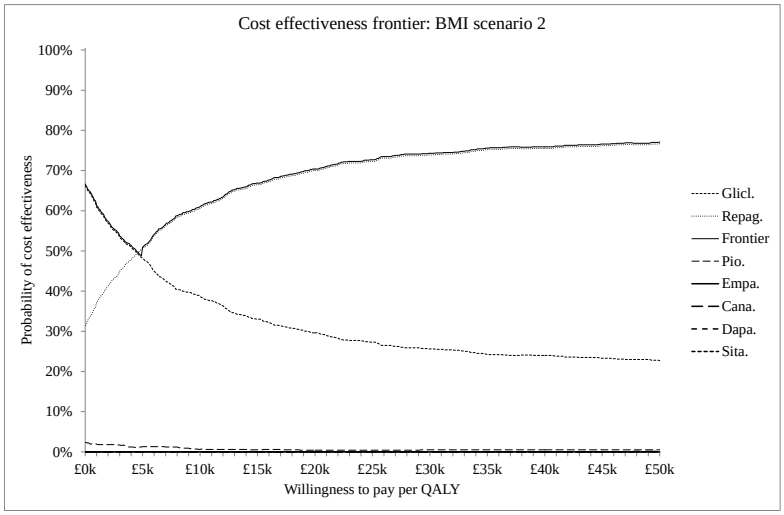

Figure 5. BMI scenario 2: CEAF across all comparators

Table 8. BMI scenario 2: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	1%	39%	61%
£20k	0%	0%	0%	0%	0%	30%	70%
£30k	0%	0%	0%	0%	1%	26%	74%
£40k	0%	0%	0%	0%	1%	24%	76%
£50k	0%	0%	0%	0%	1%	23%	77%

If weight changes are only retained for one year compared to them being retained indefinitely there is little impact upon where gliclazide and repaglinide cross over. The main impact is that canagliflozin no longer shows a probability of being cost effect as the willingness to pay increases further towards £50k per QALY.

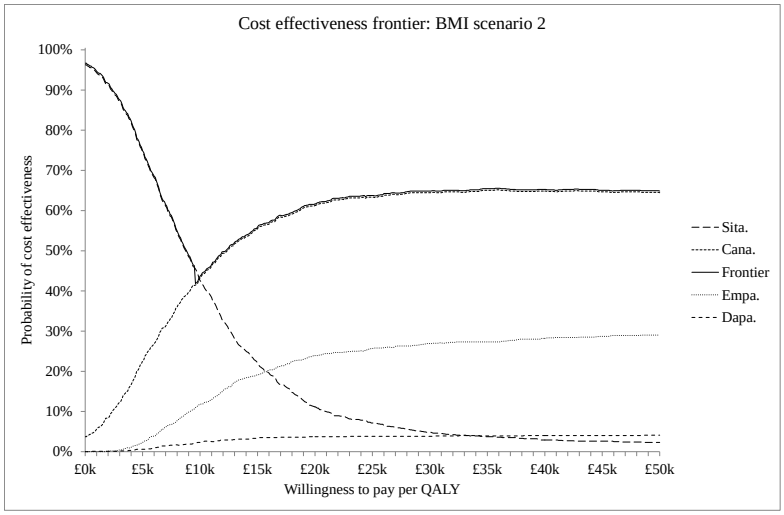

Figure 6. BMI scenario 2: CEAF for flozins and sitagliptin

Table 9. BMI scenario 2: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	12%	43%	2%	43%
£20k	24%	61%	4%	11%
£30k	27%	64%	4%	5%
£40k	28%	65%	4%	3%
£50k	29%	64%	4%	2%

Compared to the scenario of weight changes being retained indefinitely, the shorter retention of the larger weight gain from canagliflozin compared to empagliflozin means that there is greater uncertainty as to which is the most cost effective treatment. At a willingness to pay of £30k per QALY, the probability of canagliflozin being the most cost effective treatment is now only double that of empagliflozin.

2.4 BMI scenario of weight losses rebounding at treatment change.

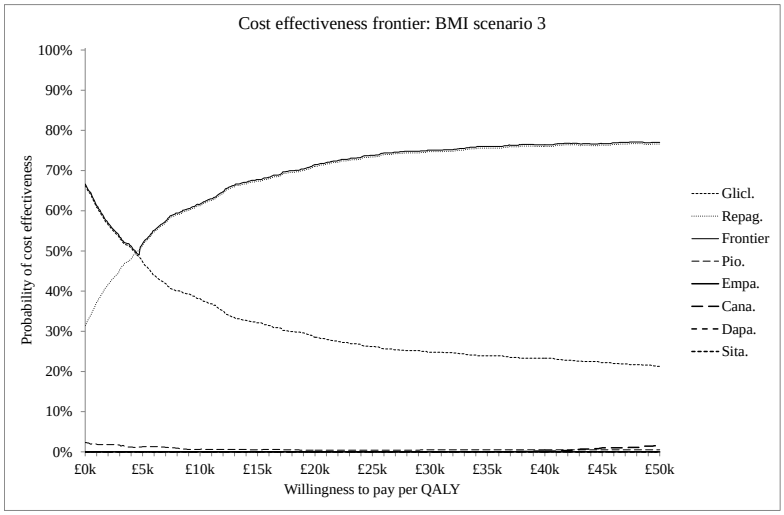

Figure 7. BMI scenario 3: CEAF across all comparators

Table 10. BMI scenario 3: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	1%	38%	61%
£20k	0%	0%	0%	0%	0%	29%	71%
£30k	0%	0%	0%	0%	1%	25%	75%
£40k	0%	0%	0%	0%	1%	23%	76%
£50k	0%	2%	0%	0%	1%	21%	77%

The scenario of weight losses rebounding at treatment change is a half-way house. But this half-way house is still insufficient for canagliflozin to be modelled as having any real probability of being the most cost effective treatment. This requires weight changes to be modelled as being retained indefinitely.

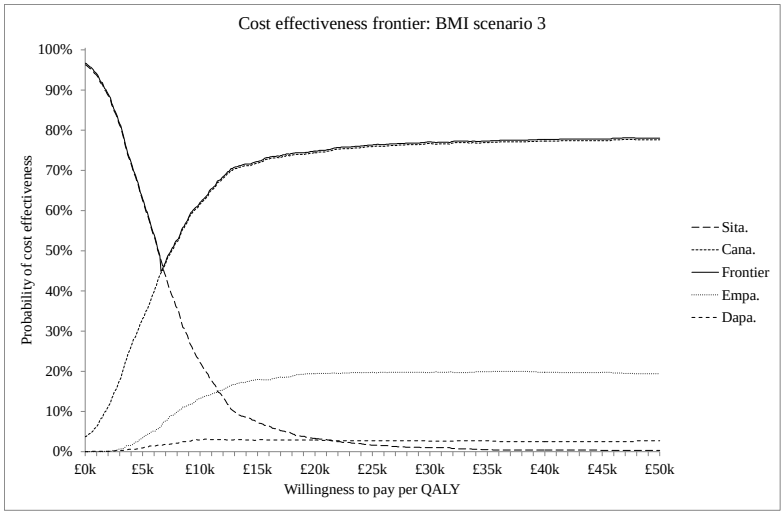

Figure 8. BMI scenario 3: CEAF for flozins and sitagliptin

Table 11. BMI scenario 3: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	13%	62%	3%	22%
£20k	19%	74%	3%	3%
£30k	20%	77%	3%	1%
£40k	20%	77%	3%	0%
£50k	19%	78%	3%	0%

The longer retention of weight changes compared to BMI scenario 2 means that the greater weight loss with canagliflozin compared to empagliflozin increases the likelihood of canagliflozin being the most cost effective and reduces that of empagliflozin.

2.5 BMI scenario of weight changes rebounding after one year.

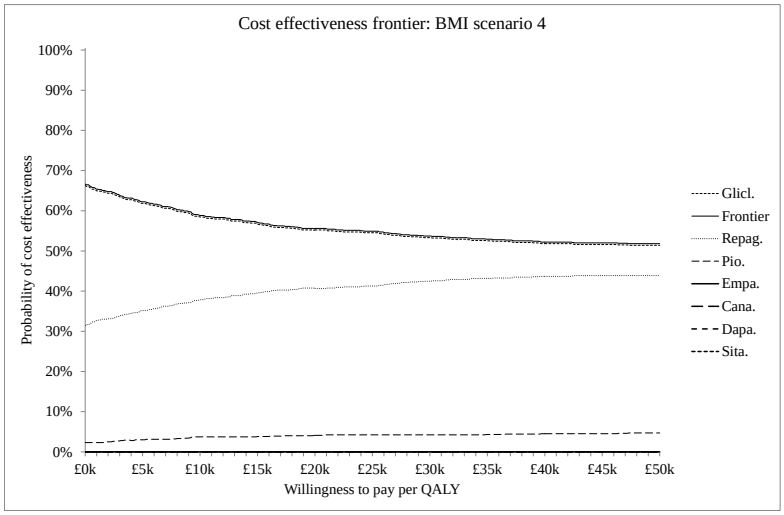

Figure 9. BMI scenario 4: CEAF across all comparators

Table 12. BMI scenario 4: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	4%	58%	38%
£20k	0%	0%	0%	0%	4%	55%	41%
£30k	0%	0%	0%	0%	4%	53%	42%
£40k	0%	0%	0%	0%	5%	52%	44%
£50k	0%	0%	0%	0%	5%	51%	44%

As would be expected given the short duration of weight changes, the CEAF is little difference from that of the scenario where BMI has no impact upon quality of life, though by a willingness to pay of £50k per QALY the curves for gliclazide and repaglinide show a slightly greater convergence.

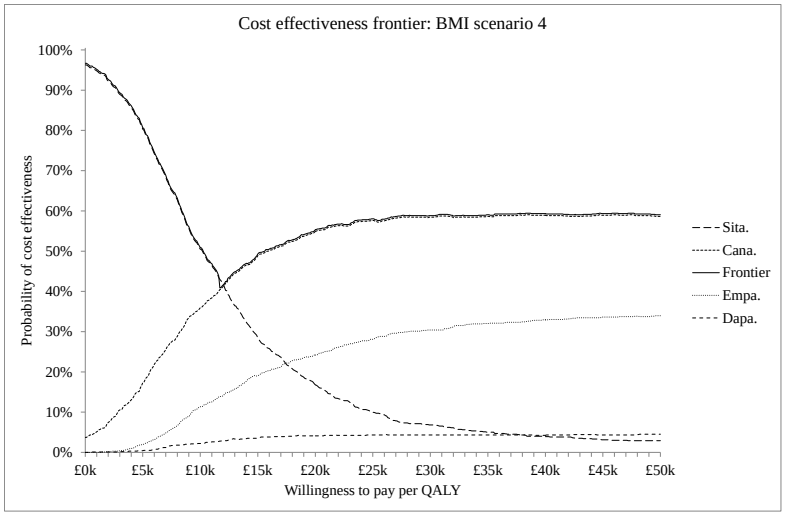

Figure 10. BMI scenario 4: CEAF for flozins and sitagliptin

Table 13. BMI scenario 4: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	11%	36%	2%	51%
£20k	24%	55%	4%	17%
£30k	30%	58%	4%	7%
£40k	33%	59%	4%	4%
£50k	34%	59%	5%	3%

Comparing weight changes being retained for one year to weight changes having no direct quality of life impact, the difference between the probability of canagliflozin being the most cost compared to that of empagliflozin is slightly greater. This increases as the willingness to pay increases.

2.6 BMI scenario of weight changes rebounding at treatment change.

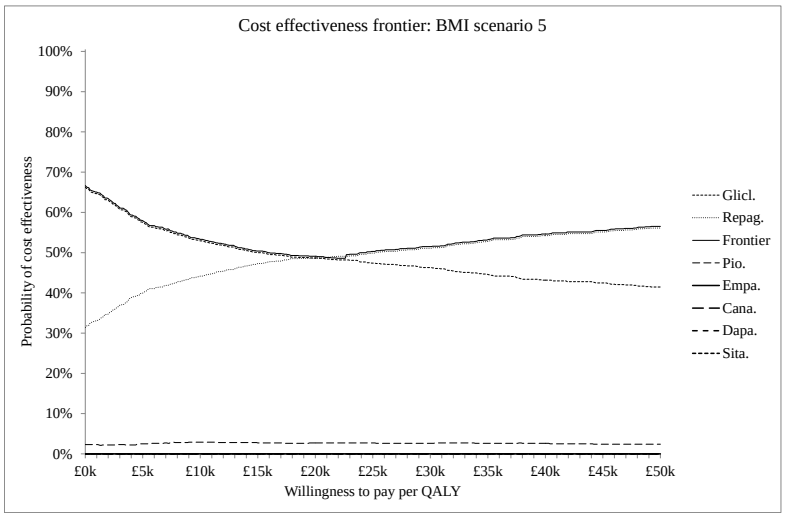

Figure 11. BMI scenario 5: CEAF across all comparators

Table 14. BMI scenario 5: Probability of cost effectiveness across all comparators

WTP	Empa.	Cana.	Dapa.	Sita.	Pio.	Glicl.	Repag.
£0k	0%	0%	0%	0%	2%	66%	31%
£10k	0%	0%	0%	0%	3%	53%	44%
£20k	0%	0%	0%	0%	3%	49%	49%
£30k	0%	0%	0%	0%	3%	46%	51%
£40k	0%	0%	0%	0%	3%	43%	54%
£50k	0%	0%	0%	0%	2%	41%	56%

If weight changes are retained until treatment change the probabilities of being the most cost effective for gliclazide and for repaglinide are roughly equal at a willingness to pay of £20k per QALY, and have diverged only slightly at a willingness to pay of £30k per QALY.

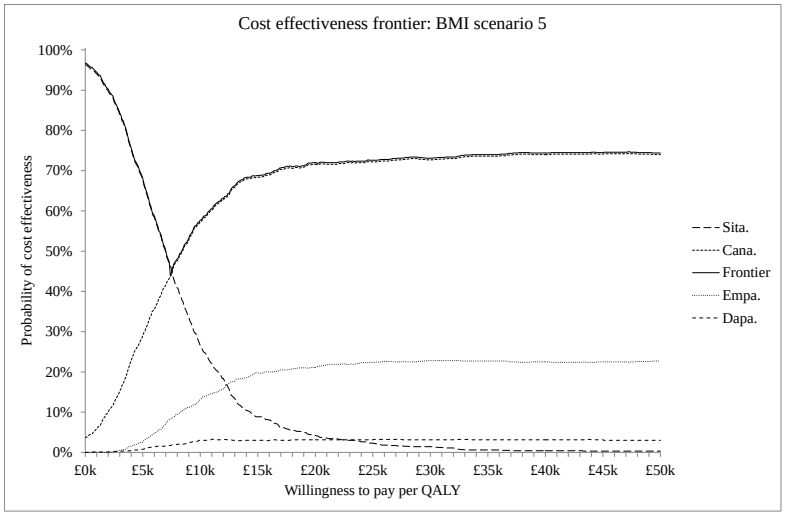

Figure 12. BMI scenario 5: CEAF for flozins and sitagliptin

Table 15. BMI scenario 5: Probability of cost effectiveness for flozins and sitagliptin

WTP	Empa.	Cana.	Dapa.	Sita.
£0k	0%	4%	0%	96%
£10k	13%	57%	3%	27%
£20k	21%	72%	3%	4%
£30k	23%	73%	3%	1%
£40k	22%	74%	3%	0%
£50k	23%	74%	3%	0%

Sitagliptin and canagliflozin have the highest estimates for their probabilities of being cost effective, with canagliflozin having the highest estimate at conventional NICE willingness to pay thresholds. Empagliflozin has some probability of being cost effective but it is only around a third that of canagliflozin.

Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes.

Erratum to assessment report. 13th October 2015.

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Erratum to assessment report.

Background

The model used to generate the probabilistic results contains information which could if circulated be regarded being under the copyright of the UKPDS OM1 modellers. This model had to be developed by the AG in order to undertake the probabilistic modelling.

As a consequence, the AG implemented an excel worksheet which outputs the model inputs in a format suitable for inputting to the UKPDS OM1 excel version 1.302 implementation. This was developed to enable consultees to the assessment to cross check the AG deterministic modelling results. Consultees can generate the set of UKPDS OM1 inputs using the AG model, run the UKPDS OM1 model to estimates the UKPDS OM1 costs, QALYs and survival curves, paste these values back into the AG model and have it automatically collate these with the data on treatment switches, hypoglycaemic events and adverse events to yield estimates for the total costs and QALYs.

During the course of cross checking the model outputs and the correspondence between the results of the different modelling exercises the AG realised that it had set the baseline IHD prevalence to zero. Identifying this error was complicated by the UKPDS OM1 excel implementation seemingly ignoring the HF at baseline indicator. It appears that the UKPDS OM1 excel implementation applies the IHD at baseline indicator to determine the modelled prevalence of HF. To see this more clearly, it appears that the following applies within the OM1 excel version 1.302.

Table 1: Hypothetical four patients within the OM1

	Prevalence of complications at baseline			
	Inputted values		Values applied in OM1	
	IHD	HF	IHD	HF
Patient 1	No	No	No	No
Patient 2	No	Yes	No	No
Patient 3	Yes	No	Yes	Yes
Patient 4	Yes	Yes	Yes	Yes

This can be checked by setting the UKPDS OM1 *Run_Model* worksheet to have the following input values.

Table 2: Illustrative inputs for the OM1

Initial utility :	1.000
Cost with no complications :	£10

	At time of event			In subsequent years	
	Fatal	Non-fatal	Utility decr.	Cost	Utility decr.
IHD :		£100	-0.500	£100	-0.500
MI :	£1,000	£1,000	-0.500	£1,000	-0.500
Heart failure :	£10,000	£10,000	-0.500	£10,000	-0.500
Stroke :	£100,000	£100,000	-0.500	£100,000	-0.500
Amputation :	£1,000,000	£1,000,000	-0.500	£1,000,000	-0.500
Blindness :		£10,000,000	-0.500	£10,000,000	-0.500
Renal failure :	£100,000,000	£100,000,000	-0.500	£100,000,000	-0.500

Running the OM1 excel version 1.302 with these inputs results in the following estimates for the patients' costs of complications and costs in the first year.

Table 3: OM1 excel version 1.302 1st year cost and QALY results

	Cost	QALY
Patient 1	£10	1.000
Patient 2	£10	1.000
Patient 3	£10,100	1.000
Patient 4	£10,100	1.000

Patient 1 is correctly simulated as incurring £10 in the first year. But Patient 2 does not have the £10,000 cost of HF applied, but instead only has the £10 cost for no complications applied. Patient 3 does have the £100 cost of IHD applied, but also has the £10,000 cost of HF applied. Patient 4 is correctly simulated as having both the £100 cost of IHD and the £10,000 cost of HF.

The above also throws up another issue. The AG had assumed that the value inputted as the initial utility was the utility with no complications. But it appears that the UKPDS OM1 excel version 1.302 is quite literal in taking this to be the initial utility. It appears that for patients with a complication which is prevalent at baseline the UKPDS OM1 does not apply the utility decrement associated with that complication. The utility decrements associated with complications appear to only be applied to complications which are modelled as occurring after baseline. While the model is literally correct in its implementation, to the AG it seems undesirable not to apply the "*in subsequent years*" utility decrements to complications which were present at baseline.

So there are three problems:

- The UKPDS OM1 excel version 1.302 appears not to apply the utility decrements for complications that are prevalent at baseline.
- The UKPDS OM1 excel version 1.302 appears not to permit baseline IHD and HF prevalences to be specified correctly.
- The AG set the baseline IHD prevalence to 0%.

The first problem could be addressed by simulating patients in subgroups according to their complications at baseline: none, only IHD, IHD and HF, etc. and applying initial utility values specific to these patient subgroups. But since there are seven complications which can be present at baseline, there would be a large number of possible combinations which would be extremely laborious to explore individually and the AG does not propose to go down this route. The simpler alternative is to run a sensitivity analysis of having no complications at baseline to see if this has any practical impact upon results.

The third problem can be addressed by the AG revising its IHD prevalence to be 2.7% and seeing if this has any practical impact upon results.

But the second problem means that the AG model for circulation to consultees can only be used to cross check the AG modelling of no complications at baseline. In order to expand this and to come as close to the AG modelling of the base case that can be replicated by consultees, the AG has also undertaken a sensitivity analysis that retain the baseline complications with the exception of IHD and HF; i.e. it sets these latter to zero for all patients.

AG report base case modelling results

For ease of references table 64 and table 66 of the AG report that present the AG base case analysis are reproduced below.

Table 4: AG report Table 64 AG base case: Lifetime total costs and QALYs

		Total QALYs					
Treatment	Total costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,314	10.392	9.633	9.633	9.633	9.771	9.739
Repag.	£27,413	10.389	9.663	9.663	9.663	9.770	9.744
Pio.	£27,543	10.384	9.612	9.612	9.612	9.762	9.728
Sita. 100	£32,358	10.355	9.657	9.655	9.655	9.739	9.719
Cana. 300	£32,676	10.380	9.780	9.691	9.707	9.770	9.767
Empa. 25	£32,775	10.378	9.747	9.683	9.694	9.766	9.756
Dapa. 10	£32,866	10.367	9.734	9.671	9.681	9.756	9.745

Table 5: AG report Table 66 AG base case: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom	£3,331	£3,331	£3,331	Dom	£18,507
Pio.	Dom	Dom	Dom	Dom	Dom	Dom
Sita. 100	Dom	Dom	Dom	Dom	Dom	Dom
Cana. 300	Dom	£44,994	£192k	£119k	Dom	£235k
Empa. 25	Dom	Dom	Dom	Dom	Dom	Dom
Dapa. 10	Dom	Dom	Dom	Dom	Dom	Dom
Dom = Dominated: i.e. more costly and less effective than another treatment						

Table 6: AG report Table 68 AG base case: Flozin cost effectiveness estimates vs sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,623	£2,590	£8,913	£6,111	£10,256	£6,627
Empa. 25	£18,341	£4,676	£14,716	£10,841	£15,734	£11,300
Dapa. 10	£40,383	£6,632	£30,710	£19,787	£30,487	£19,679

Setting the baseline prevalence of all complications to 0.0%

Assuming that there is a zero prevalence of complications at baseline results in the following.

Table 7: No complications at baseline: Lifetime total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£26,311	10.418	9.657	9.657	9.657	9.795	9.763
Repag.	£26,417	10.414	9.687	9.687	9.687	9.794	9.768
Pio.	£26,537	10.409	9.635	9.635	9.635	9.785	9.752
Sita. 100	£31,374	10.380	9.682	9.679	9.679	9.763	9.743
Cana. 300	£31,672	10.404	9.803	9.714	9.730	9.793	9.790
Empa. 25	£31,778	10.402	9.769	9.706	9.717	9.789	9.779
Dapa. 10	£31,876	10.393	9.758	9.695	9.705	9.780	9.768

As would be expected, the total costs fall somewhat if patients are assumed to have no complications at baseline. Total QALYs are also affected but this is not due to the removal of any quality of life decrements for the complications which are prevalent at baseline. Rather it appears to be due to fewer complications at baseline having a survival effect.

Table 8: No complications at baseline: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom.	£3,538	£3,538	£3,538	Dom.	£19,882
Pio.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Sita. 100	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Cana. 300	Dom.	£45,153	£197k	£121k	Dom.	£243k
Empa. 25	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dapa. 10	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dom = Dominated: i.e. more costly and less effective than another treatment						

But all treatment arms appear to have been affected to largely the same extent and the cost effectiveness estimates are essentially the same as those of the AG report base case.

Table 9: No complications at baseline: Flozin cost effectiveness estimates vs sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,405	£2,444	£8,621	£5,847	£9,979	£6,356
Empa. 25	£18,940	£4,595	£14,945	£10,871	£16,046	£11,354
Dapa. 10	£41,187	£6,574	£31,172	£19,873	£30,944	£19,764

The cost effectiveness estimates for the flozins compared to sitagliptin are similarly little changed from those of the AG report base case.

Setting the baseline IHD prevalence to 2.7%

Applying the 2.7% baseline IHD prevalence results in the following.

Table 10: 2.7% IHD baseline prevalence: Lifetime total costs and QALYs

		Total QALYs					
Treatment	Total costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,600	10.376	9.618	9.618	9.618	9.755	9.723
Repag.	£27,704	10.374	9.649	9.649	9.649	9.755	9.730
Pio.	£27,827	10.367	9.596	9.596	9.596	9.746	9.712
Sita. 100	£32,631	10.337	9.641	9.638	9.639	9.723	9.702
Cana. 300	£32,933	10.362	9.763	9.674	9.691	9.753	9.750
Empa. 25	£33,031	10.360	9.730	9.667	9.678	9.749	9.739
Dapa. 10	£33,136	10.350	9.718	9.656	9.665	9.740	9.729

Table 11: 2.7% IHD baseline prevalence: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom.	£3,388	£3,388	£3,388	£434k	£16,413
Pio.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Sita. 100	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Cana. 300	Dom.	£45,641	£207k	£124k	Dom.	£259k
Empa. 25	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dapa. 10	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dom = Dominated: i.e. more costly and less effective than another treatment						

The pattern of dominance is unchanged compared to the base case of the AG report with the exception of the BMI 4 scenario where repaglinide has changed from being modelled as being marginally inferior to being marginally superior compared to gliclazide.

The cost effectiveness estimates for canagliflozin compared to repaglinide are essentially the same as those of the AG report base case, though those in six figures show greater absolute changes due to the very small divisor.

Table 12: 2.7% IHD baseline prevalence: Flozin cost effectiveness estimates vs sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,034	£2,467	£8,494	£5,820	£9,777	£6,312
Empa. 25	£17,278	£4,471	£13,917	£10,294	£14,864	£10,724
Dapa. 10	£37,871	£6,542	£29,341	£19,172	£29,116	£19,062

The cost effectiveness estimates for the flozins compared to sitagliptin are similarly close to those of the AG report base case, though those for the scenario of weight having no direct quality of life impact show some improvement for empagliflozin and dapagliflozin. There has been a marginal improvement in those for dapagliflozin such that the cost effectiveness ratios that were previously estimated as being slightly above £30k per QALY are now slightly below £30k per QALY.

Setting the baseline prevalences of IHD and HF to 0.0%

Given the above results, setting the baseline prevalences of IHD and HF to zero has only a limited impact upon the cost effectiveness estimates, as outlined below.

Table 13: 0% IHD & HF baseline prevalence: Lifetime total costs and QALYs

		Net QALYs					
Treatment	Net costs	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	£27,208	10.399	9.640	9.640	9.640	9.777	9.745
Repag.	£27,320	10.396	9.670	9.670	9.670	9.777	9.751
Pio.	£27,437	10.392	9.619	9.619	9.619	9.769	9.735
Sita. 100	£32,261	10.362	9.664	9.661	9.662	9.746	9.725
Cana. 300	£32,571	10.387	9.787	9.697	9.714	9.777	9.773
Empa. 25	£32,668	10.385	9.753	9.690	9.701	9.773	9.762
Dapa. 10	£32,766	10.375	9.741	9.678	9.688	9.763	9.752

Table 14: 0% IHD & HF baseline prevalence: Cost effectiveness estimates

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Glicl.	..	..	..	..	..	..
Repag.	Dom.	£3,668	£3,668	£3,668	Dom.	£18,901
Pio.	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Sita. 100	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Cana. 300	Dom.	£45,126	£196k	£120k	Dom.	£241k
Empa. 25	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dapa. 10	Dom.	Dom.	Dom.	Dom.	Dom.	Dom.
Dom = Dominated: i.e. more costly and less effective than another treatment						

Table 15: 0% IHD & HF baseline prevalence: Flozin cost effectiveness estimates vs sitagliptin

	ICERs					
Treatment	No BMI	BMI 1	BMI 2	BMI 3	BMI 4	BMI 5
Cana. 300	£12,326	£2,532	£8,718	£5,975	£10,033	£6,481
Empa. 25	£17,603	£4,558	£14,218	£10,510	£15,185	£10,950
Dapa. 10	£38,046	£6,540	£29,526	£19,243	£29,307	£19,137