National Institute for Health and Care Excellence

Report version (Draft for consultation)

Type 2 diabetes in adults: management (Medicines update)

Cost-effectiveness analysis: subsequent pharmacological therapy for the management of type 2 diabetes

NICE guideline GID-NG10336

Economic analysis report

Draft for Consultation

This guideline was developed by NICE

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Contents

1 Introduction

In 2015, NICE published the Type 2 diabetes in adults: management' (NG28) guideline, which covered several aspects of diabetes management including pharmacological treatments for the management of blood glucose levels. (National Institute for Health and Care Excellence, 2015) The evidence used to inform this guideline typically focused on the effect of diabetes treatments on glycaemic control measures such as HbA1c.

Since then, the evidence base for pharmacological treatments used in type 2 diabetes has expanded. Several treatments have been explored in cardiovascular outcome trials (CVOTs); trials which differ from the 'standard' non-CVOTs in several ways:

- Population: CVOTs were typically conducted in people with type 2 diabetes who are at high risk of cardiovascular events rather than a general type 2 diabetes population
- Outcomes: CVOTs look at the effect of treatments on diabetic/cardiovascular events ('hard outcomes') rather than on blood glucose levels ('surrogate outcomes')
- Comparators: CVOTs typically follow a treat-to-target design in which the treatments given in accompaniment to the intervention and placebo are allowed to vary, meaning that the background treatments received in the comparator arm can differ to those in the intervention arm.

In 2022, an update to NG28 (2015) was published wherein recommendations were informed by the outcomes of the CVOTs.(NAtional Institute for Health and Care Excellence, 2022) It was a rapid update and therefore did not incorporate evidence of treatment effects on surrogate outcomes like HbA1c. Since HbA1c is an important determinant of certain diabetes-related microvascular complications (e.g. retinopathy, ulcerations), it may not have fully captured all important outcomes.

This guideline will incorporate the key elements of both previous guidelines by modelling the outcomes of treatment effects both on surrogate outcomes, microvascular outcomes and on CVOT outcomes.

The economic model outlined in this report uses a patient-level simulation to generate a prevalent cohort of patients about to initiate subsequent therapy. Evidence on the effectiveness of treatments has been taken from the clinical review. Risk equations estimating cardiovascular and renal outcomes, as well as cardiovascular mortality (CVM) used in the patient-level simulation have been calibrated to match the CVOT outcomes from the clinical review.

2Methods

2.1 Model overview

2.1.1 Comparators

The interventions explored in the model are:

- Biguanides
  - Modified-release metformin monotherapy
- DPP-4 inhibitors
  - Alogliptin
  - Linagliptin
  - Saxagliptin
  - Sitagliptin
  - Vildagliptin
- GLP-1 receptor agonists
  - Dulaglutide
  - Exenatide
  - Liraglutide
  - Semaglutide (oral)
  - Semaglutide (subcutaneous)
- Insulin
- SGLT2 inhibitors (considered at a class level)
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin
  - Ertugliflozin
- Sulfonylurea
  - Gliclazide
- Thiazolidinedione
  - Pioglitazone
- Triple therapy (in the ASCVD and early-onset populations)
  - SGLT2 inhibitor class in addition to a GLP-1 receptor agonist

Treatments other than modified-release metformin monotherapy were assumed to be in addition to modified-release metformin.

The committee chose to evaluate interventions as individual treatments rather than at the drug class level, except with insulin and SGLT-2 inhibitors. This decision was made a priori, on the basis that even if results for cardiovascular outcomes were comparable across agents within a class, there may be meaningful within-class differences - such as in mode of administration and treatment costs - that could influence the overall cost effectiveness of individual treatments.

Triple therapy was considered in the atherosclerotic cardiovascular disease (ASCVD) and early-onset populations, the populations in which the committee thought more intense

treatment would be most beneficial. Triple therapy is defined as concurrent use of metformin alongside both SGLT2 inhibitors and GLP-1 agonists. The living with overweight and living with obesity populations were also of interest for this analysis but as triple therapy use is covered NICE technology appraisals for these populations it was outside of the scope of this guideline update.

Insulin was modelled at a class-level as choice of insulin will depend on a number of factors including patient preference for injecting frequency, whether insulin needs to be administered by another person and local availability of insulin types. For individual SGLT-2 inhibitors, although outcomes were reported separately in the clinical evidence review, results from the model were reported at a class-level. There are a number of NICE Technology Appraisals, covering the use of SGLT-2 inhibitors in populations which were the same or significantly overlapped with those considered in the economic model. It would not be possible to make differentiating recommendations between individual SGLT-2 inhibitors whilst preserving the recommendations in the NICE Technology Appraisals. The placement of SGLT-2 inhibitors in the treatment pathway and whether that represented an efficient use of NHS resources therefore needed to be considered at a class-level.

2.1.2 Population

The population covered by the model is adults (aged ≥18 years) with type 2 diabetes mellitus (T2DM) and one of the following risk factors:

- Atherosclerotic cardiovascular disease (ASCVD)
- Chronic kidney disease (CKD) stages 1-3
- CKD stage 4
- Heart failure (HF)
- High risk of cardiovascular disease (CVD), sub-grouped by
    - Aged under 40 years (early onset T2DM)
    - Living with obesity
    - Living with overweight

The cohorts were sampled from the clinical practice research datalink (CPRD) AURUM (described in detail below) and was considered highly representative of people with T2DM in the UK. Any patient with a diagnosis of T2DM recoded in CPRD AURUM between 1st January 2001 and 1st September 2023 were included in the study. Records of patients sampled from CPRD were linked to their Hospital Episode Statistics (HES) records to capture any diagnoses or procedures recorded during hospital inpatient admissions.

A patient record of pre-existing ASCVD and/or HF were defined by the presence of a relevant SNOMED code in CPRD, or any relevant International Classification of Diseases version 10 (ICD-10) code recorded in HES (see Code lists for ASCVD and HF).

A patient record of CKD was defined by the presence of at least one estimated glomerular filtration rate (eGFR) score or urinary albumin creatinine ratio (ACR) record within the past two years. CKD severity was classified using KDIGO stages (see Table 1 and Table 2). The logic used to categorise patients into their respective CKD stages is provided in Table 3.

Table 1. eGFR and ACR definitions used

eGFR category	Cutoffs (kg ml/min/1.73 m²)
G1	> 90
G2	60-89
G3a	45-59
G3b	30-44
G4	15-29

G5	< 15
ACR category	**Cutoffs (mg/mmol)**
A1	< 3
A2	3-30
A3	> 30

Table 2. Definition of CKD stages

CKD Stage	Logic
No CKD	(G1 OR G2) + (A1 or Missing)
Stage 1	G1 + (A2 OR A3)
Stage 2	G2 + (A2 OR A3)
Stage 3a	G3a
Stage 3b	G3b
Stage 4	G4
Stage 5	G5

All patients categorised with CKD stages 1, 2, 3a and 3b were grouped into our CKD stages 1-3 population. Patients categorised with CKD stage 4 were grouped into our CKD stage 4 population. Patients categorised with no CKD or CKD stage 5 were excluded from our CKD groupings.

The definition of high risk of CVD in patients aged over 40 years was based on a QRISK2 score over 10%; the QRISK2 score itself was calculated from CPRD records using a pre-existing algorithm from Herrett 2019.(Herrett, et al., 2019) We assumed that anyone aged under 40 years with T2DM had a high lifetime risk of CVD.

The threshold for living with obesity was defined as a BMI $\geq$30kg/m^2 with white ethnicity and $\geq$27.5kg/m^2 with all other ethnicities. The boundaries for living with overweight were defined as between 25kg/m^2 and 29.9kg/m^2 in a white ethnicity and between 23kg/m^2 and 27.4kg/m^2 in all other ethnicities.

2.1.3 Time horizon, perspective, discount rates used

The model applied a 70-year time-horizon for all cohorts, which was considered representative of a lifetime horizon. This is because the average starting age was greater than 60 years in all but the early onset cohort. However, the minimum possible age of a simulated person from the early onset cohort at the end of the time horizon was 88 years, which is significantly greater than the mean life expectancy.(Kaptoge. S, et al., 2023) The analysis follows the standard assumptions of the NICE reference case including taking an NHS and PSS perspective for costs and capturing all direct health effects. Costs and effect were both discounted at 3.5% per annum.

2.1.4 Deviations from NICE reference case

Probabilistic sensitivity analysis (PSA) was not conducted as running sufficient iterations for a meaningful PSA was not possible due to the significant model run time needed. The UKPDS Global beta model captures parameter uncertainty in the risk equations via bootstrap sampling. We conducted a series of tests varying the number of bootstrap samples between 0 and 500,000 and exploring its impact on the final ICER in a few randomly selected interventions. Increasing the number of bootstraps resulted in minimal changes to the final ICERs. We ran 10,000 inner loops a graphical plot of convergence around the incremental

net monetary benefit (INMB) showed that it had stabilised by this time. All base case analyses were run using 0 bootstraps to minimise the model runtime.

2.2 Approach to modelling

A literature review of previous economic evidence found no directly applicable cost-utility analyses (CUAs) that covered most or all interventions within the populations of interest (see accompanying evidence reviews.) It was therefore not possible to rely on the prior literature to inform new recommendations. An original health economic analysis was therefore undertaken to estimate the cost-utility of interventions for the populations applicable to this guideline.

Although the previous literature did not contain any directly applicable evidence, it was useful in helping to inform the modelling approach. A large proportion of previously published economic models used existing diabetes models as the basis of their analysis. Modelling diabetes is complex given the large number of competing events, and using previous models that have been tested, scrutinised, refined and calibrated over many years would be beneficial. Consequently, these models were considered for use in our own analysis.

We restricted our selection to models from the Mount Hood Diabetes Challenge Network.(2021) This is a network of clinicians, health economists, statisticians and other researchers collaborating to improve simulation models in diabetes. We thought that these models would have gone through particular scrutiny by experts and that their methodology would be available in the literature.

The committee were presented with economic models which met the above criteria. They were asked to consider the models applicability to a UK setting, performance as discussed in the literature, flexibility to meet the aims of our analysis, source of funding and availability to NICE for use in the analysis.

Table 3. Diabetes simulation models considered by committee

Model	Reference
BRAVO	Shao 2018
Cardiff	McEwan 2015
CDC/RTI	Hoerger 2009
ECHO – T2DM	Willis 2013
IQVIA CORE	Palmer 2004
Michigan Model MMD	Zhou 2005
PROSIT Model	Schramm 2016
SPHR Diabetes Model	Thomas 2014
Treatment Transitions Model	Smolen 2014
UKPDS OM2	Hayes 2013

Based on their considerations, the IQVIA CORE and UKPDS OM2 models were most suitable for the health economic analysis. Both models had been used in previous NICE guidance and there was a large body of evidence discussing their ability to predict events associated with diabetes.

A full description of the IQVIA CORE model can be found in Palmer 2004. Progression of diabetes was simulated using a series of interdependent models which estimate diabetic and cardiovascular events. Interdependence between these models are calculated using probabilistic Monte Carlo methods. As with the UKPDS OM2, treatment effects are modelled via surrogate risk factors.

The published UKPDS OM2 model (Hayes 2013) works by extrapolating HbA1c and other risk factors for a cohort of patients with Type 2 diabetes. Treatment effects are applied to risk factors at a set point in the model and affect other relevant risk factors over time. At each model cycle, event equations are applied to the updated risk factor values to estimate whether patients experience an event. Consequently, the UKPDS OM2.2 uses the impact of treatments on surrogate outcomes such as HbA1c to calculate hard outcomes (such as stroke or cardiovascular mortality). The UKPDS OM2.2 model does not allow treatment effect inputs on NFCVE or CVM such as those estimated in the accompanying NMA.

During the development phase, we were informed by the UKPDS model development team that they were developing the Global beta version of the model, an as-yet unpublished model update. This version included a new input parameter designed to calibrate the risk prediction equations, thereby enabling directional and scale modification of the UKPDS risk equations. The risk equations can be modified through adjustment of the beta parameters as reported in Hayes 2013.

A key requirement for any model employed in NICE guideline development is its availability to stakeholders during the public consultation period. The UKPDS development team confirmed that this updated version would be accessible to stakeholders in accordance with this requirement, if we chose to employ its use.

The committee particularly highlighted that published evidence and discussion around the UKPDS OM2.2 was more plentiful than the CORE model and was much more transparent in how it worked and the mechanisms behind its estimates. The updated model also made it possible to calibrate risk equations to the accompanying NMA results. Given all these considerations the committee decided it best to employ the UKPDS OM2.2 model update that would be calibrated to clinical outcomes estimated in the accompanying NMA. We used the UKPDS OM2.2 model update in all our economic analyses.

2.2.1 Model structure

The UKPDS OM2.2 model – which is the most up-to-date version of the UKPDS OM2 model incorporates risk factor trajectory equations that forecast changes to certain risk factors over time. The risk factors can be categorised as:

- Demographic risk factors:
  - current age
  - ethnicity
  - sex
  - duration of diabetes
- Time-varied risk factors:
  - presence of atrial fibrillation
  - presence of albuminuria
  - body mass index (BMI)
  - estimated glomerular filtration rate (eGFR) score
  - haemoglobin
  - HbA1c
  - high-density lipoprotein (HDL)
  - heart rate
  - low-density lipoprotein (LDL)
  - peripheral arterial disease (PAD)
  - systolic blood pressure (SBP)
  - smoking status
  - white blood cell (WBC) count
- Event history:
  - previous ischaemic heart disease (IHD), specifically angina
  - hospitalisation for heart failure (HHF)
  - myocardial infarction (MI)
  - stroke
  - prevalent lower limb amputation
  - blindness: presence of proliferative retinopathy up to and including blindness
  - established kidney disease (EKD), specifically CKD stage 5
  - ulceration, specifically a diabetic ulcer

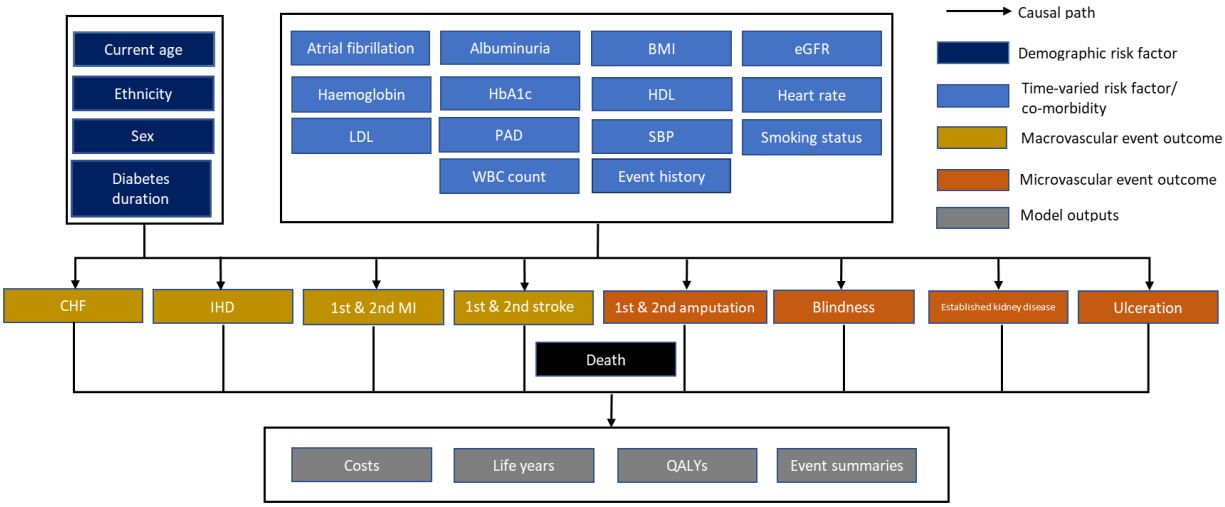
Med codes within CPRD AURUM records and ICD-10 codes recorded during hospital admissions were searched for the above terms, except with hospitalisation for heart failure event, which equated to the existing heart failure population cohort, and for lower limb amputation, where OPCS-4 codes were searched for instead of ICD-10 codes.

The risk factor equations utilise the time-varied risk factors to calculate the likelihood of certain diabetes-related complications occurring, specifically:

- IHD
- HHF
- MI
- stroke
- amputation
- blindness
- EKD
- ulceration

The cumulative occurrence of these complications is used to calculate lifetime costs and QALYs. A visual description of the UKPDS Global beta model is presented in Figure 1.

Figure 1. UKPDS Global beta model description



Abbreviations: BMI= body mass index; CHF= chronic heart failure; eGFR= estimated glomerular filtration rate; EKD= established kidney disease (CKD 5); HbA1c= glycosylated haemoglobin; HDL= high-density lipoprotein; IHD= ischaemic heart disease; LDL= low-density lipoprotein; MI= myocardial infarction; PAD= peripheral arterial disease; QALYs= quality-adjusted life years; SBP= systolic blood pressure; WBC= white blood cell

2.2.2 Model calibration

In external validation studies (Keng, et al., 2022; Pagano, et al., 2021), the UKPDS OM2.2 was reported to overpredict certain cardiovascular events such as MI, stroke and cardiovascular mortality (CVM). It also underpredicts the reduction in events by SGLT-2 inhibitors and GLP-1 agonists as these have cardio-renal benefits independent of benefits to the time-varied risk factors (such as HbA1c) in the model. Both of these combined will significantly impact cost-effectiveness in the analysis. It was therefore necessary to calibrate the model-predicted outputs so that they were concordant with the hazard ratios from the NMA. Our model population is based on CPRD data, a population that is older and with more comorbidities than participants recruited into the RCTs and that absolute improvement in outcomes from interventions maybe lower. This population is more representative of people with diabetes in the UK than the RCTs and thus this population was used as the population for our baseline. Baseline event rates were calculated by running the CPRD population through the model with no adjustment. This was assumed to represent people on metformin monotherapy which was the predominant treatment within the UKPDS trial. For other treatments in the economic model, the event rates were calibrated using the hazard ratios vs metformin alone from the accompanying NMA results assuming metformin monotherapy as the comparator.

As outlined in section 2.2, two calibration methods were available for consideration:

- Running the published version of the UKPDS model followed by post-hoc calibration of the model outputs (costs and QALYs)
- Utilising the UKPDS Global beta model, which allows for direct calibration of the risk equations within the model

Multiple calibration approaches were available within each modelling strategy. Approaches using the published version of the UKPDS model all required post-hoc adjustment of the outputs of the model to align with results reported in the accompanying NMA. These all

risked introducing a number of biases including losing co-dependency between outcomes and risks of double counting cardiovascular and other benefits.

There were several approaches available for direct calibration of the Global beta model all of which had a lower risk of bias than post-hoc calibration. A summary of these approaches is given below:

Calibration options with the UKPDS Global beta model

1. Pre-model adjustment for non-fatal cardiovascular events

Hazard ratios for NFCVE, estimated from the NMA, are used to adjust event rates within the UKPDS model prior to execution. Resulting costs and QALYs are taken directly from the model outputs.

2. Pre-model adjustment for CVM only

As in Option 5, but only CVM rates are adjusted using NMA-derived estimates. NFCVE rates remain unadjusted.

3. Combined adjustment for fatal and non-fatal cardiovascular events

As options 5 and 6 gave quite different results, an alternative approach was taken that sought to combine calibration of both fatal and non-fatal CV events but without double-counting the mortality benefits. The model is first run as in Option 5. Calibration involves translating the required adjustment from the hazard ratio scale (used in the NMA) to the log-odds scale (used in the UKPDS OM2 model for CVM). This ensures consistency between the statistical scales used in the NMA and the model.

Both modelling approaches were tested and the outputs evaluated. The results showed substantial divergence, necessitating the selection of one approach over the other. To inform this selection, advice was sought from the NICE Technical Support Unit (TSU). The TSU recommended approaches that involve modifying the risk equations within the UKPDS model, as these methods better account for the interdependencies and non-linear characteristics inherent in the risk equations. By contrast, post-hoc calibration techniques were deemed less suitable, as they do not adequately capture these complex relationships.

The Global beta version of the UKPDS model was therefore selected for our analyses. This model is identical to the UKPDS OM2.2 but allows for the adjustment of the risk equations using hazard ratios estimated by the accompanying NMA.

UKPDS risk equations 1-7, 13 (covering HF, MI, IHD, stroke and renal failure), D2 (death in first year of event) and D4 (death in subsequent years of event) were calibrated to reflect outcomes over 3 years, as reported in the clinical review NMA. {Hayes, 2013 #2654} The risk equations for NFCVE were adjusted using the estimates from the accompanying NMA presented and discussed in the Model inputs section of this report. Risk equations for cardiovascular mortality in the year of a cardiovascular event or any subsequent year had to adjusted using log odds ratios. As the accompanying NMA reported CVM as hazard ratios these had to first be converted to log odds ratios as discussed below.

Given the interdependency of NFCVE and CVM in the UKPDS risk equations inputting all the adjustments in one run of the model was likely to lead to some double counting of the in the CVM benefit. For example, reducing NFCVE in the UKPDS model will also lead to a reduction in CVM even without adjusting the relevant risk equation. Simultaneously adjusting both outcomes will capture the direct reduction in CVM as well as the indirect reduction mediated through effects on NFCVE, potentially resulting in double counting of mortality

benefits. Adjusting all UKPDS risk equations simultaneously would lead to an overestimate of the cost-effectiveness of interventions.

The model was therefore run twice. The first iteration of the model adjusted for NFCVE, hBa1C and weight. A calibration factor was than calculated for CVM that would bring the results from the first run of the model in line with those predicted by the accompanying NMA. A second and final run of the model adjusting NFCVE, weight and hBa1C as per the first run but with CVM adjusted using the calibration factor.

2.2.3 Estimation of calibration adjustment factor

The UKPDS-OM2 model uses the log odds ratio to calibrate CVM. Therefore, after the first run of the model, adjusting for NFCVE, the log odds ratio for CVM, compared to metformin were estimated for each treatment compared to metformin monotherapy. This estimate was based on the event estimates from the metformin arm of the first run of the UKPDS Global beta model and HRs estimated by the accompanying NMA. The following formula was used:

$$\log\left(OR(t)\right) = \log\left(\frac{e^{h_{met}*HR*t} - 1}{e^{h_{met}*t} - 1}\right)$$

Where t equals time, OR(t) equals the odds ratio for CVM in the relevant intervention at time t, h_{met} is the hazard of CVM and HR is the hazard ratio used as the input for the relevant intervention. The log odds ratios were calculated at 3 years post initiation of the model as this was considered a time point that was both sufficiently in the future yet was within the time horizon of a number of the trials included in the accompanying NMA estimates.

An initial calibration factor was then estimated that would bring CVM from the first run of the model in line with those estimated by the accompanying NMA (target logs odd ratio). Given that the UKPDS Global beta model defines CVM as death after the first year of the event the calibration factor had to then be divided by the probability of a non-fatal cardiovascular event (NFCVE) – see methods 3-6 below. Six different equations were used for calculating the best final calibration factor for the model.

Method 1: CVM log odds ratios in the model were adjusted to match the targeted CVM log odds ratio by multiplying by the ratio of the two values on the logs odd scale. For example, if the odds estimated by the first run of the model was a third of the target odds then the calibration factor, A, would equal the log of 3.

Method 2: This is the same as for method 1 but accounted for the impact on CVM by changes in the NFCVEs. The calibration factor, B, was calculated after running the model with the NFCVEs calibrated.

Method 3: The same as method 2 but accounting for the UKPDS Global beta model definition of CVM by dividing the calibration factor by the odds of having a NFCVE in the previous year of the model. The calibration factor was therefore effectively only applied for individuals in the model who had experienced a NFCVE in the previous year and could meet the UKPDS model's definition of CVM in the current year. The calibration factor was C= B/(1-O_i), Where O_i =odds of a non-fatal CV event

Method 4: The same as method 2 but accounting for the UKPDS Global beta model definition of CVM by dividing the calibration factor by the probability of having a NFCVE in the previous year of the model. As for method 3 this meant the calibration factor was effectively only applied for individuals in the model who could meet the UKPDS Global beta

model's definition of CVM in the current year. The calibration factor was $D=B/(1- P_i)$, Where P_i =probability of a non-fatal CV event

Method 5: As for method 3 but probabilities were converted to rates before applying the adjustment using the formula $\ln(1-(1-\exp(B))/(1-O_i))$ where B is the calibration factor estimated in method 2 and O_i is the odds of a NFCVE.

The second run of the model was undertaken 5 times adjusting the targeted logs odd ratio for CVM from the accompanying NMA with the calibration factor encountered. The predicted events for all outcomes from the 5 runs of the model were compared to the predicted events from the accompanying NMA and baseline run of the model to inspect how closely they concurred. An outlier was arbitrarily defined as an estimate from the model that was equal to or lower than 95% or greater than or equal to 105% of the NMA estimate. The method with the least number of outliers was selected as the preferred model.

Total events by population and treatment are shown in Appendix C: and Appendix D:.

Table 4 shows the expected incidence of events at 3 years predicted by the UKPDS Global beta model, which were subsequently applied to the metformin arm. Incidence of the events for the other treatments in the model were estimated by using the relevant hazard ratio estimated in the NMA. Proportional hazards were assumed when calibrating events before and after 3 years so that the rates of change were constant at all timepoints.

Table 4. Baseline risk factor incidence over 3 years predicted by UKPDS Global beta model

	ASCVD	CKD 1-3	CKD 4	HF
CVM	14.5%	11.8%	21.3%	18.4%
Angina	1.2%	1.9%	1.2%	2.7%
HF	7.1%	7.9%	4.5%	7.1%
MI	7.8%	6.3%	7.6%	12.2%
Stroke	7.6%	7.1%	12.6%	10.9%
EKD	0.6%	1.2%	7.8%	1.1%

	High risk of CVD + living with obesity	High risk of CVD + living with overweight	High risk of CVD + aged under 40 years
CVM	3.2%	3.5%	0.3%
Angina	2.0%	2.1%	1.4%
HF	0.8%	1.4%	0.5%
MI	3.3%	3.5%	1.5%
Stroke	1.8%	2.2%	0.3%
EKD	0.1%	0.3%	0.03%

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; CVM= cardiovascular mortality; EKD= established kidney disease; HF= heart failure; MI= myocardial infarction

2.2.4 Uncertainty

The UKPDS OM2.2 is a probabilistic model in that it accounts for stochastic uncertainty by simulating identical patients multiple times and taking a mean of the recorded outcomes. The number of internal loops (Monte-Carlo trials) was set to 10,000 patients, a size considered sufficient to address uncertainty in patient characteristics whilst keeping the runtime of the model reasonable.

The model incorporates bootstrap resampling to address parameter uncertainty within the underlying risk equations by generating multiple simulations based on their respective distributions. This functionality is embedded within the model framework. To explore how uncertainty has been characterised in similar contexts, a targeted literature search was conducted which identified one relevant study using the UKPDS model.(Dakin, et al., 2020) This was a simulation study using the UKPDS OM2 model to extrapolate data from individual participants in the AFORRD randomised controlled trial and employed 800 bootstrap samples in all analyses. The authors reported that 800 bootstraps was sufficient to estimate standard errors to within ±10% accuracy and produced stable results, aligning with the recommendations of O'Hagan 2007.(O'Hagan, et al., 2007)

When conducting test simulations, it was observed that increasing the number of bootstraps led to a more-than-proportional increase in computation time (i.e., doubling the bootstraps more than doubled the runtime). Given the large volume of simulations required, we prioritised computational efficiency while aiming to minimise the introduction of additional uncertainty.

To determine an optimal balance, further test simulations were conducted varying both the number of loops and bootstraps, assessing their impact on the model event estimates for a few randomly selected interventions. Increasing the number of loops from 10,000 to 1,000,000 did not significantly improve the alignment of event estimates, indicating that 10,000 loops were sufficient. Mean QALYs and costs derived from point estimates were also compared with those averaged across 800 bootstraps. The results consistently matched within 0.1%, supporting the decision to omit bootstrapping in the final analysis to reduce runtime. The base-case simulations were originally run using 10,000 loops and 800 bootstraps, while all subsequent sensitivity analyses were run with 0 bootstraps. To maintain methodological consistency between the base case and sensitivity analyses, final base case results are reported based on 10,000 loops and the point estimates.

When it came to simulating individual patient characteristics for the model inputs, a probability distribution was defined for each patient characteristic parameter. Means and standard deviations for all demographic and time-varied factors as well as event histories were obtained from a prevalent cohort of patients with T2DM as recorded in CPRD AURUM. Distributions for each characteristic were defined from histograms. A correlation matrix was also generated using the R statistical software.

Patient characteristics were stochastically sampled by combining data on the prevalence of patient characteristics and their distribution together with the correlation matrix. The use of the correlation matrix to generate the patient samples was necessary to account for co-dependencies between risk factors (i.e. one risk factor may more likely occur given the presence of another risk factor). In total, 200 hypothetical patients were simulated for each population.

In addition, various deterministic sensitivity analyses were undertaken to test the robustness of model assumptions. In these, one or more inputs were changed and the analysis rerun to evaluate the impact on results and whether conclusions on which intervention should be recommended would change.

72 # 2.3 Model inputs

73 ### 2.3.1 Initial cohort settings

74 The UKPDS OM2.2 requires a baseline dataset containing demographics, clinical risk factors
75 and pre-existing conditions, as detailed in Hayes 2013.

76 The previous guideline utilised data from The Health Improvement Network (THIN) because
77 the guideline committee were satisfied that the advantages of THIN, such as good coverage
78 of risk factors, large sample size and the ability to extract correlations between risk factors,
79 outweighed its two potential issues: an inability to select data by therapy level and lack of
80 ethnicity data.

81 The THIN dataset is based on primary care records in the UK and covers around 850
82 general practices and 3.6 million people, around 6% of the UK population.(Chutoo, et al.,
83 2022)

84 An alternative primary care database to THIN is the CPRD AURUM dataset. Unlike THIN,
85 CPRD AURUM records ethnicity data.

86 The current committee were satisfied that a larger dataset of the UK primary care population
87 would provide more robust estimates of the T2DM population and so preferred to use the
88 CPRD dataset. This was an important consideration given that the overall population would
89 be stratified into sub-groups when running the model.

90 Given that the model would consider subsequent pharmacological therapy following initiation,
91 we obtained summary statistics from a prevalent T2DM population. The initial cohort
92 characteristics are summarised in Table 5 and Table 6.

Table 5. Baseline characteristics obtained from summary CPRD statistics

Variable	Mean (SD)			
	ASCVD (n=182,826)	CKD 1-3 (n=196,212)	CKD 4 (n=12,871)	HF (n= 54,495)
Female (%)	36.8	45.1	47.9	39.0
Age (years)	73.15 (11.12)	72.71 (12.37)	79.66 (10.17)	75.62 (11.20)
Ethnicity: White (%)	83.5	80.3	83.6	86.2
Ethnicity: Asian Indian (%)	12.6	13.2	10.0	9.7
Ethnicity: Black Caribbean (%)	3.9	6.5	6.4	4.2
Height (m)	1.676 (0.102)	1.667 (0.104)	1.653 (0.102)	1.676 (0.104)
Weight (kg)	84.96 (20.19)	84.61 (20.70)	85.58 (19.94)	87.08 (22.39)
Current smoker (%)	13.8	11.3	6.7	10.7
HbA1c (%)	7.39 (1.47)	7.50 (1.54)	7.53 (1.58)	7.37 (1.51)
Heart rate (beats per minute)	74.64 (12.84)	77.06 (13.18)	74.02 (13.22)	73.75 (13.16)
Haemoglobin (g/dL)	13.34 (1.76)	13.27 (1.75)	11.81 (1.67)	13.05 (1.90)
SBP (mmHG)	130.96 (15.37)	132.37 (14.96)	133.04 (17.61)	128.48 (17.06)
HDL (mmol/L)	1.20 (0.34)	1.25 (0.36)	1.19 (0.36)	1.19 (0.35)
LDL (mmol/L)	1.92 (0.87)	2.04 (0.90)	1.98 (0.89)	1.90 (0.86)
eGFR (ml/min/1.73m^2)	68.86 (22.35)	64.53 (22.02)	24.46 (4.02)	59.11 (23.38)
White blood cell count (× 10^9/L)	7.80 (2.19)	7.79 (2.17)	7.95 (2.31)	7.89 (2.29)
Albuminuria (%)	24.9	6.23	51.2	28.8
Angina (%)	54.1	20.7	31.5	46.9
Atrial fibrillation (%)	23.5	17.6	31.0	48.9
Myocardial infarction (%)	28.4	10.5	17.5	31.6
Stroke (%)	20.6	8.1	12.4	13.4
Lower limb amputation (%)	2.4	1.5	3.0	2.7
Lower limb ulceration (%)	11.9	10.1	17.4	17.3
Diabetic retinopathy (%)	15.7	15.1	27.4	18.5
Established kidney disease (%)	1.8	0.7	5.6	3.5

Variable	Mean (SD)			
	ASCVD (n=182,826)	CKD 1-3 (n=196,212)	CKD 4 (n=12,871)	HF (n= 54,495)
Peripheral arterial disease (%)	17.2	7.0	12.7	13.4

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; dL= decilitre; eGFR= estimated glomerular filtration rate; g=gram; HbA1c= glycosylated haemoglobin; HF= heart failure; HDL= high-density lipoprotein; kg= kilogram; L= litre; LDL= low-density lipoprotein; m= metre; ml= millilitre, min= minute; mmHG= millimetre of mercury; mmol= millimole; n=number; SD= standard deviation

Table 6. Baseline characteristics obtained from summary CPRD statistics (continued)

Variable	Mean (SD)		
	High risk of CVD plus living with obesity (n=200,800)	High risk of CVD plus living with overweight (n= 115,727)	High risk of CVD plus aged under 40 years (n=2,436)
Female (%)	47.2	37.6	27.9
Age (years)	64.58 (10.92)	68.82 (11.11)	36.21 (2.97)
Ethnicity: White (%)	79.7	77.1	67.9
Ethnicity: Asian Indian (%)	13.3	18.1	29.9
Ethnicity: Black Caribbean (%)	7.0	4.8	2.2
Height (m)	1.674 (0.105)	1.684 (0.103)	1.736 (0.095)
Weight (kg)	99.72 (19.78)	77.08 (11.13)	116.75 (28.98)
Current smoker (%)	13.5	13.7	52.3
HbA1c (%)	7.49 (1.48)	7.42 (1.45)	8.01 (1.94)
Heart rate (beats per minute)	79.60 (12.55)	78.00 (12.54)	86.47 (13.26)
Haemoglobin (g/dL)	13.93 (1.60)	13.83 (1.61)	14.78 (1.50
SBP (mmHG)	133.34 (13.51)	131.45 (13.12)	135.21 (15.39)
HDL (mmol/L)	1.23 (0.32)	1.29 (0.36)	0.97 (0.23)
LDL (mmol/L)	2.25 (0.94)	2.17 (0.93)	2.86 (1.00)
eGFR (ml/min/1.73m^2)	80.68 (20.22)	78.06 (19.74)	109.34 (17.22)
White blood cell count (× 10^9/L)	7.79 (2.10)	7.45 (2.05)	8.99 (2.41)
Albuminuria (%)	20.2	21.2	18.1
Angina (%)	0.3	0.3	0.2

Variable	Mean (SD)		
	High risk of CVD plus living with obesity (n=200,800)	High risk of CVD plus living with overweight (n= 115,727)	High risk of CVD plus aged under 40 years (n=2,436)
Atrial fibrillation (%)	7.2	6.6	1.9
Myocardial infarction (%)	-	-	-
Stroke (%)	-	-	-
Lower limb amputation (%)	0.7	0.7	0.6
Lower limb ulceration (%)	6.6	5.1	4.8
Diabetic retinopathy (%)	8.9	10.8	3.7
Established kidney disease (%)	0.6	0.6	1.6
Peripheral arterial disease (%)	-	-	-

Abbreviations: CVD= cardiovascular disease; dL= decilitre; eGFR= estimated glomerular filtration rate; g=gram; HbA1c= glycosylated haemoglobin; HF= heart failure; HDL= high-density lipoprotein; kg= kilogram; L= litre; LDL= low-density lipoprotein; m= metre; ml= millilitre, min= minute; mmHG= millimetre of mercury; mmol= millimole; n=number; SD= standard deviation

2.3.2 Alternate approach to treatment intensification in model

Previous guidelines had modelled treatment intensification by applying a threshold of 7.5% (58mmol/mol) exceeded on HbA1c at which treatment is altered. The committee considered this approach too glucose-centric in nature and not reflective of current clinical practice, in which a more holistic approach is applied. In their experience, a wide range of factors determined what treatment was most suitable including the presence of certain co-morbidities, QRISK score and presence of frailty. Given the move away from a glucose-centric treatment intensification approach, and that mapping out a treatment intensification algorithm that is dependent on multiple factors would be complicated in the first instance and incorporate added uncertainty at each level of intensification, it was decided to model subsequent treatment choices to metformin monotherapy in the pre-defined cohorts.

2.3.3 Relative treatment effects

There were two types of treatment effects applied in the model; effects on 'surrogate' outcomes (HbA1c and weight) and effects on 'hard' outcomes such as those reported in CVOTs. Treatment effects were taken exclusively from the clinical review NMA in the base case. The NMA reported distinct treatment effects within each population of interest for each outcome (see Appendix A: Treatment effects reported in NMA before crossover between populations). Where an outcome was reported for one population but not another, the committee agreed that it was appropriate to transfer over the treatment effect providing the intervention remained the same. To maintain objectivity, they agreed to a hierarchy of cohorts from which treatment effects would be taken where data were absent:

High risk of CVD > ASCVD > HF > CKD

According to this hierarchy, where a treatment effect is missing it would be sourced from the high risk of CVD population where available, followed by the ASCVD population, then the HF population, and lastly, from the CKD population. Where a treatment effect was unreported in all populations, a hazard ratio of 1 were assumed for all.

Furthermore, since the model was not set up to sample probabilistic effects around the relevant confidence intervals, a decision rule was set to determine when to keep a reported treatment effect. A point estimate with large credible intervals may not be more useful in informing decisions than no evidence at all and could lead to favourable estimates of cost effectiveness based on weak evidence. As a consequence of disaggregating outcomes according to specific sub-populations, sample sizes for estimates were often small and led to treatment effect estimates having higher uncertainty. It was not appropriate to disregard all treatment effects where the 95% credible interval crossed the line of no effect. We therefore decided not to incorporate estimates based on the following criteria:

- Keep all treatment effects where the 95% credible interval suggests a treatment effect i.e. does not pass the line of no effect
- Disregard all treatment effects where the lower end of 95% credible interval is near-zero (these instances were defined as not estimable in the clinical review)
- Disregard all treatment effects where the 95% credible interval exceeds 2 minimally important differences (MID)

HbA1c

HbA1c were assumed to reach the NMA estimate, from the baseline estimate, in a linear manner by year one of the model. Following this, change was dictated in line with the UKPDS risk equations. Table 7 presents the change in HbA1c versus placebo from the NMA applied in the model. Only values from the high risk of CVD population were used as 95% credible interval estimates in the ASCVD, CKD and HF populations exceeded 2 minimally important differences.

Table 7. Change in HbA1c (%) versus placebo from the clinical review NMA used in the model

	ASCVD	CKD	HF	High risk of CVD
Canagliflozin	*-0.75*	*-0.75*	*-0.75*	-0.75
Dapagliflozin	*-0.60*	*-0.60*	*-0.60*	-0.60
Empagliflozin	*-0.70*	*-0.70*	*-0.70*	-0.70
Ertugliflozin	*-0.68*	*-0.68*	*-0.68*	-0.68
Dulaglutide	*-0.97*	*-0.97*	*-0.97*	-0.97
Exenatide	*-0.77*	*-0.77*	*-0.77*	-0.77
Liraglutide	*-0.91*	*-0.91*	*-0.91*	-0.91
Semaglutide (oral)	*-0.96*	*-0.96*	*-0.96*	-0.96
Semaglutide (subcutaneous)	*-1.28*	*-1.28*	*-1.28*	-1.28
Alogliptin	*-0.53*	*-0.53*	*-0.53*	-0.53
Linagliptin	*-0.54*	*-0.54*	*-0.54*	-0.54
Saxagliptin	*-0.52*	*-0.52*	*-0.52*	-0.52
Sitagliptin	*-0.63*	*-0.63*	*-0.63*	-0.63
Vildagliptin	*-0.66*	*-0.66*	*-0.66*	-0.66
Gliclazide	*-0.71*	*-0.71*	*-0.71*	-0.71
Insulin	*-0.73*	*-0.73*	*-0.73*	-0.73
Pioglitazone	*-0.63*	*-0.63*	*-0.63*	-0.63
Metformin	0.00	0.00	0.00	0.00

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure
Figures highlighted yellow indicate they were borrowed from another population dataset
Figures from ASCVD, CKD and HF populations were excluded as they exceeded 2 minimally important differences.

The treatment effect of metformin on HbA1C was set to 0 as the UKPDS risk equations already accounted for the effects of metformin during treatment intensification in the original cohort, and so applying an effect here would have led to double counting.

Weight change in the absence of treatment effects

The committee reviewed the predicted weight change over time with UKPDS risk equations. They noted that except in the case of the high risk of CVD and living with overweight cohort, weight in the absence of treatment declined over time. This was not in line with their clinical experience that weight tended to increase over time in people with T2DM. They were aware that some NICE technology appraisals of pharmacological interventions in people with T2DM had assumed an annual increase of 0.1kg, which was more concordant with their expectation. This assumption was therefore applied in the model as a background change in weight regardless of intervention

Treatment-related weight change in year 1

Treatment effects in year one was assumed to occur in a linear manner. The committee noted that in the case of weight loss, the effects would be similar to a negatively exponential curve. However, given that the effects occurred over a year, the committee did not think the change difference between the linear and the exponential trajectories would be substantial. A weight-loss linear trajectory was applied as a simplification of reality. Table 8 lists the treatment effects on weight applied in the first year of the model.

Table 8. Change in median weight ratios in year 1 from the clinical review NMA used in the model

	ASCVD	CKD	HF	High risk of CVD
Canagliflozin	*0.97*	0.99	*0.97*	0.97
Dapagliflozin	0.98	0.98	*0.97*	0.97
Empagliflozin	1.02	0.98	*0.98*	0.98
Ertugliflozin	*0.97*	0.98	*0.97*	0.97
Dulaglutide	*0.99*	*0.99*	*0.99*	0.99
Exenatide	*0.98*	*0.98*	*0.98*	0.98
Liraglutide	*0.97*	*0.97*	*0.97*	0.97
Semaglutide (oral)	*0.96*	*0.96*	*0.96*	0.96
Semaglutide (subcutaneous)	*0.96*	*0.96*	*0.96*	0.96
Alogliptin	*1.00*	*1.00*	*1.00*	1.00
Linagliptin	*1.00*	0.99	*1.00*	1.00
Saxagliptin	*1.00*	*1.00*	*1.00*	1.00
Sitagliptin	1.05	*0.99*	*0.99*	0.99
Vildagliptin	1.02	*1.00*	*1.00*	1.00
Gliclazide	*1.01*	*1.01*	*1.01*	1.01
Insulin	*1.03*	*1.03*	*1.03*	1.03
Pioglitazone	*1.03*	*1.03*	*1.03*	1.03
Metformin	1.00	*1.00*	*1.00*	1.00

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure
Figures highlighted yellow indicate they were borrowed from another population dataset

Treatment-related weight change in years 2-4 for SGLT-2 inhibitors and GLP-1 agonists

For years 2-4, weight loss was based on real-world data from CPRD AURUM. This was an intention-to-treat (ITT) analysis including adults aged 18 years and over with T2DM with a relevant first prescription for a relevant GLP-1 agonist or SGLT-2 inhibitor between April 2018 and November 2022 with a follow-up between April 2018 and November 2023. The outcome of interest was change in BMI versus baseline which were converted to change in weight ratios and summarised in Table 9.

Table 9. Change in weight ratios in years 2-4 reported in CPRD used in the model

	Year 2	Year 3	Year 4
Canagliflozin	0.96	0.95	0.94
Dapagliflozin	0.96	0.95	0.95
Empagliflozin	0.96	0.95	0.94
Ertugliflozin	0.97	0.95	0.91
Dulaglutide	0.96	0.96	0.94
Exenatide	0.98	1.00	0.95
Liraglutide	0.97	0.96	0.95
Semaglutide (oral)	0.96	0.95	0.95
Semaglutide (subcutaneous)	0.94	0.94	0.94

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure

In the absence of clinical data informing trajectory past 4 years, the committee decided that a more conservative approach would be appropriate. In their experience, patients continuing on SGLT-2 inhibitors and GLP-1 agonists tended to revert to a value similar to the baseline value in the absence of additional treatment. Their expectations were that the reversal of weight-related treatment effect was more gradual with SGLT-2 inhibitors than with GLP-1 agonists, and that although weight rebound tended to be noticeable, residual treatment effects, in regard to weight loss, remained. We therefore modelled a linear weight rebound over 1 year with GLP-1 agonists and more gradual linear weight rebound over 2 years with SGLT-2 inhibitors. Following this rebound period, weight followed that of metformin monotherapy in the previous year. Since weight was assumed to increase by 0.1kg annually for metformin monotherapy, the weight in any given year for someone on treatment with a GLP-1 agonist or an SGLT-2 inhibitor was 0.1kg less than for metformin alone.

CVOT treatment effects

Treatment effects from the NMA were applied to 6 CVOT model outcomes (CVM, IHD, HHF, MI, stroke and established kidney disease) and are summarised in Table 10 to Table 15. These were reported relative to placebo in the clinical review NMA. The CVM and EKD estimate for oral semaglutide in the CKD population was obtained from Perkovic 2024 which was published after the NMA had been run. Prior to that there was no evidence identified for this treatment in this population. For modelling, we assumed that treatment effects were for dual therapy relative to metformin alone since all treatments were in addition to metformin.

Table 10. Risk of CVM versus placebo (odds ratios) from the clinical review NMA used in the model

	ASCVD	CKD	HF	High risk of CVD
Canagliflozin	0.86	0.79	0.72	0.88
Dapagliflozin	0.95	0.90	1.01	1.00
Empagliflozin	0.62	0.71	*0.62*	*0.62*
Ertugliflozin	0.92	*0.92*	*0.92*	*0.92*
Dulaglutide	*0.92*	*0.92*	*0.92*	0.92
Exenatide	*0.88*	*0.88*	*0.88*	0.88
Liraglutide	*0.77*	*0.77*	0.85	0.77
Semaglutide (oral)	*0.53*	*0.53*	*0.53*	0.53
Semaglutide (subcutaneous)	*0.95*	0.71†	*0.95*	0.95

	ASCVD	CKD	HF	High risk of CVD
Alogliptin	0.85	*0.85*	0.77	*0.85*
Linagliptin	*0.98*	*0.98*	0.96	0.98
Saxagliptin	*1.03*	*1.03*	*1.03*	1.03
Sitagliptin	1.03	*1.03*	*1.03*	*1.03*
Vildagliptin	1.00	1.00	1.00	1.00
Gliclazide	1.00	1.00	1.00	1.00
Insulin	1.00	1.00	1.00	1.00
Pioglitazone	0.94	*0.94*	*0.94*	*0.94*
Metformin	1.00	1.00	1.00	1.00

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure
Figures highlighted yellow indicate they were borrowed from another population dataset
Please refer to Table 90 for hazard ratios (HR) reported in the clinical review NMA. The following HRs were excluded from the modelling on the basis that the the results were not statistically significant and the credible interval exceeded two minimally important differences:
HF: vildagliptin = 1.80 (0.54, 7.15)
High risk of CVD: empagliflozin= 4.11 (0.37, 98.87), ertugliflozin= 2.07 (0.25, 31.97), alogliptin= 3.08 (0.46, 32.11), sitagliptin= 1.22 (0.7,2.14), vildagliptin= (1.21 (0.21, 8.08), gliclazide= 6.54 (0.18, 738.69), insulin= 1.3 (0.65, 2.55), pioglitazone= 0.99 (0.09, 8.58), metformin= 1.58 (0.26, 10.63)
† Estimate from Perkovic 2024

Table 11. Risk of IHD versus placebo (hazard ratios) from the clinical review NMA used in the model

	ASCVD	CKD	HF	High risk of CVD
Canagliflozin	1.00	1.00	1.00	1.00
Dapagliflozin	*1.02*	*1.02*	*1.02*	1.02
Empagliflozin	0.97	*0.97*	*0.97*	*0.97*
Ertugliflozin	0.81	*0.81*	*0.81*	*0.81*
Dulaglutide	*1.12*	*1.12*	*1.12*	1.12
Exenatide	*1.14*	*1.14*	*1.14*	1.14
Liraglutide	*0.96*	*0.96*	*0.96*	0.96
Semaglutide (oral)	1.00	1.00	1.00	1.00
Semaglutide (subcutaneous)	1.00	1.00	1.00	1.00
Alogliptin	1.00	1.00	1.00	1.00
Linagliptin	1.00	1.00	1.00	1.00
Saxagliptin	*1.18*	*1.18*	*1.18*	1.18
Sitagliptin	0.90	*0.90*	*0.90*	*0.90*
Vildagliptin	1.00	1.00	1.00	1.00
Gliclazide	1.00	1.00	1.00	1.00
Insulin	1.00	1.00	1.00	1.00
Pioglitazone	1.00	1.00	1.00	1.00
Metformin	1.00	1.00	1.00	1.00

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure
Figures highlighted yellow indicate they were borrowed from another population dataset

Please refer to Table 91 for hazard ratios (HR) reported in the clinical review NMA. The following HRs were excluded from the modelling on the basis that the results were not statistically significant and the credible interval exceeded two minimally important differences:
ASCVD: dapagliflozin= 0.40 (0.08, 1.50); alogliptin= 0.90 (0.60, 1.37)
High risk of CVD: empagliflozin= 0.11 (0, 4.85); semaglutide (oral)= 1.92 (0.84, 4.38); semaglutide (subcutaneous)= 0.83 (0.48, 1.44); linagliptin= 0.88 (0.58, 1.34); sitagliptin= 1.54 (0.73, 3.42); insulin= 1.18 (0.51, 2.74); pioglitazone= 14.96 (0.55, 964.6); metformin= 0.45 (0, 44.74)

Table 12. Risk of HHF versus placebo (hazard ratios) from the clinical review NMA used in the model

	ASCVD	CKD	HF	High risk of CVD
Canagliflozin	0.68	0.61	0.61	0.67
Dapagliflozin	0.79	0.72	0.73	0.73
Empagliflozin	0.65	0.61	*0.65*	*0.65*
Ertugliflozin	0.70	*0.70*	0.63	*0.70*
Dulaglutide	*0.93*	*0.93*	*0.93*	0.93
Exenatide	*0.94*	*0.94*	*0.94*	0.94
Liraglutide	*0.87*	*0.87*	0.98	0.87
Semaglutide (oral)	1.00	1.00	1.00	1.00
Semaglutide (subcutaneous)	*1.08*	*1.08*	*1.08*	1.08
Alogliptin	1.19	*1.19*	1.00	*1.19*
Linagliptin	*0.90*	0.84	0.88	0.90
Saxagliptin	*1.27*	*1.27*	*1.27*	1.27
Sitagliptin	*1.92*	*1.92*	1.05	1.92
Vildagliptin	1.00	1.00	1.00	1.00
Gliclazide	1.00	1.00	1.00	1.00
Insulin	1.00	1.00	1.00	1.00
Pioglitazone	1.41	*1.41*	*1.41*	*1.41*
Metformin	1.00	1.00	1.00	1.00

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure
Figures highlighted yellow indicate they were borrowed from another population dataset.
Please refer to Table 92 for hazard ratios (HR) reported in the clinical review NMA. The following HRs were excluded from the modelling on the basis that the results were not statistically significant and the credible interval exceeded two minimally important differences:
ASCVD= sitagliptin: 1.00 (0.83, 1.20)
CKD= liraglutide: 0.82 (0.14, 4.74); sitagliptin= 0.75 (0.13, 4.48)
High risk of CVD: empagliflozin= 0.45 (0.03, 5.1); semaglutide (oral)= 0.91 (0.54, 1.54); alogliptin= 6.53 (0.31, 721.77); insulin= 1.7 (0.77, 3.65); pioglitazone= 2.1 (0.57, 9.49); metformin= 0.75 (0.15, 3.27)

Table 13. Risk of MI versus placebo (hazard ratios) from the clinical review NMA used in the model

	ASCVD	CKD	HF	High risk
Canagliflozin	0.79	*0.85*	*0.85*	0.85
Dapagliflozin	0.88	*0.89*	0.85	0.89
Empagliflozin	0.87	*0.87*	*0.87*	*0.87*

	ASCVD	CKD	HF	High risk
Ertugliflozin	1.04	*1.04*	*1.04*	*1.04*
Dulaglutide	*0.96*	*0.96*	*0.96*	0.96
Exenatide	*0.95*	*0.95*	*0.95*	0.95
Liraglutide	*0.88*	*0.88*	0.74	0.88
Semaglutide (oral)	1.00	1.00	1.00	1.00
Semaglutide (subcutaneous)	*0.73*	0.80	*0.73*	0.73
Alogliptin	1.08	*1.08*	1.04	*1.08*
Linagliptin	*1.15*	*1.15*	*1.15*	1.15
Saxagliptin	*0.95*	*0.95*	*0.95*	0.95
Sitagliptin	0.96	*0.96*	*0.96*	*0.96*
Vildagliptin	1.00	1.00	1.00	1.00
Gliclazide	1.00	1.00	1.00	1.00
Insulin	1.00	1.00	1.00	1.00
Pioglitazone	0.84	*0.84*	*0.84*	*0.84*
Metformin	1.00	1.00	1.00	1.00

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure
Figures highlighted yellow they were borrowed from another population dataset.
Please refer to Table 93 for hazard ratios (HR) reported in the clinical review NMA. The following HRs were excluded from the modelling on the basis that the results were not statistically significant and the credible interval exceeded two minimally important differences:
CKD= liraglutide= 0.90 (0.01, 20.14); linagliptin= 2.39 (0.50, 16.38); sitagliptin= 3.45 (0.29, 54.17)
High risk of CVD= semaglutide (oral)= 1.10 (0.70, 1.71); alogliptin= 2.98 (0.25, 88.99); sitagliptin= 1.58 (0.43, 5.75); gliclazide= 2.04 (0.20, 34.38); insulin= 0.99 (0.23, 4.57); pioglitazone= 0.75 (0.25, 2.11)

Table 14. Risk of stroke versus placebo (hazard ratios) from the clinical review NMA used in the model

	ASCVD	CKD	HF	High risk
Canagliflozin	0.88	*0.90*	*0.90*	0.90
Dapagliflozin	0.97	*1.01*	*1.01*	1.01
Empagliflozin	1.24	*1.24*	*1.24*	*1.24*
Ertugliflozin	1.00	1.00	1.00	1.00
Dulaglutide	*0.78*	*0.78*	*0.78*	0.78
Exenatide	*0.86*	*0.86*	*0.86*	0.86
Liraglutide	*0.88*	*0.88*	*0.88*	0.88
Semaglutide (oral)	1.00	1.00	1.00	1.00
Semaglutide (subcutaneous)	*0.62*	1.22	*0.62*	0.62
Alogliptin	1.00	1.00	1.00	1.00
Linagliptin	*0.89*	*0.89*	*0.89*	0.89
Saxagliptin	*1.11*	*1.11*	*1.11*	1.11
Sitagliptin	1.00	1.00	1.00	1.00
Vildagliptin	1.00	1.00	1.00	1.00
Gliclazide	1.00	1.00	1.00	1.00

	ASCVD	CKD	HF	High risk
Insulin	1.00	1.00	1.00	1.00
Pioglitazone	0.81	*0.81*	*0.81*	*0.81*
Metformin	1.00	1.00	1.00	1.00

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure
Figures highlighted yellow indicate they were borrowed from another population dataset.
Please refer to Table 94 for hazard ratios (HR) reported in the clinical review NMA. The following HRs were excluded from the modelling on the basis that the results were not statistically significant and the credible interval exceeded two minimally important differences:
ASCVD: alogliptin= 0.92 (0.56, 1.51)
CKD: dapagliflozin= <0.01 (<0.01, 4.30); semaglutide (subcutaneous)= 0.84 (0.01, 28.75); linagliptin= 0.84 (0.01, 28.75)
HF: dapagliflozin= 1.21 (0.76, 1.90); liraglutide= 0.89 (0.53, 1.50); alogliptin= 1.85 (0.70, 5.56); vildagliptin= 0.04 (<0.01, 1.12)
High risk of CVD: empagliflozin= 0.72 (0.04, 13.16); semaglutide (oral)= 0.77 (0.41, 1.44); sitagliptin= 0.35 (0.06, 1.55); vildagliptin= 0.33 (0.05, 1.60.09 (0, 3.92); insulin= 0.26 (0.06, 0.96); pioglitazone= 0.87 (0.2, 3.53)

Table 15. Risk of established kidney disease versus placebo (hazard ratios) from the clinical review NMA used in the model

	ASCVD	CKD	HF	High risk
Canagliflozin	*0.68*	0.68	*0.68*	*0.68*
Dapagliflozin	*0.35*	*0.35*	*0.35*	0.35
Empagliflozin	1.00	1.00	1.00	1.00
Ertugliflozin	1.00	1.00	1.00	1.00
Dulaglutide	1.00	1.00	1.00	1.00
Exenatide	*0.86*	*0.86*	*0.86*	0.86
Liraglutide	*0.89*	*0.89*	*0.89*	0.89
Semaglutide (oral)	1.00	1.00	1.00	1.00
Semaglutide (subcutaneous)	*0.84*	0.84†	*0.84*	*0.84*
Alogliptin	1.00	1.00	1.00	1.00
Linagliptin	*0.98*	*0.98*	*0.98*	0.98
Saxagliptin	*0.90*	*0.90*	*0.90*	0.90
Sitagliptin	1.00	1.00	1.00	1.00
Vildagliptin	1.00	1.00	1.00	1.00
Gliclazide	1.00	1.00	1.00	1.00
Insulin	1.00	1.00	1.00	1.00
Pioglitazone	1.00	1.00	1.00	1.00
Metformin	1.00	1.00	1.00	1.00

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure
Figures highlighted yellow indicate they were borrowed from another population dataset.
Please refer to Table 95 for hazard ratios (HR) reported in the clinical review NMA. The following HRs were excluded from the modelling on the basis that the results were not statistically significant and the credible interval exceeded two minimally important differences:
CKD: dapagliflozin= 0.48 (0.05, 4.37); saxagliptin= 0.0006 (<0.00001, 0.64)
High risk of CVD: canagliflozin= 0.77 (0.31, 1.96); dulaglutide= 0.50 (0.11, 1.87)
†Estimate from Perkovic 2024

2.3.4 Treatment-related adverse events

The committee were keen to focus on treatment-related adverse events that were uncommon but caused a significant detriment to the patient. Based on these criteria, the committee selected the following treatment-related adverse events they thought were of particular interest:

1. Acute kidney injury
2. Acute pancreatitis
3. Diabetic ketoacidosis
4. Severe hypoglycaemia, defined as requiring medical assistance

The accompanying clinical evidence review identified limited evidence for all both in terms of their incidence and their detriment to quality of life. Given this paucity of evidence, we therefore decided to refer to outcomes reported in Shi NMA 2023 instead of the guideline clinical review as outcomes were reported at a class level, which therefore lent greater statistical power to detect differences between treatments.

There were four adverse events from Shi 2023 that were modelled:

(a) Diabetic ketoacidosis
(b) Genital infection
(c) Severe gastrointestinal events
(d) Severe hypoglycaemia

Baseline probabilities for all four adverse events over a five-year period, calculated from the aforementioned NMA are shown below in Table 16. All probabilities were converted into a rate, then an annual probability. Treatment-specific hazard ratios were also taken from Shi 2023 and were calculated by dividing the different in numbers of events reported for each intervention versus baseline by the baseline number (Table 16 to Table 20).

Table 16. Baseline probability of events over five years obtained from Shi NMA 2023

DKA	Severe GI	GTI	Severe hypoglycaemia
0.002	*0.045*	*0.073*	0.03

Abbreviations: DKA= diabetic ketoacidosis; GI= gastro-intestinal; GTI= genito-urinary infection

Table 17. Hazard ratios for diabetic ketoacidosis events obtained from Shi NMA 2023

	ASCVD	CKD	HF	High risk of CVD
Metformin	1.5	1.5	1.5	1.5
Canagliflozin	2.00	2.00	2.00	2.00
Dapagliflozin	2.00	2.00	2.00	2.00
Empagliflozin	2.00	2.00	2.00	2.00
Ertugliflozin	2.00	2.00	2.00	2.00
Dulaglutide	1.00	1.00	1.00	1.00
Exenatide	1.00	1.00	1.00	1.00
Liraglutide	1.00	1.00	1.00	1.00
Semaglutide (oral)	1.00	1.00	1.00	1.00
Semaglutide (subcutaneous)	1.00	1.00	1.00	1.00
Alogliptin	1.00	1.00	1.00	1.00
Linagliptin	1.00	1.00	1.00	1.00
Saxagliptin	1.00	1.00	1.00	1.00

	ASCVD	CKD	HF	High risk of CVD
Sitagliptin	1.00	1.00	1.00	1.00
Vildagliptin	1.00	1.00	1.00	1.00
Gliclazide	0.50	0.50	0.50	0.50
Insulin	1.00	1.00	1.00	1.00
Pioglitazone	1.00	1.00	1.00	1.00

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure

Table 18. Hazard ratios for severe gastrointestinal events obtained from Shi NMA 2023

	ASCVD	CKD	HF	High risk of CVD
Metformin	2.25	2.11	2.11	2.11
Canagliflozin	1.00	1.00	1.00	1.00
Dapagliflozin	1.00	1.00	1.00	1.00
Empagliflozin	1.00	1.00	1.00	1.00
Ertugliflozin	1.00	1.00	1.00	1.00
Dulaglutide	2.00	1.89	1.89	1.89
Exenatide	2.00	1.89	1.89	1.89
Liraglutide	2.00	1.89	1.89	1.89
Semaglutide (oral)	2.00	1.89	1.89	1.89
Semaglutide (subcutaneous)	2.00	1.89	1.89	1.89
Alogliptin	1.15	1.13	1.13	1.13
Linagliptin	1.15	1.13	1.13	1.13
Saxagliptin	1.15	1.13	1.13	1.13
Sitagliptin	1.15	1.13	1.13	1.13
Vildagliptin	1.15	1.13	1.13	1.13
Gliclazide	1.00	1.00	1.00	1.00
Insulin	2.00	1.02	1.02	1.02
Pioglitazone	1.45	1.40	1.40	1.40

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure

Table 19. Hazard ratios for genito-urinary infections obtained from Shi NMA 2023

	ASCVD	CKD	HF	High risk of CVD
Metformin	1.27	1.27	1.27	1.27
Canagliflozin	2.82	1.55	2.82	2.82
Dapagliflozin	2.82	1.55	2.82	2.82
Empagliflozin	2.82	1.55	2.82	2.82
Ertugliflozin	2.82	1.55	2.82	2.82
Dulaglutide	0.71	0.71	0.71	0.71
Exenatide	0.71	0.71	0.71	0.71
Liraglutide	0.71	0.71	0.71	0.71

	ASCVD	CKD	HF	High risk of CVD
Semaglutide (oral)	0.71	0.71	0.71	0.71
Semaglutide (subcutaneous)	0.71	0.71	0.71	0.71
Alogliptin	0.73	0.73	0.73	0.73
Linagliptin	0.73	0.73	0.73	0.73
Saxagliptin	0.73	0.73	0.73	0.73
Sitagliptin	0.73	0.73	0.73	0.73
Vildagliptin	0.73	0.73	0.73	0.73
Gliclazide	0.53	0.53	0.53	0.53
Insulin	1.00	1.00	1.00	1.00
Pioglitazone	6.32	6.32	6.31	6.31

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure

Table 20. Hazard ratios for severe hypoglycaemic events obtained from Shi NMA 2023

	ASCVD	CKD	HF	High risk of CVD
Metformin	1.70	1.70	1.70	1.70
Canagliflozin	0.90	0.90	0.90	0.90
Dapagliflozin	0.90	0.90	0.90	0.90
Empagliflozin	0.90	0.90	0.90	0.90
Ertugliflozin	0.90	0.90	0.90	0.90
Dulaglutide	0.97	0.97	0.97	0.97
Exenatide	0.97	0.97	0.97	0.97
Liraglutide	0.97	0.97	0.97	0.97
Semaglutide (oral)	0.97	0.97	0.97	0.97
Semaglutide (subcutaneous)	0.97	0.97	0.97	0.97
Alogliptin	1.10	1.10	1.10	1.10
Linagliptin	1.10	1.10	1.10	1.10
Saxagliptin	1.10	1.10	1.10	1.10
Sitagliptin	1.10	1.10	1.10	1.10
Vildagliptin	1.10	1.10	1.10	1.10
Gliclazide	4.63	4.63	4.63	4.63
Insulin	4.43	4.43	4.43	4.43
Pioglitazone	1.40	1.40	1.40	1.40

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; CKD= chronic kidney disease; CVD= cardiovascular disease; HF= heart failure

Diabetic ketoacidosis (DKA)

Costs: An online search was conducted to identify recent UK based studies reporting on the costs associated with treating DKA. One study was identified, Dhatariya 2017(Dhatariya, et al., 2017), in which 283 patients were surveyed using questionnaires sent to hospitals across the country. Based on the results, an average cost of £2,064 were calculated for a single

episode. This cost was inflated to 2022/23 costs by multiplying it by the change in NHS cost inflation index since 2017, giving an updated cost of £2,440.

Disutility: A literature search was conducted to identify recently published studies, during which one was identified (Peasgood 2016).(Peasgood, et al., 2016) This study was conducted in the UK in 2,341 people with type 1 diabetes between 2009 to 2012. Fixed and random effects linear models were used to generate utility estimates using EQ-5D, SF-6D and EQ-VAS. The fixed effects model was superior to the random effects model and was therefore preferred. A disutility derived via the EQ-5D was selected, the value being -0.012.

Genital infection (GTI)

Costs: The cost of managing an episode of genital infection was assumed to be single general practitioner consultation with a prescription. Costs for both were taken from the Personal Social Services Research Unit 2022/23.

Disutility: The disutility associated with a GI event was estimated to be -0.00283, based on a cost-utility analysis evaluating different strategies of suspected urinary infections in women (Barry 1997).(Barry, et al., 1997)

Severe gastrointestinal (GI) events

Costs: The cost of managing an episode of genital infection was assumed to be single general practitioner consultation with a prescription. Costs for both were taken from the Personal Social Services Research Unit 2022/23.

Disutility: The disutility associated with a GI event was estimated to be -0.04, based on a study in seeking to identify treatment-related utilities and disutilities in people with T2DM in the UK (Matza 2007).(Matza, et al., 2007) A total of 129 patients completed standard gamble interviews to determine their current health status and the utility of hypothetical health states as well as an EQ-5D questionnaire. Based on the standard gamble technique, a disutility of -0.04 was estimated for nausea. We assumed that this disutility would be equivalent for severe GI events.

Severe hypoglycaemia

Costs: The cost of managing a severe episode of hypoglycaemia was derived from a study by Hammer 2009. The paper included a UK sample of non-randomly selected people with T2DM on insulin-based treatment options. Of 147 people, 19 reported having at least 1 severe hypoglycaemic episode in the previous 1 year. Approximately 53% of the 19 people reporting a severe hypoglycaemic episode were treated by the NHS. Weighted estimated costs of managing severe hypoglycaemic events using community and hospital episode statistics were calculated at £336.30. This value was inflated to 2022/23 costs, giving an updated cost of £530.

Disutility: Previous diabetes guidelines were searched for sources of hypoglycaemic events. It was noted that in both type 1 diabetes (NG17) and type 2 diabetes (NG28) guidelines, a utility score was sourced from Evans 2013.(Evans, et al., 2013)

This was a web-based time trade-off (TTO) study where respondents are asked to “trade off” a portion of their remaining life span for an improved health state when compared to a hypothetical health state. 8,286 respondents were included from the UK, USA, Canada and Germany, of which 551 people were diagnosed with T1DM and 1,603 with T2DM. Impact on quality of life was reported by country for severe day time, severe nocturnal, non-severe daytime and non-severe nocturnal hypoglycaemic events. A reported disutility of 0.062 for daytime severe hypoglycaemic events was applied to severe hypoglycaemic events.

A summary of costs and disutilities applied in the model are presented in Table 21.

Table 21. Costs and disutilities associated with adverse events

Treatment[(a)]	Cost	Source	Disutility	Source
Diabetic ketoacidosis	£2,440[(a)]	Dhatariya 2017(Dhatariya, Skedgel and Fordham, 2017)	0.012	Peasgood 2016(Peasgood, Brennan, Mansell, Elliott, Basarir and Kruger, 2016)
Genital infection	£77	PSSRU 2022/23(Personal Social Services Research Unit, 2023)	0.003	Barry 1997(Barry, Ebell and Hickner, 1997)
Severe gastrointestinal event	£77	PSSRU 2022/23(Personal Social Services Research Unit, 2023)	0.04	Matza 2007(Matza, Boye, Yurgin, Brewster-Jordan, Mannix, Shorr and Barber, 2007)
Severe hypoglycaemia	£530[(a)]	Hammer 2009(Hammer, et al., 2009)	0.062	Evans 2013(Evans, Khunti, Mamdani, Galbo-Jorgensen, Gundgaard, Bogelund and Harris, 2013)

(a) Inflated to 2022/23 UK pounds.

A sensitivity analysis was conducted to explore the impact on results of including treatment-related adverse events in the model.

2.3.5 Resource use and costs

Treatment costs

Medication costs were obtained from the NHS Electronic Drug Tariff (accessed 13/07/2024). (NHS Business Services Authority, 2024) The NHS Prescription Costs Analysis (PCA) 2023/24 was then referenced to calculate a weighted average cost for each treatment based on the total amount of each formulation dispensed in primary care.(NHS business Services Authority, 2024) This was considered an appropriate methodology since most interventions are dispensed in primary care. For the SGLT-2 antagonists, weighting differs for each sub-population. However, as the unit price is constant for all pack sizes and dosages annual cost does not vary. The price of liraglutide has changed significantly since costs were obtained and the model run.

NHS Electronic Drug Tariff (accessed 18/06/2025) have shown a reduction in price of 36% although the price is expected to be volatile in the near future. The impact of changes in the price of liraglutide and of using the new list prices has been explored in a sensitivity analysis discussed below. Dapagliflozin is expected to reduce in cost in the near future given it is now off patent in the UK and legal avenues to extend that have been exhausted as of July 2025. The price drop is expected to be significant and, if as is likely, the proportion of individuals prescribed dapagliflozin as their SGLT-2 inhibitor increases, it will also have a large impact on the cost at a class level.

Table 22. Unit costs of CVOT treatments

Treatment	Pack size and dosage	Unit price	Weighting	Annual cost
Alogliptin	28 x 25mg	£26.60	92.95%	£347
Alogliptin	28 x 12.5mg	£26.60	6.30%	
Alogliptin	28 x 6.25mg	£26.60	0.75%	

Treatment	Pack size and dosage	Unit price	Weighting	Annual cost
Canagliflozin	30 x 300mg	£39.20	75.99%	£477
Canagliflozin	30 x 100mg	£39.20	24.01%	
Dapagliflozin	28 x 10mg	£36.59	96.68%	£477
Dapagliflozin	28x 5mg	£36.59	3.32%	
Dulaglutide	4 x 4.5mg	£73.25	23.59%	£956
Dulaglutide	4 x 3mg	£73.25	35.95%	
Dulaglutide	4 x 1.5mg	£73.25	36.88%	
Dulaglutide	4 x 0.75mg	£73.25	3.58%	
Empagliflozin	28 x 25mg	£36.59	37.94%	£477
Empagliflozin	28 x 10mg	£36.59	62.06%	
Ertugliflozin	28 x 15mg	£29.40	61.19%	£384
Ertugliflozin	29 x 5mg	£29.40	38.81%	
Exenatide	4 x 2mg	£73.36	99.96%	£957
Exenatide	4 x 0.01mg	£81.89	0.04%	
Exenatide	4 x 0.005mg	£81.89	0%	
Gliclazide	28 x 160mg	£3.27	1.07%	£24
Gliclazide	28 x 80mg	£0.85	83.68%	
Gliclazide	28 x 40mg	£0.95	10.91%	
Gliclazide MR	28 x 60mg	£13.00	0.93%	
Gliclazide MR	28 x 30mg	£2.81	3.41%	
Insulin (weighted average of basal, bolus and biphasic preparations) [(a)]	Various	Various	Various	£303
Liraglutide	2x 18mg	£78.78	100%	£1,433
Linagliptin	28 x 5mg	£33.26	100%	£434
Metformin MR	28 x 1000mg	£2.55	41.14%	£34
Metformin MR	28 x 750mg	£6.40	1.45%	
Metformin MR	28 x 500mg	£1.68	57.52%	
Pioglitazone	28 x 45mg	£1.89	46.60%	£20
Pioglitazone	28 x 30mg	£1.37	38.94%	
Pioglitazone	28 x 15mg	£1.01	14.45%	
Saxagliptin	28 x 5mg	£31.60	92.59%	£412
Saxagliptin	28 x 2.5mg	£31.60	7.41%	
Semaglutide (injectable)	1 x 1mg	£73.25	52.58%	£937
Semaglutide (injectable)	1 x 0.5mg	£73.25	35.88%	
Semaglutide (injectable)	1 x 0.25mg	£73.25	11.53%	
Semaglutide (oral)	30 x 14mg	£78.48	52.58%	£955
Semaglutide (oral)	30 x 7mg	£78.48	35.88%	
Semaglutide (oral)	30 x 3mg	£78.48	11.53%	
Sitagliptin	28 x 100mg	£3.66	91.30%	£48
Sitagliptin	28 x 50mg	£3.52	7.37%	
Sitagliptin	28 x 25mg	£3.06	1.33%	
Vildagliptin	28 x 50mg	£28.57	100%	£373

(a) Daily units of insulin assumed to be 0.55 units per kg weight. Average weight of person with T2DM set at 87.22kg (average weight in overall T2DM population. For a basal-bolus preparations, basal preparations assumed to account for 55% of weighting, bolus preparations assumed to account for 45% of weighting,

Persistence with treatment

Treatment discontinuation was modelled by applying variable persistence rates within the first few years of treatment initiation. Persistence with GLP-1 agonists and SGLT-2 inhibitors were sourced from the SCI-Diabetes Registry in Scotland, while data for all other interventions except insulin were sourced from a study by McGovern 2018. Briefly, this study was a retrospective analysis based on a primary care cohort taken from the Royal College of General Practitioners Research and Surveillance Centre. The analysis focussed on new prescriptions for oral diabetes medicines excluding combination products in people with T2DM between January 2004 and July 2015 (n=42,810). Non-persistence was defined as a gap of ≥90 days between prescriptions. Persistence was defined as the period between treatment initiation and non-persistence. Importantly, this analysis presented results at a class level and results were available at year 1, 2 and 5. A linear trend between years 2 and 5 were assumed to fill in missing data. No evidence was identified for persistence with insulin and this was assumed to be 100% given its position towards the end of the treatment pathway.

Table 23. Persistence to treatment in years 1-5

	Year 1	Year 2	Year 3	Source
Canagliflozin	75.95%	71.15%	61.66%	SCI-Diabetes
Dapagliflozin	76.13%	71.19%	62.01%	
Empagliflozin	77.49%	73.46%	66.34%	
Ertugliflozin	82.49%	74.23%	68.15%	
Dulaglutide	80.21%	75.56%	67.03%	
Exenatide	58.12%	49.78%	36.89%	
Liraglutide	73.63%	67.09%	54.42%	
Semaglutide (oral)	61.39%	56.89%	53.58%	
Semaglutide (subcutaneous)	75.76%	71.93%	63.87%	
DPP-4 inhibitors	62.20%	45.50%	45.50%	McGovern 2018
Gliclazide	64.80%	51.30%	44.73%	
Insulin	100.00%	100.00%	100.00%	Assumption
Pioglitazone	61.20%	43.00%	33.90%	McGovern 2018
Metformin	70.10%	58.00%	51.87%	

Diabetic event costs

In NG28 2022, the committee stated a preference for diabetic event costs taken directly from a T2DM population since the costs of managing complications would likely be different in a T2DM population versus the general population. The model therefore incorporated costs taken from Alva 2015. These were based on costs directly reported in the paper, which were expected costs for a representative 60-year-old male. Alva 2015 also provided an algorithm that enables the calculation of dynamic healthcare costs that are dependent on variables such as age, gender, event type and history of events.

The UKPDS enables 5 different sets of event costs to be imputed at different age points, weighted by proportion of males and females in the CPRD data. Therefore, we selected event costs at 5 different ages. Imputed costs were calculated in the absence of any historical complications. The UKPDS Global beta model did not allow for differential cost based on other patient characteristics and thus were not calculated or inputted into the model. Costs calculated for males across different age profiles are presented below in Table 24. Costs for equivalent females were calculated by adding £218 to each individual cost as per the algorithm in Alva 2015 (Alva, et al., 2015).

Table 24. Management and complication costs

	Mean cost per year (£)*					
Input variables	**≤40 years**	**41-55 years**	**56-67 years**	**68-80 years**	**81+ years**	**Source**
Cost in the absence of complications						
No complication	£2,464	£3,180	£3,754	£4,279	£4,948	Alva 2015 (Alva, et al., 2015)
Annual cost of CVD complications						
MI 1st year	7,297	8,014	8,587	9,113	9,781	Alva 2015 (Alva, Gray, Mihaylova, Leal and Holman, 2015)
MI 2nd+ years	1,397	1,825	2,378	3,052	3,820	
Fatal MI	778	1,495	2,068	2,593	3,262	
IHD 1st year	13,320	14,037	14,610	15,135	15,804	
IHD 2nd+ years	1,423	1,869	2,449	3,163	3,987	
Fatal IHD	3,767	4,484	5,057	5,583	6,251	
Heart failure 1st year	3,906	4,622	5,196	5,721	6,390	
Heart failure 2nd+ years	1,935	2,446	3,091	3,854	4,698	
Fatal Heart failure	1,935	2,446	3,091	3,854	4,698	
Stroke 1st year	11,431	12,147	12,720	13,246	13,915	
Stroke 2nd+ years	1,461	1,881	2,438	3,140	3,971	
Fatal Stroke	3,774	4,490	5,064	5,589	6,258	
Renal Complications						
1st year	23,512	23,512	23,512	23,512	23,512	UK Renal Registry 22nd annual report(Registry), NICE guideline on Chronic Kidney Disease(National Institute for Health and Care Excellence, 2021)
2nd + years	9,375	9,375	9,375	9,375	9,375	
Blindness						
1st year	4,502	5,218	5,791	6,317	6,986	

	Mean cost per year (£)*					
Input variables	**≤40 years**	**41-55 years**	**56-67 years**	**68-80 years**	**81+ years**	**Source**
2nd+ years	967	1,191	1,501	1,913	2,428	Alva 2015(Alva, Gray, Mihaylova, Leal and Holman, 2015)
Ulcer						
Active ulcer	3,961	3,961	3,961	3,961	3,961	Kerr 2019(Kerr, et al., 2019)
Amputation						
1st year	11,912	12,629	13,202	13,727	14,396	Alva 2015(Alva, Gray, Mihaylova, Leal and Holman, 2015)
2nd + years	2,827	3,403	4,091	4,855	5,651	

**Costs were inflated to 2022/23 prices using the Unit Costs of Health and Social Care 2022 indices, where necessary*

Hospitalisation for heart failure costs for the heart failure population

Heart failure is treated as a state in the UKPDS Global beta model and thus a heart failure event can only occur once with the simulated individual incurring costs and QALY detriments for the remainder of the time they are alive. Because of this, individuals in the HF population, where HF is a preexisting condition at the initiation of the model, incur no further related events for this outcome. Costs and QALY detriments from HF are therefore identical across all the treatments considered in the model. As many treatments in the clinical review NMA had favourable point estimates for hospitalisation for heart failure (HHF), excluding any costs or QALYs for this outcome would strongly bias against such effective treatments.

To account for HHF in this population we took HHF event probabilities from the ASCVD population (the group that was considered most similar to HF for the HHF outcome) and estimated the number of events by multiplying this probability by the percentage of the cohort still alive in the model.

Administration and monitoring costs

The committee noted that some treatments will require increased costs associated with consumables and initiation time.

The committee felt that both sulfonylurea and insulin were likely to be associated with self-monitoring of blood glucose (SMBG). It was noted that the number of tests was likely to vary depending on whether the patient drove a vehicle which required increased tests, specifically 12 additional test with sulfonylureas and eight with insulin. Non-drivers were modelled to have the following SMBG rates, provided by the committee. The cost of each SMBG was assumed to be £0.26 as in the NICE diabetes in pregnancy guideline (NG3).(National Institute for Health and Care Excellence, 2015)

Table 25. Modelled SMBG tests per week

Treatment	SMBG per week
Sulfonylurea	4
Insulin	10.5

Insulin and GLP-1s also require injections and the cost of needles was accounted for in the model. NPH insulin was associated with 1 injection per day (NG28) and the GLP-1s were modelled as weekly or daily injections in accordance with the associated CVOT. The only GLP-1 which was not associated with additional consumable costs was oral semaglutide. The cost of each needle was assumed to be £0.05 in line with assumptions used in the NICE guideline on Type 1 diabetes (NG17).(National Institute for Health and Care Excellence, 2021) The committee believed this value to be reasonable and noted that needles with a cost of around £5 per 100 were widely available. Injectable semaglutide, dulaglutide and exenatide have needles included with them. Hence, additional needle costs were not assumed for these three injectable treatments.

Table 26. Additional needle costs

Treatment	Daily Injections
NPH Insulin	1
Liraglutide	1

Initiation costs for insulin and GLP-1 agonist were also applied. The method and setting for initiating these treatments vary in practice, however the committee agreed that initiation via a nurse would likely represent best practice and that the times on the following table were sufficient to initiate the treatment. Nursing costs were taken from PSSRU Unit Costs of Health and Social Care 2023(Personal Social Services Research Unit, 2023), at £49 and £59 per hour for a Band 6 and Band 7 nurse respectively.

Table 27. Administration resource use for insulins and GLP-1 agonists

Treatment	Initiation appointments	Total Time
GLP-1	2 x 20 minutes	40 minutes
Insulin	1 x 40 minutes + 5 x 20 minutes	2 hours 20 minutes

Table 28 summarises the consumable and staff costs used in the model.

Table 28. Administration costs included in the model

Treatment	Cost	Source
Needle	£0.05	NG17: type 1 diabetes in adults(National Institute for Health and Care Excellence, 2021)
SMBG	£0.26	NG3: diabetes in pregnancy(National Institute for Health and Care Excellence, 2015)
Band 7 nurse (hourly)	£68	PSSRU Unit Costs of Health and Social Care 2023(Personal Social Services Research Unit, 2023)
Band 6 nurse (hourly)	£57	
GLP-1 initiation	£38	
Insulin	£133	

Continuous glucose monitoring

The cost of continuous glucose monitoring (CGM) was calculated for insulin. Briefly, the resource impact report from NG28 was referenced wherein it mentions an annual cost of £910 for CGM.(National Institute for Health and Care Excellence, 2015) To calculate the proportion of people with T2DM who would require CGM, the annual cost was multiplied by

the proportion of people on multiple daily injections (0.8) as well as the proportion requiring CGM (0.463), which came to £337. This cost was added to the cost of insulin.

2.3.6 Quality of life (utilities)

Baseline utility

A T2DM baseline utility score of 0.772 was taken from a systematic literature review and meta-analysis by Redenz 2023.(Redenz, et al., 2023) We assumed that this score related to the mean age in our T2DM model cohort (67 years). A utility life table specific to T2DM was created by first calculating a utility multiplier for T2DM and applying that multiplier to the general population utilities as reported in Ara & Brazier 2010. (Ara, et al., 2010) We did this by dividing 0.772 by the general population utilities in males and females at age 67 years (0.805 and 0.784, respectively). Age- and sex-specific utility values were imputed into the model at five time points.

Table 29. Age- and sex-adjusted utility scores

Age point	Male	Female
35 years	0.894	0.873
50 years	0.849	0.829
62 years	0.803	0.782
73 years	0.752	0.732
87 years	0.677	0.656

Diabetic events

Utility decrements values for diabetic events were matched with those referenced in NG28 2022 (see Table 30).

Table 30. Utilities decrements associated with diabetic events

Diabetic event	Utility value	Reference
IHD	-0.090	Beaudet 2014
MI	-0.055	
HF	-0.108	
Stroke	-0.164	
Amputation	-0.280	
Ulceration	-0.170	
Retinopathy	-0.074	
EKD	-0.164	

Weight

A utility decrement of -0.0061 was assumed per 1 unit increase in BMI above 25kg/m^2. This value was taken from Bagust & Beale 2005 and is consistent with the approach taken for modelling weight in NG28.

Injection-related disutility not modelled

The previous guideline applied an injection-related disutility for the duration of treatment (assumed to be a lifetime). The committee did not believe this assumption was realistic, as in their experience any disutility associated with injecting tended to dissipate over time. It was also their experience that patients experienced a greater disutility with self-monitoring of blood glucose (SMBG) as the location for SMBG (fingertips) had a greater concentration of nerve-endings than the areas for injectable treatment. The frequency of injecting with SMBG tended to be multiple times per day, while injectable treatments were administered either once daily or weekly. The committee therefore agreed to exclude treatment-related injection disutility from the model.

2.3.7 Pooling of SGLT-2 inhibitors

All SGLT-2 inhibitors were run as separate interventions in the economic model, but are presented as a pooled estimate in the results. ICERs were estimated by weighting the costs and QALYs for the individual interventions by the frequency of people with a current prescription for each of the SGLT-2 inhibitors in each subgroup as reported in the CPRD data on the 1st September 2024. Frequency was reported separately for HF, CKD for stage 1-4, ASCVD and high risk of CVD groups. For the living with obesity, living with overweight and early onset groups the values were taken from the high-risk group. The weighting applied to the individual SGLT-2 results are presented in Table 31.

Table 31. Number and proportion of prescriptions for SGLT-2 inhibitors in people with type 2 diabetes

	ASCVD		HF		High risk of CVD		CKD 1-3,4	
	n	%	n	%	n	%	n	%
Canagliflozin	2,959	8.2	650	4.4	8,109	10.6	24,367	52.4
Dapagliflozin	20,924	57.6	10,904	73.2	39,709	51.8	16,532	35.5
Empagliflozin	12,376	34.1	3,340	22.4	28,800	37.6	5,614	12.1
Ertugliflozin	45	0.1	5	0.0	144	0.2	24	0.1

2.4 Sensitivity analyses

Since a probabilistic sensitivity analysis were not conducted, it was necessary to conduct an array of sensitivity analyses to test various assumption.

As treatment effects in the model were fixed, the committee were keen to view the effect of modelling CVOT outcomes reported from an externally conducted NMA. There were also fixed model parameters sourced from real-world evidence (RWE), namely maintenance of treatment-related weight loss and treatment persistence that the committee thought should also be modelled from a different source.

2.4.1 CVOT treatment effects taken from Shi 2023 NMA

A sensitivity analysis using the CVOT treatment effects from an external NMA (Shi 2023), comparing treatments included in this analysis at a class level. It was selected because it included all interventions of interest, reported treatment effects by three of the four subgroups being reviewed here (only the HF subgroup was not assessed) and was published recently. The Shi 2023 NMA included 816 RCTs with 471,038 participants. Evidence was searched up until October 2022. Interventions in this analysis were grouped

into their treatment class. Treatment effects for this sensitivity analysis were therefore identical for all interventions in the same treatment class.

2.4.2 Subsequent HF event costs set to zero

Sometimes a life-extending treatment is not cost-effective at any price for populations who have high care costs (e.g. people who need kidney dialysis). This seems to be the case for the HF subpopulation, which has high prevalence of comorbidities. A sensitivity analysis was conducted removing the background care costs for heart failure and recalculating the ICER.

2.4.3 Subsequent CVD costs set to zero

A further sensitivity analysis was conducted removing the background care costs for all CVD and renal events and recalculating the ICER. This was conducted only in subpopulations with high background care costs: ASCVD, CKD1-3, CKD4 and HF.

2.4.4 Persistence with treatment sourced from randomised controlled trials

The base case analysis sourced persistence to treatment with GLP-1 agonists and SGLT-2 inhibitors from the SCI-Diabetes Registry and metformin, DPP-4 inhibitors, gliclazide and pioglitazone from published literature. In the absence of any information of persistence with insulin, we assumed it to be 100%. The committee were interested in obtaining persistence data from clinical trials to match treatment effectiveness with treatment update. However, data related to treatment discontinuation were not extracted during the guideline clinical review. We therefore referred to select individual RCTs for our trial discontinuation data. We obtained data for all interventions except insulin and therefore maintained our assumption here that persistence to insulin was 100%. We applied annual discontinuation probabilities for the first three years of the model cycle to align it with model calibration period. Table 32 presents the trial discontinuation data.

Table 32. Discontinuation data sourced from RCTs

Drug	Trial/study name	Trial length (years)	Overall discontinuation (%)	Annual rate	Annual probability
Metformin	ADOPT	4.0	0.12	0.03	0.03
Canagliflozin	CANVAS	4.5	0.29	0.08	0.07
Dapagliflozin	DECLARE	4.2	0.21	0.06	0.05
Empagliflozin	EMPA-REG	3.1	0.23	0.09	0.08
Ertugliflozin	VERTIS-CV	3.5	0.10	0.03	0.03
Dulaglutide	REWIND	5.4	0.18	0.04	0.04
Exenatide	EXSCEL	3.2	0.43	0.18	0.16
Liraglutide	LEADER	3.8	0.10	0.03	0.03
Semglutide (oral)	PIONEER	1.9	0.12	0.06	0.06
Semaglutide (sub)	SUSTAIN-6	2.1	0.20	0.11	0.10
Alogliptin	EXAMINE	1.5	0.21	0.16	0.14
Linagliptin	CARMELINA	2.2	0.24	0.12	0.12
Saxagliptin	SAVOR-TIMI	2.1	0.18	0.10	0.09
Sitagliptin	TECOS	3	0.26	0.10	0.10

Drug	Trial/study name	Trial length (years)	Overall discontinuation (%)	Annual rate	Annual probability
Vildagliptin	Lukashevich 2013	0.5	0.09	0.20	0.18
Gliclazide	ADOPT	4	0.15	0.04	0.04
Insulin	NR	NR	NR	NR	NR
Pioglitazone	PROactive	3.9	0.30	0.09	0.09

Abbreviations: NR= not reported

2.4.5 Comparison between GLP-1 agonists and insulin

Current NICE guidelines position access to GLP-1 agonists ahead of insulin only in:

1. people with a BMI of 35kg/m2 or higher and specific psychological or other medical problems
2. people with a BMI lower than 35kg/m2 for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity related comorbidities.

The committee wanted to assess the cost effectiveness of GLP-1 agonists versus insulin to determine whether it could be positioned ahead of insulin in a wider population than the current guideline recommends.

2.4.6 Treatment-related weight loss sourced from SCI-Diabetes

In the base case analysis, treatment-related weight loss in years 2-5 were based on data extracted from the CPRD. In this sensitivity analysis, we utilised data obtained from the SCI-Diabetes Registry in Scotland. This is a pseudo anonymised database of diabetes records linked to datasets including prescribing information in all those with a diagnostic code for diabetes in Scotland. The data extract used contained adults aged 18 years and above alive with T2DM in Scotland between May 2007 and October 2022 who had used two classes of medicines at any time during this period. Change in weight in kilograms versus baseline were recorded up to 3 years. In the absence of data beyond this timepoint, we applied the assumptions around treatment waning from 3 years instead of the 5 years in the base case.

Table 33. Weight-change hazard ratios versus baseline weight for SGLT-2 inhibitors and GLP-1 agonists

	Year 2	Year 3
Canagliflozin	0.96	0.95
Dapagliflozin	0.95	0.95
Empagliflozin	0.95	0.95
Ertugliflozin	0.98	0.96
Dulaglutide	0.97	0.97
Exenatide	0.96	0.95
Liraglutide	0.96	0.96
Semaglutide (oral)	0.96	0.95
Semaglutide (subcutaneous)	0.93	0.93

2.4.7 Treatment-related weight loss assumed to last for a lifetime

Data from CPRD showed that weight loss with GLP-1 agonists and SGLT-2 inhibitors remained while on treatment up to four years from initiation. In the absence of data beyond four years, the base case analysis conservatively assumed that weight rebounded towards baseline from year five. A scenario analysis was therefore conducted wherein treatment-related weight loss was assumed to last for a lifetime.

2.4.8 Adverse events excluded

A sensitivity analysis exploring the effect of removing costs and disutilities associated with modelled adverse events was conducted.

2.4.9 Changes to liraglutide list price

As discussed above the price for liraglutide is expected to be volatile over the coming months for liraglutide with its patent expiring alternatives in the form of biosimilars entering the market causing changes in the list price. A threshold analysis was therefore conducted exploring the impact of price reductions at select price points in the final cost per QALY. This analysis was conducted in all populations of interest. ICERs were also reported for a reduction in price of 36% the reduction in price from the base-case on the NHS Electronic Drug Tariff (accessed 18/06/2025).

2.4.10 Triple therapy of metformin, SGLT-2 inhibitor and GLP-1 agonist

No evidence was identified, around the use of triple therapy (metformin, SGLT-2 inhibitor and GLP-1 agonist prescribed simultaneously) for people with T2DM, that was eligible for inclusion in the clinical evidence review. The committee were interested in the use of triple therapy in populations where they considered that intense intervention could have a large effect. The committee highlighted that SGLT-2 inhibitors and GLP-1 agonists work through different biological mechanisms and prescribing both, alongside metformin, would lead to additional benefits. The committee considered that the clinical impact of combining them would be additive such that the additional benefit from the addition of a GLP-1 to metformin monotherapy would be the same as if it was added to metformin in addition to a SGLT-2 inhibitor. Therefore, in the absence of evidence, the hazard ratios for the addition of a GLP-1 to metformin and a SGLT-2 inhibitor were assumed to be identical to the hazard ratio for the addition of a GLP-1 to metformin monotherapy. This assumption was made for all NFCVE and CVM inputs in the model.

Weight loss was assumed to follow the trajectory of the GLP-1 agonist and that weight loss effects would not be additive. Discontinuation was assumed to be the same as for the individual treatments allowing for the stopping of only part of the treatment. Whilst it was certain that individuals would be less likely to tolerate a triple therapy and discontinuation would be higher they were likely to drop only the part of the treatment combination most associated with any adverse outcomes.

2.5 Estimation of cost effectiveness

The widely used cost-effectiveness metric is the incremental cost-effectiveness ratio (ICER). This is calculated by dividing the difference in costs associated with 2 alternatives by the difference in QALYs. The decision rule then applied is that if the ICER falls below a given cost per QALY threshold the result is considered to be cost effective. If both costs are lower and QALYs are higher the option is said to dominate and an ICER is not calculated.

$$ICER = \frac{Costs(B) - Costs(A)}{QALYs(B) - QALYs(A)}$$ Where: Costs(A) = total costs for option A; QALYs(A) = total QALYs for option A	Cost effective if: • ICER < Threshold

When there are more than 2 comparators, as in this analysis, options must be ranked in order of increasing cost then options ruled out by dominance or extended dominance before calculating ICERs excluding these options. An option is said to be dominated, and ruled out, if another intervention is less costly and more effective. An option is said to be extendedly dominated if a combination of 2 other options would prove to be less costly and more effective.

It is also possible, for a particular cost-effectiveness threshold, to re-express cost-effectiveness results in term of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs (formula below). The decision rule then applied is that the comparator with the highest NMB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost.

$$Net\ Monetary\ Benefit(X) = \left(QALYs(X) \times \lambda\right) - Costs(X)$$ *Where: λ = threshold (£20,000 per QALY gained)*	Cost effective if: • Highest net benefit

Both methods of determining cost effectiveness will identify exactly the same optimal strategy. For ease of computation NMB is used in this analysis to identify the optimal strategy.

2.6 Interpreting results

NICE's report 'Our Principles' (Excellence, 2025) sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

As we have several interventions, we have used the NMB to rank the strategies on the basis of their relative cost effectiveness. The highest NMB identifies the optimal strategy for a cost effectiveness threshold of £20,000 per QALY gained.

3Results

3.1 Base case

The base-case analysis results are presented in Table 34 to Table 40.

For the ASCVD population (Table 34) subcutaneous semaglutide the most cost-effective intervention with an ICER of under £15k per QALY. This result is being driven by its large impact on strokes which is amongst the most common cardiovascular events which is also associated with a high cost. Subcutaneous semaglutide as triple therapy alongside metformin and had an ICER below £20k per QALY but the ICER was above £20k per QALY when compared to subcutaneous semaglutide and metformin in dual therapy. Pioglitazone was the second most cost-effective treatment but was associated with a smaller QALY gain than other interventions. The only other intervention that was cost-effective (compared to metformin monotherapy) assuming a £20k per QALY threshold was gliclazide although this had a small QALY gain of the equivalent of 2 days in perfect health.

Oral semaglutide had the largest incremental QALY value although that was with an ICER above £30k per QALY. The SGLT-2 inhibitor class had an ICER of just over £21k per QALY.

Table 34. Results: base-case analysis (ASCVD)

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£45,193	4.71	Reference	Reference	Reference	£0	5
SGLT-2 inhibitor	£50,430	4.95	£5,237	0.2394	£21,877	-£449	6
Dulaglutide	£49,724	4.83	£4,531	0.1211	£37,434	-£2,110	11
Exenatide	£49,601	4.87	£4,408	0.1672	£26,363	-£1,064	9
Liraglutide	£55,160	5.01	£9,967	0.3067	£32,499	-£3,833	16
Semaglutide; Oral	£63,340	5.30	£18,147	0.5962	£30,436	-£6,223	19
Semaglutide; Subcutaneous	£47,583	4.87	£2,390	0.1645	£14,529	£900	1
Alogliptin	£49,903	4.83	£4,711	0.1213	£38,835	-£2,285	14
Linagliptin	£46,522	4.73	£1,329	0.0243	£54,772	-£844	8
Saxagliptin	£46,727	4.67	£1,534	-0.0347	Dominated	-£2,227	13
Sitagliptin	£45,933	4.64	£740	-0.0701	Dominated	-£2,141	12
Vildagliptin	£46,124	4.72	£931	0.0103	£90,279	-£725	7
Gliclazide	£45,181	4.71	-£12	0.0058	Dominant	£127	4
Insulin	£49,966	4.70	£4,774	-0.0059	Dominated	-£4,892	17
Pioglitazone	£46,232	4.79	£1,039	0.0837	£12,422	£634	2
SGLT-2i + Dulaglutide	£54,982	5.05	£9,789	0.3417	£28,647	-£2,955	15
SGLT-2i + Exenatide	£54,534	5.10	£9,341	0.3908	£23,901	-£1,525	10

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
SGLT-2i + Liraglutide	£61,350	5.25	£16,157	0.5398	£29,931	-£5,361	18
SGLT-2i + Semaglutide; Oral	£71,236	5.56	£26,043	0.8557	£30,435	-£8,929	20
SGLT-2i + Semaglutide; Subcutaneous	£51,709	5.05	£6,516	0.3406	£19,134	£295	3

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

The base-case results for CKD 1-3 (Table 35) show the SGLT-2 inhibitor class as the most cost-effective intervention with an ICER of below £15k per QALY. Oral semaglutide was associated with the largest gain in QALYs but with an ICER above £28k per QALY. Pioglitazone and gliclazide were the only other two interventions which were cost-effective compared to metformin monotherapy at an assumed £20k per QALY threshold. No GLP-1 agonist had an ICER below £25k per QALY.

Table 35. Results: base-case analysis (CKD 1-3)

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£41,595	5.60	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£45,538	5.86	£3,943	0.27	£14,716	£1,416	1
Dulaglutide	£46,613	5.69	£5,018	0.09	£53,197	-£3,132	11
Exenatide	£45,952	5.74	£4,358	0.15	£29,469	-£1,400	7
Liraglutide	£51,572	5.90	£9,978	0.30	£33,239	-£3,974	12
Semaglutide; Oral	£57,648	6.15	£16,054	0.55	£28,934	-£4,957	14
Semaglutide; Subcutaneous	£52,199	5.90	£10,604	0.30	£35,328	-£4,601	13
Alogliptin	£45,976	5.72	£4,382	0.13	£34,567	-£1,847	8
Linagliptin	£42,991	5.64	£1,397	0.04	£33,546	-£564	5
Saxagliptin	£43,336	5.55	£1,741	-0.04	Dominated	-£2,606	10
Sitagliptin	£42,230	5.52	£635	-0.08	Dominated	-£2,221	9
Vildagliptin	£42,669	5.61	£1,075	0.01	£94,453	-£847	6
Gliclazide	£41,547	5.59	-£47	0.00	SW Quadrant	£2	3
Insulin	£47,200	5.59	£5,605	-0.01	Dominated	-£5,758	15
Pioglitazone	£42,468	5.66	£874	0.07	£12,567	£517	2

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class
(b) Pairwise comparison between intervention plus metformin versus metformin alone
(c) INMB is calculated using a value of £20,000 per QALY
(d) Rank in descending order of INMB

For the CKD4 population (Table 36) the SGLT-2 inhibitor class is the most cost-effective intervention with an ICER of under £12k per QALY. Linagliptin and gliclazide are the only other two interventions which are cost-effective compared to standard care. Semaglutide oral is associated with the largest increase in QALYs but with an ICER of £33k per QALY.

Table 36. Results: base-case analysis (CKD 4)

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Standard Care	£34,466	3.39	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£37,847	3.68	£3,381	0.29	£11,666	£2,415	1
Dulaglutide	£38,254	3.50	£3,787	0.11	£33,030	-£1,494	8
Exenatide	£37,723	3.53	£3,257	0.15	£22,053	-£303	6
Liraglutide	£41,390	3.61	£6,924	0.22	£31,097	-£2,471	11
Semaglutide; Oral	£50,592	3.87	£16,125	0.49	£33,196	-£6,410	15
Semaglutide; Subcutaneous	£43,075	3.61	£8,609	0.23	£37,838	-£4,059	14
Alogliptin	£37,914	3.45	£3,447	0.07	£51,244	-£2,102	10
Linagliptin	£35,392	3.44	£926	0.05	£17,598	£126	2
Saxagliptin	£35,631	3.35	£1,164	-0.03	Dominated	-£1,857	9
Sitagliptin	£35,487	3.31	£1,020	-0.08	Dominated	-£2,562	12
Vildagliptin	£35,337	3.41	£871	0.02	£47,798	-£506	7
Gliclazide	£34,584	3.40	£118	0.01	£12,628	£69	3
Insulin	£38,225	3.39	£3,759	0.00	£1,711,758	-£3,715	13
Pioglitazone	£35,073	3.41	£606	0.03	£22,815	-£75	5

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west
(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class
(b) Pairwise comparison between intervention plus metformin versus metformin alone
(c) INMB is calculated using a value of £20,000 per QALY
(d) Rank in descending order of INMB

For the HF population (Table 37) subcutaneous semaglutide is the most cost-effective intervention with an ICER of £10k per QALY. The SGLT-2 inhibitor class has an ICER of £27k despite being the third most effective intervention in terms of QALYs gained. Sitagliptin and gliclazide were the only other interventions in which the ICER was below £20k per QALY. Sitagliptin was estimated to be cost saving and health improving compared to metformin monotherapy but it only had a small incremental QALY.

Table 37. Results: base-case analysis (HF)

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£47,554	3.133	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£50,709	3.250	£3,154	0.117	£26,919	-£811	6
Dulaglutide	£51,054	3.226	£3,500	0.093	£37,812	-£1,649	10
Exenatide	£50,975	3.242	£3,421	0.109	£31,320	-£1,236	9
Liraglutide	£52,777	3.294	£5,223	0.160	£32,571	-£2,016	12
Semaglutide; Oral	£61,055	3.489	£13,501	0.355	£37,993	-£6,394	14
Semaglutide; Subcutaneous	£49,246	3.298	£1,691	0.165	£10,274	£1,601	1
Alogliptin	£52,130	3.261	£4,575	0.128	£35,674	-£2,010	11
Linagliptin	£48,879	3.153	£1,325	0.020	£66,787	-£928	8
Saxagliptin	£48,215	3.123	£661	-0.010	Dominated	-£870	7
Sitagliptin	£46,779	3.151	-£776	0.018	Dominant	£1,127	2
Vildagliptin	£48,154	3.149	£600	0.015	£38,780	-£290	5
Gliclazide	£47,500	3.142	-£55	0.009	Dominant	£239	3
Insulin	£50,821	3.144	£3,266	0.011	£291,349	-£3,042	13
Pioglitazone	Contra-indicated						

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

In the high risk of CVD and living with obesity population (Table 38) SGLT-2 inhibitor class is the most cost-effective intervention with an ICER just below £20k per QALY. Metformin monotherapy is the most cost-effective intervention compared to all other interventions. The intervention ranked in third place, pioglitazone, is both more costly and less effective than metformin monotherapy. Subcutaneous semaglutide is the most cost-effective GLP-1 agonist but this has an ICER of £28k per QALY compared to metformin monotherapy.

Table 38. Results: base-case analysis (high risk of CVD and living with obesity)

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£51,289	8.38	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£56,013	8.62	£4,724	0.237	£19,942	£14	1
Dulaglutide	£59,067	8.51	£7,779	0.127	£61,348	-£5,243	13
Exenatide	£56,574	8.54	£5,285	0.151	£34,938	-£2,260	9
Liraglutide	£62,362	8.66	£11,073	0.271	£40,787	-£5,643	14
Semaglutide; Oral	£62,531	8.79	£11,242	0.406	£27,693	-£3,123	11
Semaglutide; Subcutaneous	£58,363	8.64	£7,074	0.252	£28,117	-£2,042	7
Alogliptin	£54,241	8.43	£2,953	0.043	£69,077	-£2,098	8
Linagliptin	£53,548	8.42	£2,259	0.034	£65,790	-£1,572	6
Saxagliptin	£53,194	8.28	£1,905	-0.101	Dominated	-£3,931	12
Sitagliptin	£51,061	8.24	-£228	-0.146	SW Quadrant	-£2,686	10
Vildagliptin	£52,955	8.39	£1,666	0.005	£326,586	-£1,564	5
Gliclazide	£51,452	8.38	£163	-0.006	Dominated	-£280	4
Insulin	£59,394	8.35	£8,105	-0.031	Dominated	-£8,716	15
Pioglitazone	£51,369	8.38	£80	-0.004	Dominated	-£158	3

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

In people with high risk of CVD and overweight (Table 39) pioglitazone is the only intervention which is cost-effective compared to metformin monotherapy with a small incremental QALY gain of 0.05. The SGLT-2 inhibitor class has an ICER just over £20k per QALY. Subcutaneous semaglutide is the GLP-1 agonist with the lowest ICER at £29k per QALY.

Table 39. Results: base-case analysis (high risk of CVD and living with overweight)

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£48,193	7.60	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£52,410	7.79	£4,218	0.18	£23,039	-£556	4
Dulaglutide	£55,285	7.70	£7,092	0.10	£71,570	-£5,110	13
Exenatide	£52,875	7.71	£4,682	0.10	£45,397	-£2,620	10
Liraglutide	£58,218	7.81	£10,025	0.21	£47,165	-£5,774	14
Semaglutide; Oral	£57,169	7.87	£8,976	0.27	£33,843	-£3,671	12
Semaglutide; Subcutaneous	£54,684	7.82	£6,491	0.22	£29,243	-£2,052	9
Alogliptin	£50,563	7.63	£2,370	0.03	£88,111	-£1,832	8
Linagliptin	£50,223	7.62	£2,030	0.02	£106,214	-£1,648	7
Saxagliptin	£49,999	7.53	£1,806	-0.07	Dominated	-£3,237	11
Sitagliptin	£47,825	7.52	-£368	-0.09	SW Quadrant	-£1,367	5
Vildagliptin	£49,788	7.61	£1,596	0.01	£159,244	-£1,395	6
Gliclazide	£48,469	7.61	£276	0.01	£40,612	-£140	3
Insulin	£55,825	7.59	£7,632	-0.01	Dominated	-£7,796	15
Pioglitazone	£48,325	7.65	£132	0.05	£2,568	£898	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

In the under 40 years of age population (Table 40) only gliclazide and pioglitazone are cost-effective to metformin monotherapy although with a small QALY increment. SGLT-2 inhibitor class is ranked 4th with an ICER above 28k. The highest ranked GLP-1 agonist, exenatide has an ICER of £77k significantly above the value at which NICE usually recommend interventions.

Table 40. Results: base-case analysis (aged under 40 years)

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£75,441	16.18	Reference	Reference	Reference	£0	3
SGLT-2 inhibitor	£82,329	16.43	£6,888	0.25	£28,056	-£1,978	4
Dulaglutide	£88,632	16.31	£13,191	0.13	£102,108	-£10,607	16
Exenatide	£83,329	16.29	£7,888	0.11	£73,521	-£5,742	11
Liraglutide	£92,931	16.48	£17,491	0.29	£59,398	-£11,601	17
Semaglutide; Oral	£89,433	16.54	£13,992	0.35	£39,537	-£6,914	12
Semaglutide; Subcutaneous	£87,036	16.41	£11,595	0.23	£50,900	-£7,039	13
Alogliptin	£79,133	16.20	£3,692	0.02	£191,240	-£3,306	8
Linagliptin	£79,458	16.22	£4,017	0.04	£99,942	-£3,213	7
Saxagliptin	£78,596	16.06	£3,156	-0.13	Dominated	-£5,700	10
Sitagliptin	£74,860	16.05	-£581	-0.14	SW Quadrant	-£2,144	5
Vildagliptin	£78,436	16.20	£2,996	0.02	£197,044	-£2,691	6
Gliclazide	£75,798	16.20	£358	0.02	£18,100	£38	2
Insulin	£89,694	16.16	£14,254	-0.03	Dominated	-£14,833	20
Pioglitazone	£75,581	16.20	£141	0.02	£7,212	£250	1
SGLT-2i + Dulaglutide	£96,716	16.64	£21,275	0.45	£46,884	-£12,199	18
SGLT-2i + Exenatide	£90,073	16.64	£14,632	0.45	£32,394	-£5,598	9
SGLT-2i + Liraglutide	£101,262	16.77	£25,822	0.59	£44,015	-£14,089	19
SGLT-2i + Semaglutide; Oral	£97,310	16.82	£21,869	0.63	£34,533	-£9,204	15
SGLT-2i + Semaglutide; Subcutaneous	£96,253	16.77	£20,812	0.59	£35,552	-£9,104	14

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

3.2 Sensitivity analyses

The results of the sensitivity analyses undertaken (described in full in Section 2.4 above) are presented below.

3.2.1 CVOT treatment effects from Shi 2023 NMA

This analysis replaces the treatment effects estimated in the accompanying NMA with class level effect estimates from Shi 2023. (Table 41 to Table 47)

For the SGLT-2 inhibitors the ICER remained the same side of £20k per QALY as for the base-case in all analyses

ASCVD

Compared to the base-case the SGLT-2 inhibitor class is less expensive but with lower incremental QALYs. The ICER has reduced to below £20k per QALY. Its ranking has improved from sixth place to second place. The only intervention which performed better was sitagliptin. Sitagliptin was cost increasing and health decreasing compared to metformin monotherapy in the base-case.

Subcutaneous semaglutide which has an ICER below £20k per QALY in the base-case has an ICER above £20k per QALY in this sensitivity analysis.

Table 41. Results: ASCVD

Treatment[(a)]	Cost[(b)]	QALY [(b)]	Inc. cost[(b)]	Inc. QALYs[(b)]	ICER[(b)]	INMB[(c)]	Rank [(d)]
Metformin	£45,193	4.71	Reference	Reference	Reference	£0	3
SGLT-2 inhibitor	£48,343	4.89	£3,150	0.1794	£17,564	£437	2
Dulaglutide	£51,031	4.89	£5,839	0.1811	£32,233	-£2,216	13
Exenatide	£49,531	4.90	£4,338	0.1894	£22,905	-£550	7
Liraglutide	£52,445	4.89	£7,252	0.1852	£39,149	-£3,547	14
Semaglutide; Oral	£50,065	4.89	£4,872	0.1859	£26,206	-£1,154	11
Semaglutide; Subcutaneous	£50,475	4.89	£5,282	0.1858	£28,433	-£1,567	12
Alogliptin	£45,980	4.72	£787	0.0171	£45,903	-£444	5
Linagliptin	£46,174	4.72	£981	0.0157	£62,625	-£668	9
Saxagliptin	£46,188	4.73	£995	0.0191	£51,964	-£612	8
Sitagliptin	£44,812	4.71	-£380	0.0082	Dominant	£544	1
Vildagliptin	£45,920	4.72	£727	0.0138	£52,689	-£451	6
Gliclazide	£45,127	4.70	-£66	-0.0059	SW Quadrant	-£53	4
Insulin	£45,856	4.54	£663	-0.1709	Dominated	-£4,080	15
Pioglitazone	£47,139	4.77	£1,946	0.0592	£32,891	-£763	10

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class
(b) Pairwise comparison between intervention plus metformin versus metformin alone
(c) INMB is calculated using a value of £20,000 per QALY
(d) Rank in descending order of INMB

CKD 1-3

SGLT-2 inhibitors class remains the most cost-effective intervention with a marginally lower ICER compared to the base-case. Gliclazide which was cost-effective compared to metformin monotherapy in the base-case is now no-longer cost-effective when directly compared.

Table 42. Results: CKD 1-3

Treatment[(a)]	Cost[(b)]	QALY [(b)]	Inc. cost[(b)]	Inc. QALYs[(b)]	ICER[(b)]	INMB[(c)]	Rank [(d)]
Metformin	£41,595	5.60	Reference	Reference	Reference	£0	3
SGLT-2 inhibitor	£44,318	5.79	£2,724	0.19	£14,316	£1,081	1
Dulaglutide	£47,485	5.77	£5,890	0.17	£34,320	-£2,458	13
Exenatide	£45,529	5.77	£3,935	0.17	£22,745	-£475	7
Liraglutide	£48,937	5.76	£7,343	0.17	£43,822	-£3,991	14
Semaglutide; Oral	£46,194	5.76	£4,600	0.16	£28,143	-£1,331	11
Semaglutide; Subcutaneous	£46,683	5.75	£5,088	0.15	£32,970	-£2,002	12
Alogliptin	£42,463	5.62	£868	0.02	£36,697	-£395	5
Linagliptin	£42,704	5.61	£1,109	0.02	£58,797	-£732	10
Saxagliptin	£42,706	5.62	£1,111	0.02	£53,592	-£696	8
Sitagliptin	£41,250	5.62	-£344	0.03	Dominant	£847	2
Vildagliptin	£42,475	5.62	£880	0.02	£42,956	-£470	6
Gliclazide	£41,582	5.58	-£13	-0.01	SW Quadrant	-£263	4
Insulin	£43,388	5.39	£1,794	-0.20	Dominated	-£5,824	15
Pioglitazone	£43,319	5.65	£1,724	0.05	£33,592	-£698	9

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2
(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class
(b) Pairwise comparison between intervention plus metformin versus metformin alone
(c) INMB is calculated using a value of £20,000 per QALY
(d) Rank in descending order of INMB

CKD 4

The SGLT-2 inhibitor class remains the most cost-effective intervention but with a marginally lower ICER compared to the base-case results.

Table 43. Results: CKD 4

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£34,466	3.39	Reference	Reference	Reference	£0	5
SGLT-2 inhibitor	£37,120	3.63	£2,654	0.24	£11,057	£2,146	1
Dulaglutide	£38,886	3.57	£4,419	0.18	£24,587	-£824	12
Exenatide	£37,637	3.56	£3,170	0.18	£17,850	£382	3
Liraglutide	£40,008	3.57	£5,541	0.18	£30,156	-£1,866	14
Semaglutide; Oral	£38,131	3.57	£3,664	0.18	£19,977	£4	4
Semaglutide; Subcutaneous	£38,605	3.58	£4,138	0.19	£21,940	-£366	11
Alogliptin	£35,122	3.42	£656	0.03	£22,730	-£79	6
Linagliptin	£35,333	3.42	£867	0.03	£27,911	-£246	10
Saxagliptin	£35,285	3.42	£819	0.03	£28,482	-£244	9
Sitagliptin	£34,285	3.42	-£182	0.03	Dominant	£825	2
Vildagliptin	£35,192	3.42	£725	0.03	£22,969	-£94	7
Gliclazide	£34,619	3.39	£152	0.00	Dominated	-£181	8
Insulin	£35,978	3.31	£1,511	-0.07	Dominated	-£2,993	15
Pioglitazone	£35,361	3.38	£895	-0.01	Dominated	-£1,114	13

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

HF

For the HF population subcutaneous semaglutide which was the most cost-effective treatment in the base-case now has an ICER above £20k per QALY and ranks in 11th place. Sitagliptin becomes the most cost-effective treatment and is the only intervention with an ICER below £20k per QALY when directly compared to metformin monotherapy. The ICER for the SGLT-2 inhibitor class drops slightly but is still above £20k per QALY.

Table 44. Results: HF

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£47,554	3.133	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£50,739	3.252	£3,185	0.119	£26,868	-£814	9
Dulaglutide	£51,890	3.259	£4,335	0.126	£34,470	-£1,820	12
Exenatide	£50,893	3.259	£3,338	0.126	£26,435	-£813	8
Liraglutide	£52,992	3.262	£5,438	0.129	£42,212	-£2,861	14
Semaglutide; Oral	£51,216	3.253	£3,662	0.120	£30,616	-£1,270	10
Semaglutide; Subcutaneous	£51,578	3.270	£4,024	0.137	£29,445	-£1,291	11
Alogliptin	£48,060	3.151	£505	0.018	£28,188	-£147	5
Linagliptin	£48,182	3.149	£627	0.016	£39,946	-£313	7
Saxagliptin	£48,173	3.149	£619	0.016	£39,186	-£303	6
Sitagliptin	£47,227	3.152	-£327	0.019	Dominant	£698	1
Vildagliptin	£47,948	3.148	£393	0.014	£27,325	-£105	4
Gliclazide	£47,686	3.139	£131	0.006	£22,149	-£13	3
Insulin	£47,783	3.053	£229	-0.081	Dominated	-£1,839	13

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

High risk of CVD and living with obesity

For the high risk of CVD and living with obesity population the SGLT-2 inhibitor class becomes the second most cost-effective intervention behind sitagliptin and was the only intervention with an ICER that was on different sides of £20k per QALY between this sensitivity analysis and the base-case.

Table 45. Results: high risk of CVD and living with obesity

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£51,289	8.38	Reference	Reference	Reference	£0	3
SGLT-2 inhibitor	£55,487	8.61	£4,198	0.230	£18,242	£405	2
Dulaglutide	£59,314	8.56	£8,025	0.175	£45,867	-£4,526	13
Exenatide	£56,554	8.58	£5,265	0.199	£26,446	-£1,283	6
Liraglutide	£61,584	8.58	£10,295	0.197	£52,202	-£6,351	14
Semaglutide; Oral	£57,938	8.58	£6,649	0.199	£33,354	-£2,662	11
Semaglutide; Subcutaneous	£58,997	8.61	£7,708	0.221	£34,931	-£3,295	12
Alogliptin	£52,885	8.40	£1,596	0.018	£86,749	-£1,228	5
Linagliptin	£53,341	8.40	£2,053	0.015	£134,638	-£1,748	10
Saxagliptin	£53,199	8.40	£1,910	0.017	£113,252	-£1,573	9
Sitagliptin	£51,274	8.41	-£15	0.030	Dominant	£615	1
Vildagliptin	£52,977	8.40	£1,689	0.019	£90,167	-£1,314	7
Gliclazide	£51,504	8.37	£216	-0.014	Dominated	-£499	4
Insulin	£58,150	8.28	£6,861	-0.101	Dominated	-£8,890	15
Pioglitazone	£51,351	8.31	£62	-0.073	Dominated	-£1,524	8

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

High risk of CVD and living with overweight

For the CVD and living with overweight population pioglitazone which was the most cost-effective intervention in the base-case is now ranked fourth below metformin monotherapy. The ICER for the SGLT-2 inhibitor class decreases slightly but is still above £20k per QALY. Sitagliptin becomes the most cost-effective intervention becoming both cost saving and health improving.

Table 46. Results: high risk of CVD and living with overweight

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£48,193	7.60	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£51,986	7.78	£3,794	0.18	£21,299	-£231	3
Dulaglutide	£55,564	7.75	£7,371	0.15	£49,351	-£4,384	13
Exenatide	£52,871	7.75	£4,678	0.15	£31,473	-£1,705	10
Liraglutide	£57,546	7.75	£9,353	0.15	£62,487	-£6,360	14
Semaglutide; Oral	£54,157	7.75	£5,964	0.15	£40,317	-£3,005	11
Semaglutide; Subcutaneous	£55,067	7.76	£6,874	0.16	£43,983	-£3,748	12
Alogliptin	£49,673	7.63	£1,480	0.02	£61,865	-£1,001	6
Linagliptin	£50,100	7.62	£1,908	0.02	£90,104	-£1,484	9
Saxagliptin	£50,022	7.62	£1,829	0.02	£83,545	-£1,391	8
Sitagliptin	£48,094	7.63	-£99	0.02	Dominant	£556	1
Vildagliptin	£49,765	7.62	£1,572	0.02	£87,211	-£1,212	7
Gliclazide	£48,449	7.59	£257	-0.01	Dominated	-£430	5
Insulin	£54,651	7.52	£6,458	-0.08	Dominated	-£8,090	15
Pioglitazone	£48,337	7.59	£144	-0.01	Dominated	-£303	4

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

High risk of CVD and aged 40 years

For the population with high risk of CVD and under 40 years of age sitagliptin and pioglitazone the only intervention which has changed side of £20k per QALY between this sensitivity analysis and base-case. Pioglitazone which was the most cost-effective intervention in the base-case is now dominated (health decreasing and cost increasing) with sitagliptin becoming the most cost-effective treatment in this sensitivity analysis whilst being in fifth place in the base-case. The ICERs for SGLT-2 inhibitor class have decreased slightly but remain above £20k per QALY.

Table 47. Results: aged under 40 years

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£75,441	16.18	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£82,117	16.43	£6,676	0.25	£26,787	-£1,692	5
Dulaglutide	£88,679	16.38	£13,238	0.20	£67,445	-£9,313	13
Exenatide	£83,380	16.37	£7,939	0.19	£42,341	-£4,189	10

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Liraglutide	£91,985	16.37	£16,545	0.19	£88,053	-£12,787	14
Semaglutide; Oral	£86,192	16.38	£10,751	0.20	£54,161	-£6,781	11
Semaglutide; Subcutaneous	£87,855	16.39	£12,414	0.20	£61,037	-£8,347	12
Alogliptin	£78,196	16.20	£2,755	0.02	£177,524	-£2,445	6
Linagliptin	£79,013	16.20	£3,572	0.02	£207,918	-£3,228	9
Saxagliptin	£78,759	16.20	£3,318	0.02	£220,643	-£3,017	8
Sitagliptin	£75,520	16.22	£80	0.03	£2,410	£580	1
Vildagliptin	£78,360	16.20	£2,919	0.01	£221,619	-£2,655	7
Gliclazide	£75,765	16.19	£324	0.01	£38,472	-£155	3
Insulin	£88,363	16.06	£12,923	-0.13	Dominated	-£15,466	15
Pioglitazone	£75,443	16.11	£2	-0.07	Dominated	-£1,473	4

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

3.2.2 Subsequent HF costs set to zero

The incremental cost versus metformin has fallen for all interventions. Subcutaneous semaglutide, sitagliptin and gliclazide remain the three interventions ranked higher than metformin. The SGLT-2 inhibitor has improved its ranking from sixth to fifth as a result of an ICER now slightly more than £21k per QALY.

Table 48. Results: HF

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£28,950	3.133	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£31,432	3.250	£2,482	0.117	£21,181	-£138	5
Dulaglutide	£32,039	3.226	£3,089	0.093	£33,376	-£1,238	12
Exenatide	£31,772	3.242	£2,822	0.109	£25,838	-£638	7
Liraglutide	£33,354	3.294	£4,404	0.160	£27,466	-£1,197	11
Semaglutide; Oral	£39,623	3.489	£10,673	0.355	£30,036	-£3,566	14
Semaglutide; Subcutaneous	£30,043	3.298	£1,092	0.165	£6,635	£2,200	1
Alogliptin	£32,527	3.261	£3,577	0.128	£27,887	-£1,012	10
Linagliptin	£30,157	3.153	£1,207	0.020	£60,837	-£810	8
Saxagliptin	£29,703	3.123	£753	-0.010	Dominated	-£962	9
Sitagliptin	£28,181	3.151	-£769	0.018	Dominant	£1,121	2
Vildagliptin	£29,509	3.149	£559	0.015	£36,153	-£250	6
Gliclazide	£28,854	3.142	-£96	0.009	Dominant	£280	3
Insulin	£32,143	3.144	£3,193	0.011	£284,854	-£2,969	13

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

3.2.3 Subsequent CVD costs set to zero

ASCVD

Oral semaglutide is now ranked first, it was previously ranked 15th. Subcutaneous semaglutide, which was ranked first in the base case is now ranked fourth; its ICER versus metformin has increased from £14,529 to £16,743. Pioglitazone is still ranked second. SGLT-2 inhibitors are now ranked third with an ICER of £14,360 per QALY gained. Whereas gliclazide was previously ranked third in the base case, it now ranks fifth. Exenatide now ranks sixth, followed by metformin in seventh.

Table 49. Results: ASCVD

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£19,937	4.71	Reference	Reference	Reference	£0	7
SGLT-2 inhibitor	£23,375	4.95	£3,438	0.2394	£14,360	£1,350	3
Dulaglutide	£24,163	4.83	£4,226	0.1211	£34,914	-£1,805	13
Exenatide	£23,241	4.87	£3,304	0.1672	£19,759	£40	6
Liraglutide	£27,583	5.01	£7,647	0.3067	£24,933	-£1,513	12
Semaglutide; Oral	£30,048	5.30	£10,111	0.5962	£16,958	£1,814	1
Semaglutide; Subcutaneous	£22,691	4.87	£2,754	0.1645	£16,743	£536	4
Alogliptin	£22,534	4.83	£2,597	0.1213	£21,413	-£171	8
Linagliptin	£21,225	4.73	£1,288	0.0243	£53,110	-£803	10
Saxagliptin	£21,223	4.67	£1,286	-0.0347	Dominated	-£1,980	14
Sitagliptin	£20,024	4.64	£87	-0.0701	Dominated	-£1,489	11
Vildagliptin	£20,921	4.72	£984	0.0103	£95,474	-£778	9
Gliclazide	£19,970	4.71	£33	0.0058	£5,774	£82	5
Insulin	£24,759	4.70	£4,822	-0.0059	Dominated	-£4,940	15
Pioglitazone	£19,971	4.79	£35	0.0837	£414	£1,639	2

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(e) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(f) Pairwise comparison between intervention plus metformin versus metformin alone

(g) INMB is calculated using a value of £20,000 per QALY

(h) Rank in descending order of INMB

CKD1-3

SGLT-2 inhibitors and pioglitazone remain ranked first and second, respectively. Oral semaglutide is now ranked third, followed by metformin in fourth. In the base case, gliclazide was ranked third, being cheaper and less effective than metformin. Here, it is now dominated by metformin, given costs for metformin are now lower.

Table 50. Results: CKD1-3

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£30,200	5.60	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£33,736	5.86	£3,535	0.27	£13,195	£1,823	1
Dulaglutide	£35,341	5.69	£5,141	0.09	£54,495	-£3,254	14
Exenatide	£34,041	5.74	£3,840	0.15	£25,971	-£883	8
Liraglutide	£39,018	5.90	£8,817	0.30	£29,374	-£2,814	13

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Semaglutide; Oral	£40,755	6.15	£10,554	0.55	£19,022	£542	3
Semaglutide; Subcutaneous	£38,220	5.90	£8,020	0.30	£26,718	-£2,017	11
Alogliptin	£32,857	5.72	£2,656	0.13	£20,955	-£121	5
Linagliptin	£31,759	5.64	£1,558	0.04	£37,426	-£726	7
Saxagliptin	£31,470	5.55	£1,270	-0.04	Dominated	-£2,135	12
Sitagliptin	£29,832	5.52	-£368	-0.08	SW Quadrant	-£1,218	10
Vildagliptin	£31,383	5.61	£1,183	0.01	£103,954	-£955	9
Gliclazide	£30,290	5.59	£90	0.00	Dominated	-£135	6
Insulin	£35,879	5.59	£5,678	-0.01	Dominated	-£5,831	15
Pioglitazone	£30,258	5.66	£57	0.07	£821	£1,334	2

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(i) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(j) Pairwise comparison between intervention plus metformin versus metformin alone

(k) INMB is calculated using a value of £20,000 per QALY

(l) Rank in descending order of INMB

CKD4

In the base case analysis, only SGLT-2 inhibitors, linagliptin and gliclazide were ranked above metformin. Now, pioglitazone and exenatide are added to the list. SGLT-2 inhibitors are still ranked first. Pioglitazone and exenatide are now second and third, respectively, followed by linagliptin, gliclazide and metformin.

Table 51. Results: CKD4

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£22,752	3.39	Reference	Reference	Reference	£0	6
SGLT-2 inhibitor	£25,269	3.68	£2,517	0.29	£8,685	£3,279	1
Dulaglutide	£26,267	3.50	£3,515	0.11	£30,656	-£1,222	10
Exenatide	£25,425	3.53	£2,673	0.15	£18,103	£280	3
Liraglutide	£28,676	3.61	£5,924	0.22	£26,607	-£1,471	11
Semaglutide; Oral	£33,344	3.87	£10,593	0.49	£21,807	-£878	8
Semaglutide; Subcutaneous	£29,132	3.61	£6,380	0.23	£28,043	-£1,830	14
Alogliptin	£25,045	3.45	£2,294	0.07	£34,094	-£948	9
Linagliptin	£23,720	3.44	£969	0.05	£18,409	£84	4
Saxagliptin	£23,684	3.35	£933	-0.03	Dominated	-£1,625	12
Sitagliptin	£22,989	3.31	£237	-0.08	Dominated	-£1,779	13

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Vildagliptin	£23,599	3.41	£847	0.02	£46,520	-£483	7
Gliclazide	£22,869	3.40	£117	0.01	£12,620	£69	5
Insulin	£26,507	3.39	£3,755	0.00	£1,710,181	-£3,712	15
Pioglitazone	£22,829	3.41	£77	0.03	£2,905	£454	2

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(m) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(n) Pairwise comparison between intervention plus metformin versus metformin alone

(o) INMB is calculated using a value of £20,000 per QALY

(p) Rank in descending order of INMB

HF

Subcutaneous semaglutide and sitagliptin maintain rankings of first and second, respectively. Whereas gliclazide was ranked third in the base-case, it now ranks sixth, though still higher than metformin, which is ranked seventh. SGLT-2 inhibitors, alogliptin and oral semaglutide are now ranked above metformin and fill in the positions between third and fifth.

Table 52. Results: HF

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£13,585	3.133	Reference	Reference	Reference	£0	7
SGLT-2 inhibitor	£15,434	3.250	£1,849	0.117	£15,781	£494	3
Dulaglutide	£16,419	3.226	£2,834	0.093	£30,620	-£983	12
Exenatide	£15,805	3.242	£2,220	0.109	£20,322	-£35	8
Liraglutide	£17,598	3.294	£4,013	0.160	£25,025	-£806	11
Semaglutide; Oral	£20,329	3.489	£6,744	0.355	£18,980	£362	5
Semaglutide; Subcutaneous	£14,883	3.298	£1,298	0.165	£7,885	£1,995	1
Alogliptin	£15,754	3.261	£2,169	0.128	£16,910	£396	4
Linagliptin	£14,593	3.153	£1,008	0.020	£50,816	-£611	10
Saxagliptin	£14,395	3.123	£810	-0.010	Dominated	-£1,019	13
Sitagliptin	£13,065	3.151	-£520	0.018	Dominant	£871	2
Vildagliptin	£14,203	3.149	£618	0.015	£39,954	-£308	9
Gliclazide	£13,539	3.142	-£46	0.009	Dominant	£230	6
Insulin	£16,795	3.144	£3,210	0.011	£286,358	-£2,986	14

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(q) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(r) Pairwise comparison between intervention plus metformin versus metformin alone

(s) INMB is calculated using a value of £20,000 per QALY
(t) Rank in descending order of INMB

3.2.4 Persistence to treatment sourced from randomised controlled trials

Table 53 to Table 59 how the results when persistence data were sourced from randomised controlled trials. Compared to the base case, the incremental costs versus metformin were higher for all interventions except insulin. The incremental QALYs remained the same as the base case. Although this change caused movement in rankings between interventions, there were no instances where the ICER changed side of £20,000 per QALY.

Table 53. Results: ASCVD

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£45,283	4.71	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£50,969	4.95	£5,686	0.239	£23,750	-£898	5
Dulaglutide	£50,987	4.83	£5,704	0.121	£47,120	-£3,283	12
Exenatide	£50,968	4.87	£5,685	0.167	£33,999	-£2,341	9
Liraglutide	£58,497	5.01	£13,214	0.307	£43,085	-£7,080	14
Semaglutide; Oral	£65,381	5.30	£20,098	0.596	£33,709	-£8,174	15
Semaglutide; Subcutaneous	£48,144	4.87	£2,861	0.165	£17,394	£429	2
Alogliptin	£50,329	4.83	£5,046	0.121	£41,601	-£2,620	10
Linagliptin	£47,188	4.73	£1,905	0.024	£78,532	-£1,420	7
Saxagliptin	£47,485	4.67	£2,202	-0.035	Dominated	-£2,895	11
Sitagliptin	£46,017	4.64	£735	-0.070	Dominated	-£2,136	8
Vildagliptin	£46,400	4.72	£1,117	0.010	£108,315	-£911	6
Gliclazide	£45,383	4.71	£100	0.005	£17,266	£16	3
Insulin	£49,966	4.70	£4,684	-0.005	Dominated	-£4,802	13
Pioglitazone	£46,283	4.79	£1,001	0.083	£11,959	£673	1

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west
(u) All treatments have a background of metformin therapy. Treatments are listed in order of drug class
(v) Pairwise comparison between intervention plus metformin versus metformin alone
(w) INMB is calculated using a value of £20,000 per QALY
(x) Rank in descending order of INMB

Table 54. Results: CKD 1-3

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£41,703	5.60	Reference	Reference	Reference	£0	3
SGLT-2 inhibitor	£46,188	5.86	£4,485	0.27	£16,741	£873	1

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Dulaglutide	£48,099	5.69	£6,397	0.09	£67,810	-£4,510	11
Exenatide	£47,542	5.74	£5,840	0.15	£39,492	-£2,882	9
Liraglutide	£55,488	5.90	£13,786	0.30	£45,925	-£7,782	15
Semaglutide; Oral	£59,966	6.15	£18,263	0.55	£32,916	-£7,166	14
Semaglutide; Subcutaneous	£52,887	5.90	£11,184	0.30	£37,260	-£5,181	12
Alogliptin	£46,467	5.72	£4,765	0.13	£37,590	-£2,230	8
Linagliptin	£43,770	5.64	£2,067	0.04	£49,652	-£1,234	6
Saxagliptin	£44,224	5.55	£2,521	-0.04	Dominated	-£3,386	10
Sitagliptin	£42,329	5.52	£627	-0.08	Dominated	-£2,213	7
Vildagliptin	£42,983	5.61	£1,281	0.01	£112,579	-£1,053	5
Gliclazide	£41,785	5.59	£82	0.00	Dominated	-£128	4
Insulin	£47,200	5.59	£5,497	-0.01	Dominated	-£5,650	13
Pioglitazone	£42,529	5.66	£826	0.07	£11,881	£565	2

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 55. Results: CKD 4

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£34,530	3.39	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£38,260	3.68	£3,730	0.29	£12,870	£2,066	1
Dulaglutide	£39,165	3.50	£4,635	0.11	£40,427	-£2,342	8
Exenatide	£38,727	3.53	£4,197	0.15	£28,423	-£1,244	7
Liraglutide	£43,755	3.61	£9,225	0.22	£41,433	-£4,772	14
Semaglutide; Oral	£52,119	3.87	£17,590	0.49	£36,210	-£7,874	15
Semaglutide; Subcutaneous	£43,521	3.61	£8,991	0.23	£39,518	-£4,441	13
Alogliptin	£38,229	3.45	£3,699	0.07	£54,986	-£2,354	10
Linagliptin	£35,886	3.44	£1,356	0.05	£25,772	-£304	5
Saxagliptin	£36,183	3.35	£1,653	-0.03	Dominated	-£2,345	9
Sitagliptin	£35,548	3.31	£1,019	-0.08	Dominated	-£2,560	11
Vildagliptin	£35,549	3.41	£1,019	0.02	£55,955	-£655	6
Gliclazide	£34,729	3.40	£199	0.01	£21,381	-£13	3

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Insulin	£38,225	3.39	£3,696	0.00	£1,683,001	-£3,652	12
Pioglitazone	£35,109	3.41	£580	0.03	£21,810	-£48	4

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 56. Results: HF

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£47,610	3.133	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£51,074	3.250	£3,464	0.117	£29,564	-£1,121	6
Dulaglutide	£51,854	3.226	£4,244	0.093	£45,858	-£2,393	11
Exenatide	£51,866	3.242	£4,256	0.109	£38,970	-£2,072	9
Liraglutide	£54,810	3.294	£7,201	0.160	£44,908	-£3,994	13
Semaglutide; Oral	£62,370	3.489	£14,760	0.355	£41,538	-£7,653	14
Semaglutide; Subcutaneous	£49,627	3.298	£2,017	0.165	£12,253	£1,276	1
Alogliptin	£52,421	3.261	£4,811	0.128	£37,513	-£2,246	10
Linagliptin	£49,322	3.153	£1,712	0.020	£86,300	-£1,315	8
Saxagliptin	£48,711	3.123	£1,102	-0.010	Dominated	-£1,311	7
Sitagliptin	£46,835	3.151	-£775	0.018	Dominant	£1,126	2
Vildagliptin	£48,349	3.149	£739	0.015	£47,826	-£430	5
Gliclazide	£47,628	3.142	£18	0.009	£1,949	£166	3
Insulin	£50,821	3.144	£3,211	0.011	£286,421	-£2,987	12

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 57. Results: high risk of CVD and living with obesity

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£51,454	8.38	Reference	Reference	Reference	£0	1
SGLT-2 inhibitor	£56,913	8.62	£5,460	0.237	£23,046	-£722	4
Dulaglutide	£61,297	8.51	£9,843	0.127	£77,628	-£7,307	13
Exenatide	£58,887	8.54	£7,434	0.151	£49,145	-£4,409	10
Liraglutide	£68,088	8.66	£16,634	0.271	£61,272	-£11,205	15
Semaglutide; Oral	£65,690	8.79	£14,237	0.406	£35,068	-£6,117	12
Semaglutide; Subcutaneous	£59,313	8.64	£7,859	0.252	£31,238	-£2,827	9
Alogliptin	£54,931	8.43	£3,478	0.043	£81,355	-£2,623	7
Linagliptin	£54,680	8.42	£3,226	0.034	£93,949	-£2,539	6
Saxagliptin	£54,489	8.28	£3,035	-0.101	Dominated	-£5,062	11

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Sitagliptin	£51,205	8.24	-£248	-0.146	SW Quadrant	-£2,666	8
Vildagliptin	£53,391	8.39	£1,938	0.005	£379,921	-£1,836	5
Gliclazide	£51,807	8.38	£354	-0.006	Dominated	-£470	3
Insulin	£59,394	8.35	£7,940	-0.031	Dominated	-£8,551	14
Pioglitazone	£51,457	8.38	£3	-0.004	Dominated	-£82	2

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 58. Results: high risk of CVD and living with overweight

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£48,343	7.60	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£53,234	7.79	£4,891	0.18	£26,717	-£1,230	4
Dulaglutide	£57,319	7.70	£8,977	0.10	£90,588	-£6,995	13
Exenatide	£54,991	7.71	£6,648	0.10	£64,454	-£4,585	11
Liraglutide	£63,426	7.81	£15,083	0.21	£70,960	-£10,832	15
Semaglutide; Oral	£60,025	7.87	£11,682	0.27	£44,047	-£6,378	12
Semaglutide; Subcutaneous	£55,559	7.82	£7,216	0.22	£32,510	-£2,777	9
Alogliptin	£51,198	7.63	£2,855	0.03	£106,142	-£2,317	7
Linagliptin	£51,263	7.62	£2,920	0.02	£152,805	-£2,538	8
Saxagliptin	£51,192	7.53	£2,849	-0.07	Dominated	-£4,281	10
Sitagliptin	£47,958	7.52	-£385	-0.09	SW Quadrant	-£1,350	5
Vildagliptin	£50,195	7.61	£1,852	0.01	£184,871	-£1,652	6
Gliclazide	£48,794	7.61	£452	0.01	£66,439	-£316	3
Insulin	£55,825	7.59	£7,482	-0.01	Dominated	-£7,646	14
Pioglitazone	£48,407	7.65	£64	0.05	£1,237	£966	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 59. Results: aged under 40 years

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£75,746	16.18	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£83,918	16.43	£8,172	0.25	£33,282	-£3,261	6
Dulaglutide	£92,638	16.31	£16,891	0.13	£130,750	-£14,308	13
Exenatide	£87,373	16.29	£11,627	0.11	£108,370	-£9,481	11
Liraglutide	£103,180	16.48	£27,433	0.29	£93,163	-£21,544	15
Semaglutide; Oral	£94,823	16.54	£19,077	0.35	£53,905	-£11,999	12
Semaglutide; Subcutaneous	£88,661	16.41	£12,915	0.23	£56,693	-£8,359	10
Alogliptin	£80,310	16.20	£4,564	0.02	£236,377	-£4,178	7
Linagliptin	£81,430	16.22	£5,684	0.04	£141,414	-£4,880	8
Saxagliptin	£80,885	16.06	£5,138	-0.13	Dominated	-£7,683	9
Sitagliptin	£75,115	16.05	-£631	-0.14	SW Quadrant	-£2,094	4
Vildagliptin	£79,154	16.20	£3,408	0.02	£224,176	-£3,104	5
Gliclazide	£76,437	16.20	£691	0.02	£34,958	-£296	3
Insulin	£89,694	16.16	£13,948	-0.03	Dominated	-£14,528	14
Pioglitazone	£75,740	16.20	-£6	0.02	Dominant	£396	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

3.2.5 Comparison between GLP-1 agonists and insulin

Table 60 to Table 66 present a comparative analysis between GLP-1 agonists and insulin at an INMB threshold of £20k. Insulin was never ranked higher than fourth place. Subcutaneous semaglutide was the most cost-effective intervention in the ASCVD, living with obesity and overweight and HF populations. Exenatide was the most cost-effective intervention in all other populations.

Table 60. Results: ASCVD

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Insulin	£49,966	4.701	Reference	Reference	Reference	0	5

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Dulaglutide	£49,724	4.828	-£242	0.127	Dominant	£2,782	3
Exenatide	£49,601	4.874	-£365	0.173	Dominant	£3,828	2
Liraglutide	£55,160	5.013	£5,194	0.313	£16,614	£1,059	4
Semaglutide; Oral	£63,340	5.303	£13,374	0.602	£22,210	-£1,331	6
Semaglutide; Subcutaneous	£47,583	4.871	-£2,384	0.170	Dominant	£5,792	1

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus insulin plus metformin

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 61. Results: CKD 1-3

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Insulin	£47,200	5.59	Reference	Reference	Reference	£0	6
Dulaglutide	£46,613	5.69	-£587	0.10	Dominant	£2,626	2
Exenatide	£45,952	5.74	-£1,248	0.16	Dominant	£4,358	1
Liraglutide	£51,572	5.90	£4,372	0.31	£14,205	£1,784	3
Semaglutide; Oral	£57,648	6.15	£10,449	0.56	£18,576	£801	5
Semaglutide; Subcutaneous	£52,199	5.90	£4,999	0.31	£16,241	£1,157	4

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus insulin plus metformin

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 62. Results: CKD 4

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Insulin	£38,225	3.389	Reference	Reference	Reference	£0	4
Dulaglutide	£38,254	3.502	£28	0.112	£251	£2,221	2
Exenatide	£37,723	3.535	-£502	0.145	Dominant	£3,412	1
Liraglutide	£41,390	3.610	£3,165	0.220	£14,355	£1,244	3
Semaglutide; Oral	£50,592	3.873	£12,366	0.484	£25,573	-£2,695	6

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Semaglutide; Subcutaneous	£43,075	3.615	£4,850	0.225	£21,525	-£344	5

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus insulin plus metformin

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 63. Results: HF

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Insulin	£50,821	3.144	Reference	Reference	Reference	0	5
Dulaglutide	£51,054	3.226	£233	0.081	£2,870	£1,393	3
Exenatide	£50,975	3.242	£155	0.098	£1,578	£1,806	2
Liraglutide	£52,777	3.294	£1,956	0.149	£13,118	£1,026	4
Semaglutide; Oral	£61,055	3.489	£10,234	0.344	£29,740	-£3,352	6
Semaglutide; Subcutaneous	£49,246	3.298	-£1,575	0.153	Dominant	£4,643	1

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus insulin plus metformin

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 64. Results: high risk of CVD and living with obesity

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Insulin	£59,394	8.354	Reference	Reference	Reference	0	6
Dulaglutide	£59,067	8.511	-£326	0.157	Dominant	£3,473	4
Exenatide	£56,574	8.536	-£2,820	0.182	Dominant	£6,457	2
Liraglutide	£62,362	8.656	£2,968	0.302	£9,826	£3,073	5
Semaglutide; Oral	£62,531	8.790	£3,137	0.437	£7,187	£5,593	3
Semaglutide; Subcutaneous	£58,363	8.636	-£1,031	0.282	Dominant	£6,674	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus insulin plus metformin

(c) INMB is calculated using a value of £20,000 per QALY
(d) Rank in descending order of INMB

Table 65. Results: high risk of CVD and living with overweight

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Insulin	£55,825	7.594	Reference	Reference	Reference	0	6
Dulaglutide	£55,285	7.701	-£540	0.11	Dominant	£2,685	4
Exenatide	£52,875	7.705	-£2,950	0.11	Dominant	£5,176	2
Liraglutide	£58,218	7.815	£2,393	0.22	£10,843	£2,021	5
Semaglutide; Oral	£57,169	7.867	£1,344	0.27	£4,915	£4,124	3
Semaglutide; Subcutaneous	£54,684	7.824	-£1,141	0.23	Dominant	£5,744	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2
(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class
(b) Pairwise comparison between intervention plus metformin versus insulin plus metformin
(c) INMB is calculated using a value of £20,000 per QALY
(d) Rank in descending order of INMB

Table 66. Results: aged under 40 years

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Insulin	£89,694	16.155	Reference	Reference	Reference	£0	6
Dulaglutide	£88,632	16.313	-£1,063	0.158	Dominant	£4,226	4
Exenatide	£83,329	16.291	-£6,366	0.136	Dominant	£9,091	1
Liraglutide	£92,931	16.478	£3,237	0.323	£10,008	£3,232	5
Semaglutide; Oral	£89,433	16.538	-£262	0.383	Dominant	£7,919	2
Semaglutide; Subcutaneous	£87,036	16.412	-£2,658	0.257	Dominant	£7,794	3

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2
(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class
(b) Pairwise comparison between intervention plus metformin versus insulin plus metformin
(c) INMB is calculated using a value of £20,000 per QALY
(d) Rank in descending order of INMB

3.2.6 Treatment-related weight loss sourced from SCI-Diabetes

Table 67 to Table 73 show the results when the weight change estimates in the first four years with GLP-1 agonists and SGLT-2 inhibitors were sourced from SCI-Diabetes. The results across all populations remain similar to what was reported in the base case.

Table 67. Results: ASCVD

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£45,193	4.71	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£50,430	4.95	£5,237	0.2394	£21,875	-£449	5
Dulaglutide	£49,724	4.83	£4,531	0.1209	£37,494	-£2,114	9
Exenatide	£49,601	4.87	£4,408	0.1676	£26,305	-£1,057	8
Liraglutide	£55,160	5.01	£9,967	0.3067	£32,495	-£3,833	13
Semaglutide; Oral	£63,340	5.30	£18,147	0.5964	£30,430	-£6,220	15
Semaglutide; Subcutaneous	£47,583	4.87	£2,390	0.1647	£14,516	£903	1
Alogliptin	£49,903	4.83	£4,711	0.1213	£38,835	-£2,285	12
Linagliptin	£46,522	4.73	£1,329	0.0243	£54,772	-£844	7
Saxagliptin	£46,727	4.67	£1,534	-0.0347	Dominated	-£2,227	11
Sitagliptin	£45,933	4.64	£740	-0.0701	Dominated	-£2,141	10
Vildagliptin	£46,124	4.72	£931	0.0103	£90,279	-£725	6
Gliclazide	£45,181	4.71	-£12	0.0058	Dominant	£127	3
Insulin	£49,966	4.70	£4,774	-0.0059	Dominated	-£4,892	14
Pioglitazone	£46,232	4.79	£1,039	0.0837	£12,422	£634	2

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 68. Results: CKD 1-3

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£41,595	5.60	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£45,538	5.86	£3,943	0.27	£14,718	£1,415	1
Dulaglutide	£46,613	5.69	£5,018	0.09	£53,308	-£3,135	11
Exenatide	£45,952	5.74	£4,358	0.15	£29,395	-£1,393	7
Liraglutide	£51,572	5.90	£9,978	0.30	£33,235	-£3,973	12
Semaglutide; Oral	£57,648	6.15	£16,054	0.55	£28,927	-£4,954	14
Semaglutide; Subcutaneous	£52,199	5.90	£10,604	0.30	£35,310	-£4,598	13
Alogliptin	£45,976	5.72	£4,382	0.13	£34,567	-£1,847	8
Linagliptin	£42,991	5.64	£1,397	0.04	£33,546	-£564	5
Saxagliptin	£43,336	5.55	£1,741	-0.04	Dominated	-£2,606	10
Sitagliptin	£42,230	5.52	£635	-0.08	Dominated	-£2,221	9
Vildagliptin	£42,669	5.61	£1,075	0.01	£94,453	-£847	6
Gliclazide	£41,547	5.59	-£47	0.00	SW Quadrant	£2	3
Insulin	£47,200	5.59	£5,605	-0.01	Dominated	-£5,758	15
Pioglitazone	£42,468	5.66	£874	0.07	£12,567	£517	2

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 69. Results: CKD 4

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£34,466	3.39	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£37,847	3.68	£3,381	0.29	£11,691	£2,403	1
Dulaglutide	£38,254	3.50	£3,787	0.11	£33,086	-£1,498	8
Exenatide	£37,723	3.54	£3,257	0.15	£21,998	-£296	6
Liraglutide	£41,390	3.61	£6,924	0.22	£31,091	-£2,470	11
Semaglutide; Oral	£50,592	3.87	£16,125	0.49	£33,187	-£6,407	15
Semaglutide; Subcutaneous	£43,075	3.61	£8,609	0.23	£37,812	-£4,055	14
Alogliptin	£37,914	3.45	£3,447	0.07	£51,244	-£2,102	10
Linagliptin	£35,392	3.44	£926	0.05	£17,598	£126	2

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Saxagliptin	£35,631	3.35	£1,164	-0.03	Dominated	-£1,857	9
Sitagliptin	£35,487	3.31	£1,020	-0.08	Dominated	-£2,562	12
Vildagliptin	£35,337	3.41	£871	0.02	£47,798	-£506	7
Gliclazide	£34,584	3.40	£118	0.01	£12,628	£69	3
Insulin	£38,225	3.39	£3,759	0.00	£1,711,758	-£3,715	13
Pioglitazone	£35,073	3.41	£606	0.03	£22,815	-£75	5

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 70. Results: HF

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£47,554	3.133	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£50,709	3.250	£3,154	0.117	£27,030	-£820	6
Dulaglutide	£51,054	3.222	£3,500	0.089	£39,257	-£1,717	10
Exenatide	£50,975	3.242	£3,421	0.109	£31,299	-£1,235	9
Liraglutide	£52,777	3.293	£5,223	0.160	£32,683	-£2,027	12
Semaglutide; Oral	£61,055	3.489	£13,501	0.355	£37,979	-£6,391	14
Semaglutide; Subcutaneous	£49,246	3.299	£1,691	0.165	£10,224	£1,617	1
Alogliptin	£52,130	3.261	£4,575	0.128	£35,674	-£2,010	11
Linagliptin	£48,879	3.153	£1,325	0.020	£66,787	-£928	8
Saxagliptin	£48,215	3.123	£661	-0.010	Dominated	-£870	7
Sitagliptin	£46,779	3.151	-£776	0.018	Dominant	£1,127	2
Vildagliptin	£48,154	3.149	£600	0.015	£38,780	-£290	5
Gliclazide	£47,500	3.142	-£55	0.009	Dominant	£239	3
Insulin	£50,821	3.144	£3,266	0.011	£291,349	-£3,042	13

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 71. Results: high risk of CVD and living with obesity

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£51,289	8.38	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£56,013	8.62	£4,724	0.237	£19,940	£14	1
Dulaglutide	£59,067	8.51	£7,779	0.127	£61,460	-£5,247	13
Exenatide	£56,574	8.54	£5,285	0.152	£34,838	-£2,251	9
Liraglutide	£62,362	8.66	£11,073	0.272	£40,780	-£5,642	14
Semaglutide; Oral	£62,531	8.79	£11,242	0.406	£27,682	-£3,120	11
Semaglutide; Subcutaneous	£58,363	8.64	£7,074	0.252	£28,096	-£2,038	7
Alogliptin	£54,241	8.43	£2,953	0.043	£69,077	-£2,098	8
Linagliptin	£53,548	8.42	£2,259	0.034	£65,790	-£1,572	6
Saxagliptin	£53,194	8.28	£1,905	-0.101	Dominated	-£3,931	12

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Sitagliptin	£51,061	8.24	-£228	-0.146	SW Quadrant	-£2,686	10
Vildagliptin	£52,955	8.39	£1,666	0.005	£326,586	-£1,564	5
Gliclazide	£51,452	8.38	£163	-0.006	Dominated	-£280	4
Insulin	£59,394	8.35	£8,105	-0.031	Dominated	-£8,716	15
Pioglitazone	£51,369	8.38	£80	-0.004	Dominated	-£158	3

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 72. Results: high risk of CVD and living with overweight

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£48,193	7.60	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£52,410	7.79	£4,218	0.18	£23,035	-£556	4
Dulaglutide	£55,285	7.70	£7,092	0.10	£71,699	-£5,114	13
Exenatide	£52,875	7.71	£4,682	0.10	£45,250	-£2,613	10
Liraglutide	£58,218	7.81	£10,025	0.21	£47,157	-£5,773	14
Semaglutide; Oral	£57,169	7.87	£8,976	0.27	£33,828	-£3,669	12
Semaglutide; Subcutaneous	£54,684	7.82	£6,491	0.22	£29,755	-£2,128	9
Alogliptin	£50,563	7.63	£2,370	0.03	£88,111	-£1,832	8
Linagliptin	£50,223	7.62	£2,030	0.02	£106,214	-£1,648	7
Saxagliptin	£49,999	7.53	£1,806	-0.07	Dominated	-£3,237	11
Sitagliptin	£47,825	7.52	-£368	-0.09	SW Quadrant	-£1,367	5
Vildagliptin	£49,788	7.61	£1,596	0.01	£159,244	-£1,395	6
Gliclazide	£48,469	7.61	£276	0.01	£40,612	-£140	3
Insulin	£55,825	7.59	£7,632	-0.01	Dominated	-£7,796	15
Pioglitazone	£48,325	7.65	£132	0.05	£2,568	£898	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 73. Results: aged under 40 years

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£75,441	16.18	Reference	Reference	Reference	£0	3
SGLT-2 inhibitor	£82,329	16.43	£6,888	0.25	£28,053	-£1,977	4
Dulaglutide	£88,632	16.31	£13,191	0.13	£102,306	-£10,612	13
Exenatide	£83,329	16.29	£7,888	0.11	£73,200	-£5,733	10
Liraglutide	£92,931	16.48	£17,491	0.29	£59,387	-£11,600	14
Semaglutide; Oral	£89,433	16.54	£13,992	0.35	£39,518	-£6,911	11
Semaglutide; Subcutaneous	£87,036	16.41	£11,595	0.23	£50,856	-£7,035	12
Alogliptin	£79,133	16.20	£3,692	0.02	£191,240	-£3,306	8
Linagliptin	£79,458	16.22	£4,017	0.04	£99,942	-£3,213	7
Saxagliptin	£78,596	16.06	£3,156	-0.13	Dominated	-£5,700	9
Sitagliptin	£74,860	16.05	-£581	-0.14	SW Quadrant	-£2,144	5
Vildagliptin	£78,436	16.20	£2,996	0.02	£197,044	-£2,691	6
Gliclazide	£75,798	16.20	£358	0.02	£18,100	£38	2
Insulin	£89,694	16.16	£14,254	-0.03	Dominated	-£14,833	15
Pioglitazone	£75,581	16.20	£141	0.02	£7,212	£250	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

3.2.7 Treatment-related weight loss assumed to remain for lifetime

Table 74 to Table 80 show the results when treatment-related weight loss with SGLT-2 inhibitors and GLP-1 agonists were assumed to remain for the lifetime of the individual. Costs remained the same as the base case, QALYs were slightly improved. There were minimal changes to the final results versus base case.

Table 74. Results: ASCVD

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£45,193	4.71	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£50,430	4.95	£5,237	0.25	£21,175	-£291	5
Dulaglutide	£49,724	4.84	£4,531	0.13	£35,074	-£1,947	9

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Exenatide	£49,601	4.88	£4,408	0.17	£25,229	-£914	8
Liraglutide	£55,160	5.02	£9,967	0.31	£31,780	-£3,695	13
Semaglutide; Oral	£63,340	5.31	£18,147	0.60	£30,101	-£6,090	15
Semaglutide; Subcutaneous	£47,583	4.88	£2,390	0.17	£13,729	£1,092	1
Alogliptin	£49,903	4.83	£4,711	0.12	£38,835	-£2,285	12
Linagliptin	£46,522	4.73	£1,329	0.02	£54,772	-£844	7
Saxagliptin	£46,727	4.67	£1,534	-0.03	Dominated	-£2,227	11
Sitagliptin	£45,933	4.64	£740	-0.07	Dominated	-£2,141	10
Vildagliptin	£46,124	4.72	£931	0.01	£90,279	-£725	6
Gliclazide	£45,181	4.71	-£12	0.01	Dominant	£127	3
Insulin	£49,966	4.70	£4,774	-0.01	Dominated	-£4,892	14
Pioglitazone	£46,232	4.79	£1,039	0.08	£12,422	£634	2

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 75. Results: CKD 1-3

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£41,595	5.60	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£45,538	5.87	£3,943	0.28	£14,275	£1,581	1
Dulaglutide	£46,613	5.70	£5,018	0.10	£48,929	-£2,967	11
Exenatide	£45,952	5.75	£4,358	0.16	£28,030	-£1,248	7
Liraglutide	£51,572	5.90	£9,978	0.31	£32,481	-£3,834	12
Semaglutide; Oral	£57,648	6.16	£16,054	0.56	£28,588	-£4,823	14
Semaglutide; Subcutaneous	£52,199	5.91	£10,604	0.31	£34,224	-£4,407	13
Alogliptin	£45,976	5.72	£4,382	0.13	£34,567	-£1,847	8
Linagliptin	£42,991	5.64	£1,397	0.04	£33,546	-£564	5
Saxagliptin	£43,336	5.55	£1,741	-0.04	Dominated	-£2,606	10
Sitagliptin	£42,230	5.52	£635	-0.08	Dominated	-£2,221	9
Vildagliptin	£42,669	5.61	£1,075	0.01	£94,453	-£847	6
Gliclazide	£41,547	5.59	-£47	0.00	SW Quadrant	£2	3
Insulin	£47,200	5.59	£5,605	-0.01	Dominated	-£5,758	15
Pioglitazone	£42,468	5.66	£874	0.07	£12,567	£517	2

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 76. Results: CKD 4

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Metformin	£34,466	3.39	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£37,847	3.68	£3,381	0.29	£11,500	£2,499	1
Dulaglutide	£38,254	3.51	£3,787	0.12	£30,834	-£1,331	8
Exenatide	£37,723	3.54	£3,257	0.16	£20,983	-£153	6
Liraglutide	£41,390	3.62	£6,924	0.23	£30,155	-£2,332	11
Semaglutide; Oral	£50,592	3.88	£16,125	0.49	£32,747	-£6,277	15
Semaglutide; Subcutaneous	£43,075	3.62	£8,609	0.24	£36,306	-£3,866	14
Alogliptin	£37,914	3.45	£3,447	0.07	£51,244	-£2,102	10
Linagliptin	£35,392	3.44	£926	0.05	£17,598	£126	2

Treatment[a]	Cost[b]	QALY [b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank [d]
Saxagliptin	£35,631	3.35	£1,164	-0.03	Dominated	-£1,857	9
Sitagliptin	£35,487	3.31	£1,020	-0.08	Dominated	-£2,562	12
Vildagliptin	£35,337	3.41	£871	0.02	£47,798	-£506	7
Gliclazide	£34,584	3.40	£118	0.01	£12,628	£69	3
Insulin	£38,225	3.39	£3,759	0.00	£1,711,758	-£3,715	13
Pioglitazone	£35,073	3.41	£606	0.03	£22,815	-£75	5

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 77. Results: HF

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£47,554	3.133	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£50,709	3.250	£3,154	0.117	£26,919	-£811	6
Dulaglutide	£51,054	3.226	£3,500	0.093	£37,812	-£1,649	10
Exenatide	£50,975	3.242	£3,421	0.109	£31,320	-£1,236	9
Liraglutide	£52,777	3.294	£5,223	0.160	£32,571	-£2,016	12
Semaglutide; Oral	£61,055	3.495	£13,501	0.362	£37,278	-£6,257	14
Semaglutide; Subcutaneous	£49,246	3.298	£1,691	0.165	£10,274	£1,601	1
Alogliptin	£52,130	3.261	£4,575	0.128	£35,674	-£2,010	11
Linagliptin	£48,879	3.153	£1,325	0.020	£66,787	-£928	8
Saxagliptin	£48,215	3.123	£661	-0.010	Dominated	-£870	7
Sitagliptin	£46,779	3.151	-£776	0.018	Dominant	£1,127	2
Vildagliptin	£48,154	3.149	£600	0.015	£38,780	-£290	5
Gliclazide	£47,500	3.142	-£55	0.009	Dominant	£239	3
Insulin	£50,821	3.144	£3,266	0.011	£291,349	-£3,042	13

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW=south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 78. Results: high risk of CVD and living with obesity

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£51,289	8.38	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£56,013	8.63	£4,724	0.246	£19,172	£204	1
Dulaglutide	£59,067	8.52	£7,779	0.136	£56,991	-£5,049	13
Exenatide	£56,574	8.54	£5,285	0.160	£32,987	-£2,081	8
Liraglutide	£62,362	8.66	£11,073	0.280	£39,582	-£5,478	14
Semaglutide; Oral	£62,531	8.80	£11,242	0.414	£27,164	-£2,965	11
Semaglutide; Subcutaneous	£58,363	8.65	£7,074	0.263	£26,898	-£1,814	7
Alogliptin	£54,241	8.43	£2,953	0.043	£69,077	-£2,098	9
Linagliptin	£53,548	8.42	£2,259	0.034	£65,790	-£1,572	6

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Saxagliptin	£53,194	8.28	£1,905	-0.101	Dominated	-£3,931	12
Sitagliptin	£51,061	8.24	-£228	-0.146	SW Quadrant	-£2,686	10
Vildagliptin	£52,955	8.39	£1,666	0.005	£326,586	-£1,564	5
Gliclazide	£51,452	8.38	£163	-0.006	Dominated	-£280	4
Insulin	£59,394	8.35	£8,105	-0.031	Dominated	-£8,716	15
Pioglitazone	£51,369	8.38	£80	-0.004	Dominated	-£158	3

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 79. Results: high risk of CVD and living with overweight

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£48,193	7.60	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£52,410	7.79	£4,218	0.19	£22,163	-£412	4
Dulaglutide	£55,285	7.71	£7,092	0.11	£66,584	-£4,962	13
Exenatide	£52,875	7.71	£4,682	0.11	£42,572	-£2,483	10
Liraglutide	£58,218	7.82	£10,025	0.22	£45,803	-£5,648	14
Semaglutide; Oral	£57,169	7.87	£8,976	0.27	£33,089	-£3,551	12
Semaglutide; Subcutaneous	£54,684	7.83	£6,491	0.23	£28,136	-£1,877	9
Alogliptin	£50,563	7.63	£2,370	0.03	£88,111	-£1,832	8
Linagliptin	£50,223	7.62	£2,030	0.02	£106,214	-£1,648	7
Saxagliptin	£49,999	7.53	£1,806	-0.07	Dominated	-£3,237	11
Sitagliptin	£47,825	7.52	-£368	-0.09	SW Quadrant	-£1,367	5
Vildagliptin	£49,788	7.61	£1,596	0.01	£159,244	-£1,395	6
Gliclazide	£48,469	7.61	£276	0.01	£40,612	-£140	3
Insulin	£55,825	7.59	£7,632	-0.01	Dominated	-£7,796	15
Pioglitazone	£48,325	7.65	£132	0.05	£2,568	£898	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 80. Results: aged under 40 years

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£75,441	16.18	Reference	Reference	Reference	£0	3
SGLT-2 inhibitor	£82,329	16.44	£6,888	0.26	£26,922	-£1,771	4
Dulaglutide	£88,632	16.32	£13,191	0.14	£94,427	-£10,397	13
Exenatide	£83,329	16.30	£7,888	0.12	£67,426	-£5,548	9
Liraglutide	£92,931	16.49	£17,491	0.30	£57,644	-£11,422	14
Semaglutide; Oral	£89,433	16.55	£13,992	0.36	£38,601	-£6,742	11
Semaglutide; Subcutaneous	£87,036	16.42	£11,595	0.24	£48,282	-£6,792	12
Alogliptin	£79,133	16.20	£3,692	0.02	£191,240	-£3,306	8
Linagliptin	£79,458	16.22	£4,017	0.04	£99,942	-£3,213	7
Saxagliptin	£78,596	16.06	£3,156	-0.13	Dominated	-£5,700	10
Sitagliptin	£74,860	16.05	-£581	-0.14	SW Quadrant	-£2,144	5
Vildagliptin	£78,436	16.20	£2,996	0.02	£197,044	-£2,691	6
Gliclazide	£75,798	16.20	£358	0.02	£18,100	£38	2
Insulin	£89,694	16.16	£14,254	-0.03	Dominated	-£14,833	15
Pioglitazone	£75,581	16.20	£141	0.02	£7,212	£250	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

3.2.8 Adverse events excluded

Table 81 to Table 87 present results of a sensitivity analysis where costs and disutilities associated select adverse events were removed. The results have not deviated much from the base case and there are no major changes of note.

Table 81. Results: ASCVD

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£45,130	4.72	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£50,372	4.95	£5,243	0.24	£22,282	-£537	5

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Dulaglutide	£49,684	4.83	£4,555	0.12	£38,407	-£2,183	9
Exenatide	£49,561	4.88	£4,431	0.16	£26,897	-£1,136	8
Liraglutide	£55,115	5.02	£9,985	0.31	£32,727	-£3,883	13
Semaglutide; Oral	£63,295	5.31	£18,166	0.59	£30,548	-£6,272	15
Semaglutide; Subcutaneous	£47,543	4.88	£2,413	0.16	£14,892	£828	1
Alogliptin	£49,864	4.83	£4,735	0.12	£40,400	-£2,391	12
Linagliptin	£46,483	4.74	£1,353	0.02	£67,124	-£950	7
Saxagliptin	£46,687	4.68	£1,558	-0.04	Dominated	-£2,333	11
Sitagliptin	£45,893	4.64	£764	-0.07	Dominated	-£2,247	10
Vildagliptin	£46,085	4.72	£955	0.01	£153,888	-£831	6
Gliclazide	£45,077	4.73	-£53	0.01	Dominant	£244	3
Insulin	£49,855	4.72	£4,725	0.00	Dominated	-£4,729	14
Pioglitazone	£46,147	4.80	£1,017	0.08	£12,339	£631	2

Abbreviations: ASCVD= atherosclerotic cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 82. Results: CKD 1-3

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£41,524	5.61	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£45,482	5.87	£3,957	0.26	£15,023	£1,311	1
Dulaglutide	£46,568	5.70	£5,044	0.09	£55,044	-£3,211	11
Exenatide	£45,908	5.75	£4,383	0.15	£30,194	-£1,480	7
Liraglutide	£51,523	5.90	£9,999	0.30	£33,518	-£4,033	12
Semaglutide; Oral	£57,599	6.16	£16,075	0.55	£29,070	-£5,015	14
Semaglutide; Subcutaneous	£52,149	5.90	£10,625	0.30	£35,620	-£4,659	13
Alogliptin	£45,932	5.73	£4,408	0.12	£35,999	-£1,959	8
Linagliptin	£42,947	5.64	£1,423	0.04	£38,126	-£677	5
Saxagliptin	£43,292	5.56	£1,768	-0.05	Dominated	-£2,719	10
Sitagliptin	£42,186	5.52	£662	-0.08	Dominated	-£2,334	9
Vildagliptin	£42,625	5.61	£1,101	0.01	£155,767	-£960	6
Gliclazide	£41,429	5.61	-£95	0.00	Dominant	£142	3
Insulin	£47,079	5.60	£5,555	0.00	Dominated	-£5,622	15
Pioglitazone	£42,372	5.67	£848	0.07	£12,409	£519	2

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 83. Results: CKD 4

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£34,420	3.39	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£37,807	3.68	£3,387	0.29	£11,789	£2,359	1
Dulaglutide	£38,219	3.51	£3,799	0.11	£33,380	-£1,523	8
Exenatide	£37,689	3.54	£3,269	0.15	£22,339	-£342	6
Liraglutide	£41,356	3.62	£6,935	0.22	£31,269	-£2,499	11
Semaglutide; Oral	£50,557	3.88	£16,137	0.48	£33,278	-£6,439	15
Semaglutide; Subcutaneous	£43,041	3.62	£8,621	0.23	£38,032	-£4,087	14
Alogliptin	£37,880	3.46	£3,460	0.07	£53,084	-£2,156	10
Linagliptin	£35,364	3.44	£943	0.05	£18,947	£52	3

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Saxagliptin	£35,602	3.36	£1,182	-0.04	Dominated	-£1,931	9
Sitagliptin	£35,458	3.31	£1,037	-0.08	Dominated	-£2,636	12
Vildagliptin	£35,308	3.41	£888	0.02	£57,717	-£580	7
Gliclazide	£34,507	3.41	£86	0.01	£7,003	£160	2
Insulin	£38,146	3.40	£3,726	0.01	£743,453	-£3,626	13
Pioglitazone	£35,010	3.42	£589	0.03	£22,851	-£74	5

Abbreviations: CKD= chronic kidney disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 84. Results: HF

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£47,508	3.140	Reference	Reference	Reference	£0	4
SGLT-2 inhibitor	£50,668	3.254	£3,159	0.114	£27,664	-£875	6
Dulaglutide	£51,025	3.231	£3,517	0.091	£38,736	-£1,701	10
Exenatide	£50,946	3.248	£3,438	0.107	£31,994	-£1,289	9
Liraglutide	£52,748	3.299	£5,239	0.159	£33,041	-£2,068	11
Semaglutide; Oral	£61,020	3.495	£13,512	0.354	£38,118	-£6,422	14
Semaglutide; Subcutaneous	£49,217	3.303	£1,708	0.163	£10,489	£1,549	1
Alogliptin	£52,101	3.265	£4,593	0.125	£36,618	-£2,084	12
Linagliptin	£48,851	3.157	£1,342	0.017	£78,917	-£1,002	8
Saxagliptin	£48,187	3.127	£678	-0.013	Dominated	-£944	7
Sitagliptin	£46,750	3.155	-£759	0.015	Dominant	£1,053	2
Vildagliptin	£48,125	3.153	£617	0.013	£48,843	-£364	5
Gliclazide	£47,422	3.152	-£86	0.012	Dominant	£331	3
Insulin	£50,741	3.154	£3,233	0.014	£230,502	-£2,952	13

Abbreviations: HF= heart failure; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 85. Results: high risk of CVD and living with obesity

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£51,190	8.40	Reference	Reference	Reference	£0	1
SGLT-2 inhibitor	£55,925	8.63	£4,735	0.231	£20,540	-£124	3
Dulaglutide	£59,005	8.52	£7,815	0.123	£63,534	-£5,355	13
Exenatide	£56,511	8.55	£5,321	0.147	£36,082	-£2,372	9
Liraglutide	£62,299	8.67	£11,109	0.268	£41,500	-£5,755	14
Semaglutide; Oral	£62,469	8.80	£11,279	0.402	£28,044	-£3,235	11
Semaglutide; Subcutaneous	£58,300	8.65	£7,110	0.248	£28,693	-£2,154	7
Alogliptin	£54,180	8.44	£2,990	0.037	£81,492	-£2,256	8
Linagliptin	£53,486	8.43	£2,296	0.028	£81,192	-£1,731	6
Saxagliptin	£53,132	8.29	£1,942	-0.107	Dominated	-£4,090	12

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Sitagliptin	£51,003	8.25	-£187	-0.152	SW Quadrant	-£2,861	10
Vildagliptin	£52,893	8.40	£1,703	-0.001	Dominated	-£1,722	5
Gliclazide	£51,287	8.40	£97	0.001	£150,948	-£84	2
Insulin	£59,224	8.37	£8,034	-0.025	Dominated	-£8,525	15
Pioglitazone	£51,234	8.39	£44	-0.006	Dominated	-£156	4

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 86. Results: high risk of CVD and living with overweight

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£48,101	7.62	Reference	Reference	Reference	£0	3
SGLT-2 inhibitor	£52,329	7.79	£4,228	0.18	£23,867	-£685	4
Dulaglutide	£55,227	7.71	£7,126	0.10	£74,569	-£5,215	13
Exenatide	£52,817	7.72	£4,716	0.10	£47,345	-£2,724	10
Liraglutide	£58,160	7.82	£10,059	0.21	£48,124	-£5,879	14
Semaglutide; Oral	£57,110	7.88	£9,010	0.26	£34,429	-£3,776	12
Semaglutide; Subcutaneous	£54,625	7.83	£6,525	0.22	£29,870	-£2,156	9
Alogliptin	£50,506	7.64	£2,405	0.02	£113,123	-£1,980	8
Linagliptin	£50,165	7.63	£2,065	0.01	£153,266	-£1,795	7
Saxagliptin	£49,942	7.54	£1,841	-0.08	Dominated	-£3,385	11
Sitagliptin	£47,767	7.52	-£334	-0.09	SW Quadrant	-£1,514	5
Vildagliptin	£49,731	7.62	£1,630	0.00	£372,378	-£1,543	6
Gliclazide	£48,315	7.63	£214	0.01	£16,683	£43	2
Insulin	£55,667	7.61	£7,566	0.00	Dominated	-£7,617	15
Pioglitazone	£48,199	7.67	£99	0.05	£1,974	£900	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

Table 87. Results: aged under 40 years

Treatment[a]	Cost[b]	QALY[b]	Inc. cost[b]	Inc. QALYs[b]	ICER[b]	INMB[c]	Rank[d]
Metformin	£75,295	16.21	Reference	Reference	Reference	£0	2
SGLT-2 inhibitor	£82,200	16.44	£6,904	0.24	£29,235	-£2,181	4
Dulaglutide	£88,540	16.33	£13,244	0.12	£110,524	-£10,848	13
Exenatide	£83,237	16.31	£7,941	0.10	£78,076	-£5,907	9
Liraglutide	£92,839	16.49	£17,544	0.29	£60,729	-£11,766	14
Semaglutide; Oral	£89,341	16.55	£14,045	0.35	£40,323	-£7,079	11
Semaglutide; Subcutaneous	£86,944	16.43	£11,649	0.22	£52,417	-£7,204	12
Alogliptin	£79,041	16.22	£3,746	0.01	£272,788	-£3,471	8
Linagliptin	£79,367	16.24	£4,072	0.03	£130,143	-£3,446	7
Saxagliptin	£78,506	16.07	£3,210	-0.14	Dominated	-£5,933	10
Sitagliptin	£74,769	16.06	-£526	-0.15	SW Quadrant	-£2,377	5
Vildagliptin	£78,346	16.21	£3,050	0.01	£484,564	-£2,924	6
Gliclazide	£75,708	16.22	£412	0.01	£37,999	-£195	3
Insulin	£89,451	16.19	£14,156	-0.02	Dominated	-£14,545	15
Pioglitazone	£75,332	16.23	£36	0.03	£1,285	£531	1

Abbreviations: CVD= cardiovascular disease; ICER= incremental cost-effectiveness ratio; Inc.= incremental; INMB= Incremental net monetary benefit; QALY= quality-adjusted life-year; SGLT-2= sodium-glucose cotransporter-2; SW= south-west

(a) All treatments have a background of metformin therapy. Treatments are listed in order of drug class

(b) Pairwise comparison between intervention plus metformin versus metformin alone

(c) INMB is calculated using a value of £20,000 per QALY

(d) Rank in descending order of INMB

3.2.9 Changes to liraglutide list price

Liraglutide in addition to metformin monotherapy was not considered cost-effective at list price used in the model in any of the populations of interest in the base-case. A reduction in the current list price between 35-45% would reduce the ICER below £20k per QALY in all populations with the largest reduction needed in the under 40 population and the largest in the living with obesity population. Since the prices were collected in the model the list price of liraglutide has reduced by 36% (NHS Electronic Drug Tariff (accessed 19/06/2025) which would bring the ICER below £20k per QALY in the CKD1-3 (£19,319), CKD4 (£18,066), HF (£17,889) and living with obesity population (£18,745). The ICER would be £20,668 and £21,236 for the ASCVD and living with overweight populations. The under-40 population returned an ICER significantly over £20k per QALY at £26,071.

Figure 2: effect of liraglutide list price changes on ICER: ASCVD

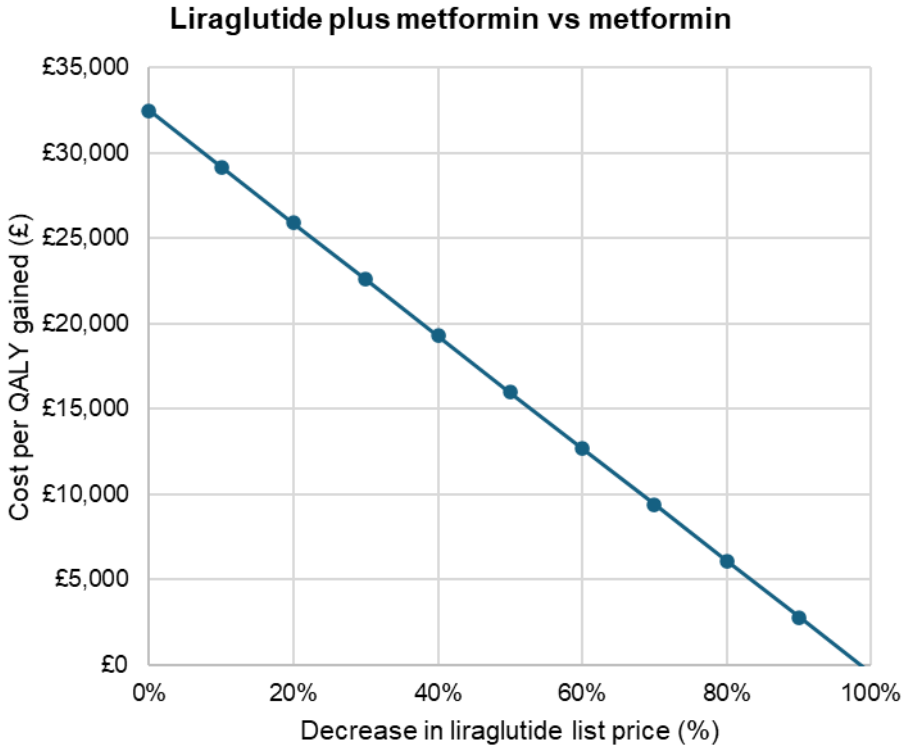


Figure 3: effect of liraglutide list price changes on ICER: CKD 1-3

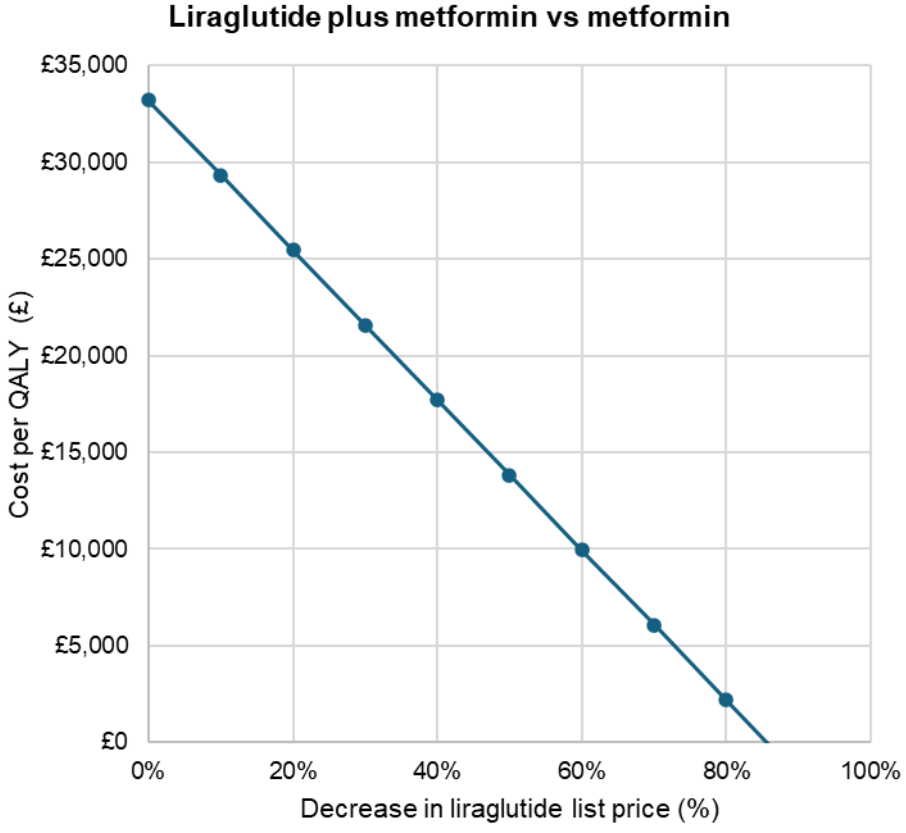


Figure 4: effect of liraglutide list price changes on ICER: CKD 4

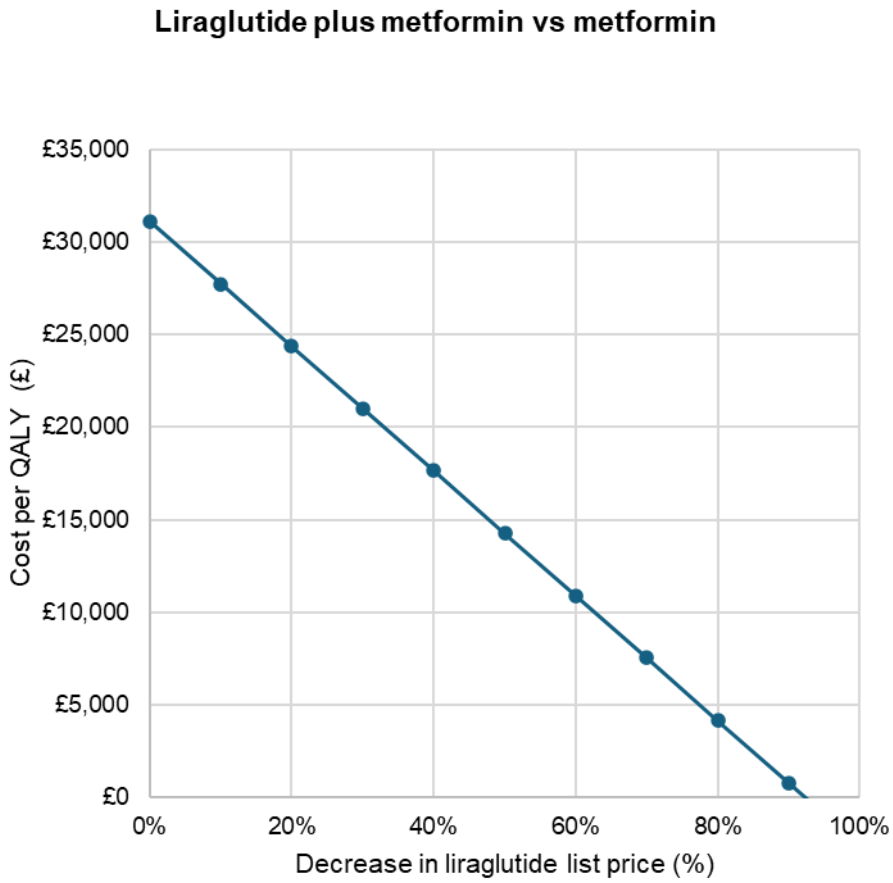


Figure 5: effect of liraglutide list price changes on ICER: HF

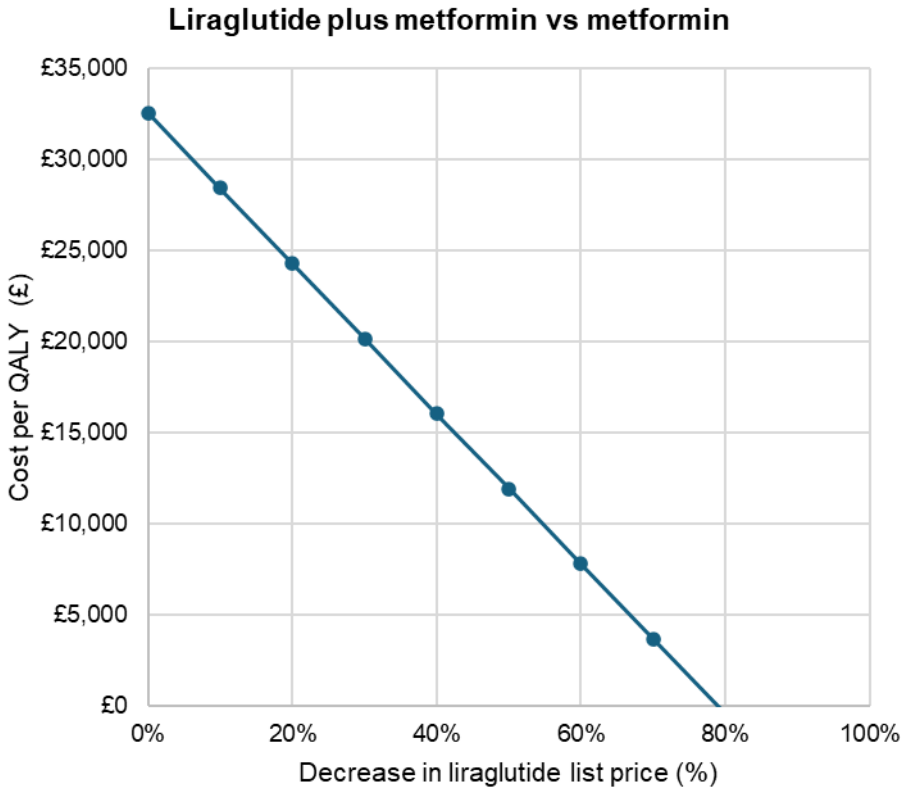


Figure 6: effect of liraglutide list price changes on ICER: high risk of CVD and living with obesity

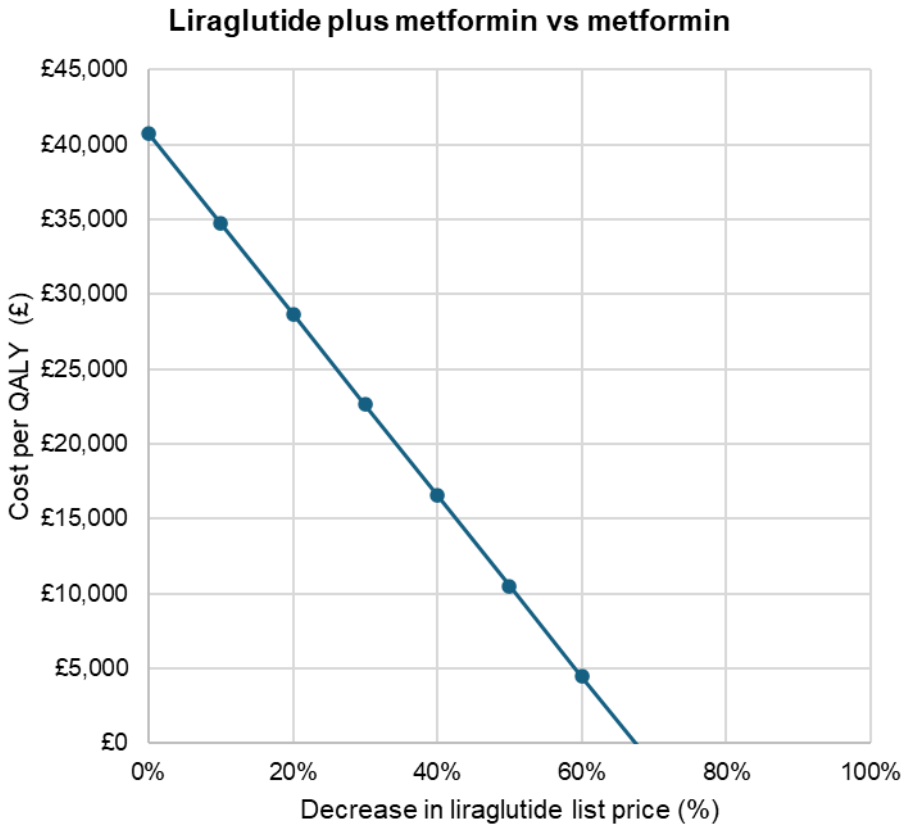


Figure 7: effect of liraglutide list price changes on ICER: high risk of CVD and living with overweight

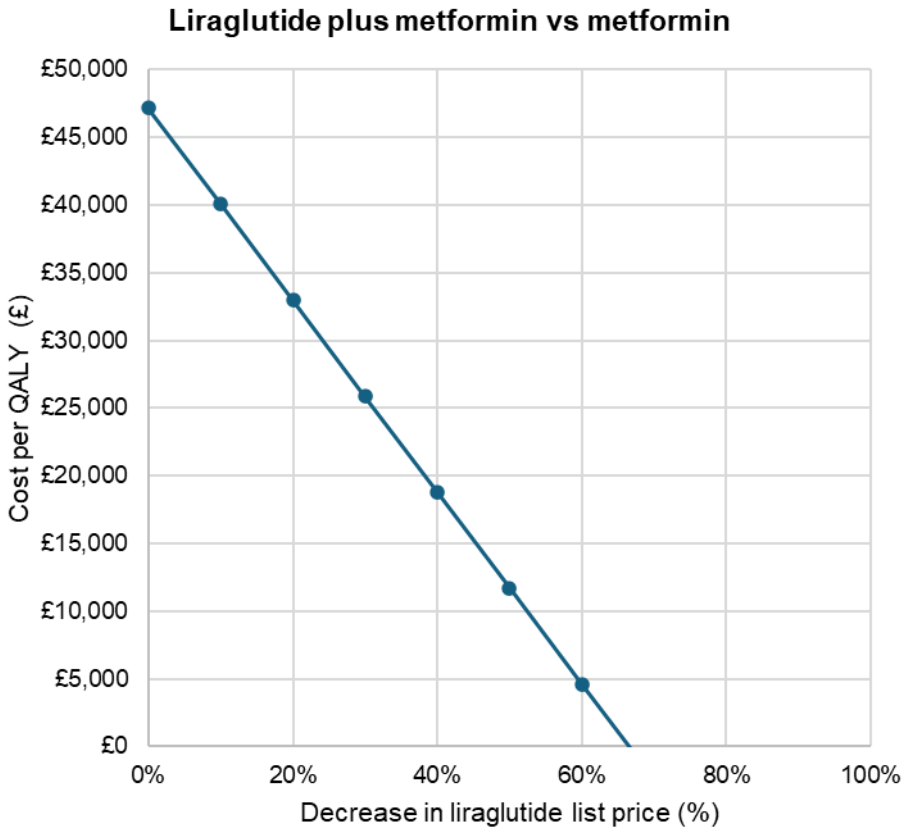
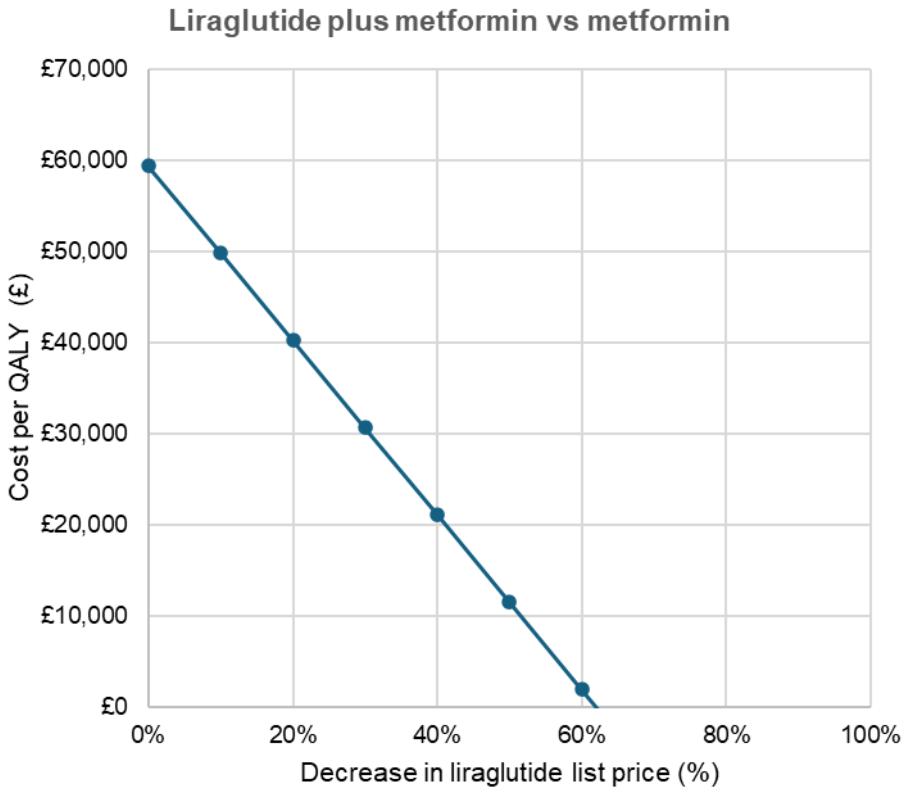


Figure 8: effect of liraglutide list price changes on ICER: Aged under 40 years



4Discussion

4.1.1Discussion of results

In the base-case SGLT-2 inhibitors in combination with metformin was cost-effective compared to metformin monotherapy in the CKD 1-3, CKD 4 and living with obesity populations. The ICERs for the living with overweight, and ASCVD populations were marginally over £20k per QALY, the value below which NICE usually recommend interventions. For all populations other than under 40s at least one of the SGLT-2 inhibitors in the pooled estimate was cost-effective compared to metformin monotherapy. This pooled result was driven by a few unfavourable point estimates for some SGLT-2s around stroke and CVM in the accompanying NMA. These unfavourable results had wide 95% credible intervals that passed the line of no effect. Based on these wide intervals and the committee's opinion that SGLT-2 inhibitors would not be harmful for these outcomes, a lesser weight was attributed to model outcomes impacted by them.

When pooled estimates from the Shi 2023 NMA were used in the analysis, SGLT-2 inhibitors became cost-effective compared to metformin monotherapy in the ASCVD population and the ICER decreased but did not go below £20k per QALY in the living with overweight population. The SGLT-2 inhibitor class ICER remained significantly above £20k per QALY in the population aged under 40 years.

Since the model was run, the UK court has declared the UK patent for dapagliflozin to be no longer valid This will significantly reduce the cost of the drug with estimates of up to an 80% drop. If, as would be expected, dapagliflozin is prescribed as a greater percentage of all SGLT-2s there would be similar reductions in the price of SGLT-2 inhibitors at a class level. It is therefore likely that for populations where the ICER is slightly above £20k per QALY that it would be under that value once these price drops take effect.

Oral semaglutide resulted in the largest number of QALYs in all the base-case analyses. The same was also true for either oral or subcutaneous semaglutide in the sensitivity analyses. However, both types of semaglutide were bore the largest costs in all analyses if insulin was excluded.

Of the dual therapies, oral semaglutide resulted in the largest number of QALYs in all the base-case analyses. These results were driven by a strong point estimate (HR=0.53) for CVM. Although not passing the line of no effect, this estimate had wide credible intervals between 0.30 and 0.93. This intervention was not cost-effective compared to metformin monotherapy in any of the populations.

Subcutaneous semaglutide was cost-effective compared to metformin monotherapy in the ASCVD and HF populations. This result did not hold when the Shi 2023 pooled estimates were used. Caution should be given to results for GLP-1 agonists from the Shi 2023 analysis as the accompanying clinical review NMA showed differences in effectiveness between GLP-1 agonists, thus indicating that pooling of effect estimates with regards to GLP-1 agonists may not be appropriate.

Pioglitazone was the most cost-effective intervention in the living with overweight and under 40 populations although the incremental QALYs were comparably lower than other interventions considered. The effect estimates used in the analysis had large uncertainty around them as shown by the credible intervals in the accompanying NMA.

No GLP-1 agonists were cost-effective compared to metformin monotherapy or SGLT-2 inhibitors in either the living with obesity or living with overweight populations although the base-case made conservative assumptions about continuation of weight loss. During sensitivity analysis that explored more favourable assumptions around weight loss

maintenance after the first year of treatment, GLP-1 agonists reported increasing numbers of QALYs compared to the base-case, thus reducing the ICER. This was more pronounced in people living with obesity compared to those living with overweight. GLP-1 agonists were never the most cost-effective intervention in any of the sensitivity analyses for these two populations.

A triple therapy regimen of a SGLT-2 inhibitor and subcutaneous semaglutide compared to metformin monotherapy was cost-effective in the ASCVD population. However, it had an ICER above £20k per QALY when compared to dual therapy with metformin and subcutaneous semaglutide. No other triple therapy regimens considered had an ICER below £20k per QALY in the base-case. No triple therapy regimens had an ICER below £20k in the under 40 population.

At least one GLP-1 agonist was cost effective compared to insulin in all populations. Insulin was never ranked higher than fourth when compared directly to the considered GLP-1 agonists. This reinforces the view of the committee that insulin should be a treatment of last resort and treatments such as GLP-1 agonists should be placed before inulin in the treatment pathway.

4.1.2Comparison with previous guideline update

The previous iteration of this guideline looked at the use of CVOT drugs in a general T2DM population with subgroup analyses specifically for those with a BMI of greater than or equal to 30kg/m^2, those with a previous cardiovascular event, those at high risk of a future cardiovascular event without a previous event and a subgroup that combined the final two populations. The model also stratified populations by treatment stage in keeping with the treatment intensification approach to modelling. In the general T2DM population most of the SGLT-2 inhibitors had ICERs between £20k and £30k with all GLP-1 agonists having ICERs greater than £24k, whether the drugs were used as additions to baseline treatment or replacements. Only dapagliflozin reported an ICER below £20k in all the base-case analyses, at all intensification stages and regardless of whether it was considered as an addition to baseline treatment or a replacement. These results were robust during sensitivity analyses except for canagliflozin, which reported ICERs below £20k in a number of the tested assumptions.

These results held when subgroups were considered. ICERs for subcutaneous semaglutide did reduce versus the base case with the ICER being just above £21k for those with a prior cardio-vascular event. This differs somewhat from our analysis where in high-risk individuals with HF, CKD or living with obesity, SGLT-2 inhibitors returned an ICER below £20k per QALY. For people with a BMI greater than or equal to 30kg/m^2 the previous guideline update did not return any ICERs below £20k other than for dapagliflozin. This is similar to our analysis where only the SGLT-2 inhibitor class returned an ICER below £20k per QALY. Our analysis differed quite substantially around GLP-1 agonists. The previous guideline update did not estimate any GLP-1 agonist being cost-effective in any of the base-case or sensitivity analyses. In this analysis subcutaneous semaglutide had an ICER below £20k per QALY in both the ASCVD and HF populations when compared directly to metformin monotherapy.

Differences in the results can be partially explained by differences in populations. None of the populations perfectly aligned between the two analyses although there was significant overlap. For example, people with previous cardiovascular events considered in the prior guideline update were largely split out into people with ASCVD and HF for this update, with results differing significantly between the two. This could be explained by the greater life expectancy in the ASCVD population compared to the heart failure population (just over 2 additional years lived) and the larger underlying costs for the HF population who have a higher level of co-morbidities. Individuals with a greater life expectancy will benefit from

improvements in quality-of-life for a longer period of time improving the cost-effectiveness of interventions.

It is also worth noting that the previous guideline modelled an incident population with T2DM in whom first intensification (i.e. treatment in addition to metformin) was simulated uniformly for all people at 4.5 years. The mean age of that population at first intensification was slightly over 61 years. By contrast, the mean age across our modelled populations – excluding people with early onset T2DM- ranged from over 64 years in people with high risk of CVD and living with obesity to slightly under 76 years in people with HF. This would explain differences in the estimates of cost-effectiveness between these analyses.

Finally, this analysis captured a greater range of benefits encapsulating both micro and macro-vascular events; the previous guideline model only included cardiovascular (macrovascular) benefits. Additional benefits from any of the CVOT drugs, identified in the accompanying clinical evidence review, are therefore likely to lead to higher QALY gains in our model.

4.1.3 Strengths and limitations

Strengths

This model assessed multiple relevant treatment options directly to each other based on RCT evidence synthesised in an NMA. This represents the best available clinical evidence on treatment options for the populations under consideration.

The model moved away from a treatment intensification approach which has been a mainstay of previous economic modelling of T2DM. The treatment intensification approach is a stepwise approach to treatment with new additional treatments given following inadequate control of HbA1c levels or other measures of unsuccessful treatment. This approach no longer mirrors current practice where treatments are available which have cardiovascular and renal protective properties independent of glycaemic control and are often prescribed even when treatment goals are being achieved successfully. Considering treatment options based on patient characteristics and co-morbidities is therefore more appropriate in decision making.

This model sub-grouped the high-risk T2DM population rather than considering them as one homogenous group as was done in previously published economic evaluations and previous updates of this guideline. When making decisions around care in T2DM, clinicians and patients are likely to consider a range of factors including glycaemic control, Q-Risk score, age at onset, cardiovascular disease, renal disease and current BMI. Optimal treatment pathways are likely to differ based upon these factors and sub-grouping allows for differential recommendations to be made based on these. This economic evaluation has allowed for tailored recommendations to be made for different groups of people with T2DM.

The model also used a recent, large sample from the CPRD database for its population. Given this covers a large number of primary care centres in England this data is representative of the T2DM population in the UK. Results from the model should be highly applicable to the UK population.

The model was largely based on the UKPDS OM2.2 model. Although the outcomes from the NMA used to inform the model were estimated in isolation, the risk equations within the UKPDS Global beta model allowed progression of competing events, morbidity and mortality to be captured in the economic model allowing for interactions between different comorbidities and events.

Limitations

Despite using the best available clinical evidence to inform the economic model there were many treatments for which no evidence was identified in a particular sub-group. These were replaced in the model with a hazard ratio reported for the same intervention from another sub-group if available, or 1 if none were available indicating that they showed no difference to metformin monotherapy for that intervention. This may not necessarily match the expectations of the committee and there were several interventions where this may have missed a large benefit (or harm) for this treatment. Best estimates could have been sourced from committee members but given the large number of treatments a systematic approach was considered most appropriate. Where data was missing for a particular intervention, the committee considered how this may have impacted the cost-effectiveness results when making recommendations. For example, for oral semaglutide no evidence was identified in the clinical review around IHD, HHF, MI, stroke or EKD and were set to one in the analysis. Given benefits in these outcomes for other GLP-1 agonists the committee thought that there would also be a benefit for these outcomes in oral semaglutide and the economic model therefore underestimates both effectiveness and cost-effectiveness for this intervention.

There were also several estimates for which the credible intervals were very wide and crossed the line of no effect. In some cases, favourable point estimates were put into the model which had a large credible interval passing the line of no effect and consequently demonstrating significant uncertainty around the true estimate of treatment effectiveness. In NICE economic evaluations this uncertainty would usually be captured in a PSA although, as discussed earlier, the computational power required to make this model probabilistic made doing so unfeasible. Therefore, some results from the economic analysis appear to strongly favour a particular intervention based on very uncertain evidence. Again, the committee considered this when making their recommendations.

The decision to apply a hierarchical set of rules to determine what treatment effects were included in the model was agreed by the committee since this was their preference to picking and choosing what treatment effects were included themselves. The advantage of such a method is it eliminated any risk of bias. Where the 95% credible intervals were wide, it would have lacked face validity if such point estimates were included in the model. However, there were a few instances where the 95% credible interval was narrow for a particular intervention, yet the point estimates were not applied, with treatment effects instead being borrowed from another population. Examples include sitagliptin, HR= 1.22 (0.7,2.14) for CVD, 1.03 used instead; subcutaneous semaglutide, HR= 0.83 (0.48, 1.44) and linagliptin, HR= 0.88 (0.58, 1.34) for angina, a value of 1 applied instead; and alogliptin, HR= 0.92 (0.56, 1.51) for HHF, where a value of 1 was applied instead. Except for sitagliptin, all ICERs would have been more conservative with the application of the treatment borrowing rule. This was something the committee considered whilst making recommendations.

Around 8% of the CPRD cohort did not have any observations for the 18 months preceding the upper date limit. This was largely because of practices failing to submit their patient data for that year. We could have removed these patients from our data set but it would have reduced sample size used for simulating demographic characteristics for the patient cohort. Removing these patients from the analysis had very limited impact on the estimates with most estimates changing by less than a tenth of a percentage point. The proportion of patients prescribed SGLT-2 inhibitors and the prevalence of HF both increased but neither of these inputs feed directly into this economic model. Given the increase in HF there would have been patients, diagnosed with HF in the preceding 18 months, who would not have contributed to the estimation of the demographics for that cohort in the model and been included in alternative cohorts. Given the very marginal change in the estimates between the differing approaches it is very unlikely to have changed the conclusions of any of the analyses.

The UKPDS study, on which the model is based, is reasonably old and there have been improvements in overall diabetes management beyond medicinal treatments, for example retinal screening which has reduced the incidence of blindness from diabetic complications.

Other risk factors have also changed within this time, such as the prevalence of smoking. These risk factors were outside the scope of the clinical evidence review and were not updated as part of the economic modelling.

The UKPDS OM2.2 model treats HF as a state rather than an event. Therefore, the UKPDS OM2.2 model could not predict differentiating event rates for HF, between treatments, in a population where HF had already occurred. In other populations it could also not predict where HF events would be different between treatments after the first event. The outcome reported in the accompanying NMA was for hospitalisation due to heart failure and had favourable estimates, compared to metformin monotherapy, for many of the treatments. Differences in subsequent HF related events are therefore missed by the model and where treatments are effective at reducing these subsequent events in the model, the costs and QALY detriments associated with heart failure are likely to be overestimated. This is the case for all populations considered by the model but in particular the HF cohort.

A sensitivity analysis was run which attempted to calibrate CVM hazard ratios to those derived in the accompanying NMA. This analysis provided a poor fit for a number of interventions such as oral semaglutide and subcutaneous semaglutide. This was particular the case in the CKD 1-3 population where the predicted hazard ratios were significantly higher than those reported in the NMA. For example, in the CKD 1-3 population the hazard ratio for CVM was 0.91 in the model over 125% larger than the 0.71 predicted in the accompanying NMA. These discrepancies in hazard ratios are most likely explained by assumptions around the hazard ratios for non-fatal events being set to 1 in line with the decision rule for inputting unestimated values and caution should be placed when interpreting these outcomes from the sensitivity analysis. In general, they underestimate the cost-effectiveness of these interventions.

Triple therapy analysis

The analysis around the use of triple therapy in people with ASCVD and early-onset T2DM estimated that prescribing metformin, a SGLT-2 inhibitor and GLP-1 agonist in parallel could be cost effective in the ASCVD population. However, these estimates were not underpinned by RCT evidence and were instead based on assumptions that treatment effects would be additive in nature. This inherently reduced the weight that could be placed on these results.

However, there is some evidence available that taking SGLT-2 inhibitors and GLP-1 agonists in combination is additive in terms of treatment benefits. For example, a population-based cohort study compared people with T2DM starting a GLP-1 agonist followed by an SGLT-2 inhibitor to those starting an SGLT-2 inhibitor followed by a GLP-1 agonist to determine the impact of additional treatment to the background treatment.(Simms-Williams, et al., 2024) Cases were matched based on background treatment, the duration the baseline treatment was prescribed and a diabetes-related propensity score. The cohort was taken from the CPRD database, as used by this economic model, but from an earlier time-period. Myocardial infarction, stroke, heart failure, cardiovascular mortality, all-cause mortality and a combined MACE were the outcomes reported. This study supported the hypothesis that the impact from taking both treatments in combination were broadly additive.

From the committee's own experience, these treatments were already prescribed in combination where people were eligible for either, and cardiovascular and renal risk factors were high. They also highlighted that generally people were likely to progress through these treatment options as soon as health and treatment-related factors changed, meaning that a large proportion of people will ultimately receive all three treatments and that treatment costs would only be deferred rather than avoided.

Additionally, cost savings from cardiovascular events averted would likely be significant while leading to improved health outcomes. People with ASCVD and early onset T2DM especially

had particularly high incidences of cardiovascular disease. The UKPDS study that was used to inform the model reported that people with early onset T2DM had an 11% probability of a diabetes-related death and an 18% probability of a major cardiovascular event during a median follow-up of 18 years.(Lin, et al., 2024) The risk of death and major adverse cardiovascular outcomes were higher for people with early onset T2DM compared to the general T2DM population at all timepoints. For people with heart failure, myocardial infarction, stroke and peripheral arterial disease the lifetime risks of further cardiovascular outcome or diabetes related death were 97%, 98%, 89% and 91% respectively compared to an 80% probability for people with T2DM without ASCVD. (Zhang, et al., 2022) Targeting these two populations with earlier therapeutic intervention would therefore likely to lead to the largest benefit through reductions in major cardiovascular.

Only pioglitazone was estimated with an ICER below £20k per QALY for the under 40 population in the base-case. No evidence was identified specifically for the under 40 population which could inform the base-case and they formed only a very small proportion of participants in the RCTs underpinning the accompanying NMA and UKPDS risk equations. Evidence for this group was therefore exclusively drawn from other populations. Given the paucity of evidence for this population it is difficult to predict how applicable such inputs are. Consequently, there is uncertainty about the cost and QALY estimates from the economic model.

Appendices

Appendix A: Treatment effects reported in NMA before crossover between populations

Table 88. Change in HbA1c (%) versus placebo[a]

	ASCVD[b]	CKD[c]	HF[d]	High risk of CVD [e]
Canagliflozin		-0.20 (-0.32, -0.08)		-0.75 (-0.89, -0.62)
Dapagliflozin	-0.58 (-1.11, -0.05)	-0.23 (-0.39, -0.06)		-0.60 (-0.71, -0.50)
Empagliflozin	-0.24 (-0.63, 0.16)	-0.50 (-0.62, -0.37)		-0.70 (-0.81, -0.59)
Ertugliflozin	-0.17 (-0.92, 0.58)	-0.10 (-0.22, 0.02)		-0.68 (-0.88, -0.48)
Dulaglutide		-0.41 (-0.61, -0.22)		-0.97 (-1.08, -0.85)
Exenatide	-0.57 (-2.39, 1.21)	-0.10 (-0.79, 0.61)	0.20 (-0.99, 1.40)	-0.77 (-0.87, -0.67)
Liraglutide	-1.11 (-2.29, 0.10)	-0.55 (-0.72, -0.38)	1.30 (0.10, 2.50)	-0.91 (-1.00, -0.82)
Semaglutide (oral)		-0.92 (-1.13, -0.72)		-0.96 (-1.12, -0.80)
Semaglutide (subcutaneous)		**-0.81 (-0.9, -0.72)**		-1.28 (-1.41, -1.16)
Alogliptin	-0.36 (-1.12, 0.38)			-0.53 (-0.76, -0.32)
Linagliptin		-0.54 (-0.67, -0.41)		-0.54 (-0.67, -0.42)
Saxagliptin		-0.63 (-1.24, -0.01)		-0.52 (-0.66, -0.39)
Sitagliptin	-0.23 (-0.75, 0.34)	-0.22 (-0.56, 0.14)	0.30 (-0.88, 1.48)	-0.63 (-0.71, -0.56)
Vildagliptin	-0.79 (-1.96, 0.37)	-0.20 (-0.68, 0.3)		-0.66 (-0.77, -0.54)
Gliclazide				-0.71 (-0.99, -0.42)
Insulin	-0.86 (-1.98, 0.22)	-0.31 (-0.62, -0.01)		-0.73 (-0.83, -0.63)
Pioglitazone	-1.17 (-2.08, -0.27)	-0.80 (-1.45, -0.16)		-0.63 (-0.73, -0.54)

(a) Except for the HF population, where the reference was insulin.
(b) Figures obtained from Table17 of document F9: subsequent NMA comorbidities
(c) Figures obtained from Table1 of document F12: subsequent NMA CKD continuous rerun HbA1c
(d) Figures obtained from Table 11 of document F9: subsequent NMA comorbidities
(e) Figures obtained from Table 6 of document F11: subsequent NMA higher risk continuous

Table 89. Change in weight hazard ratios in year 1 versus placebo

	ASCVD[(a)]	CKD[(b)]	HF	High risk of CVD[(c)]
Canagliflozin		0.99 (0.98, 1.00)		0.97 (0.96, 0.98)
Dapagliflozin	0.98 (0.97, 0.98)	0.98 (0.97, 0.99)		0.97 (0.96, 0.98)
Empagliflozin	1.02 (0.93, 1.11)	0.98 (0.98, 0.99)		0.98 (0.97, 0.98)
Ertugliflozin		0.98 (0.97, 0.99)		0.97 (0.95, 0.99)
Dulaglutide				0.99 (0.98, 0.99)
Exenatide				0.98 (0.98, 0.99)
Liraglutide				0.97 (0.96, 0.98)
Semaglutide (oral)				0.96 (0.95, 0.98)
Semaglutide (subcutaneous)				0.96 (0.95, 0.98)
Alogliptin				1.00 (0.98, 1.02)
Linagliptin		0.99 (0.92, 1.05)		1.00 (0.99, 1.02)
Saxagliptin				1.00 (0.99, 1.02)
Sitagliptin	1.05 (0.95, 1.17)			0.99 (0.99, 1.00)
Vildagliptin	1.02 (1.00, 1.04)			1.00 (0.99, 1.02)
Gliclazide				1.01 (0.98, 1.04)
Insulin				1.03 (1.02, 1.03)
Pioglitazone				1.03

				(1.02, 1.04)
Metformin				

(a) Figures obtained from Table 18 of document F9: subsequent NMA comorbidities
(b) Figures obtained from Table 3 of document F9: subsequent NMA comorbidities
(c) Figures obtained from Table 9 of document F11: subsequent NMA higher risk continuous

Table 90. Risk of CVM versus placebo (hazard ratios)

	ASCVD[a]	CKD[b]	HF[c]	High risk of CVD[d]
Canagliflozin	0.86 (0.70, 1.06)	0.79 (0.62, 1.01)	0.72 (0.51, 1.02)	0.88 (0.73, 1.06)
Dapagliflozin	0.95 (0.77, 1.19)	0.90 (0.71, 1.15)	1.01 (0.73, 1.39)	1 (0.84, 1.19)
Empagliflozin	0.62 (0.49, 0.78)	0.71 (0.52, 0.97)		4.11 (0.37, 98.87)
Ertugliflozin	0.92 (0.77, 1.11)	*Not estimable*		2.07 (0.25, 31.97)
Dulaglutide				0.92 (0.78, 1.06)
Exenatide				0.88 (0.76, 1.02)
Liraglutide		*Not estimable*	0.85 (0.63, 1.15)	0.77 (0.65, 0.9)
Semaglutide (oral)		*Not estimable*		0.53 (0.3, 0.93)
Semaglutide (subcutaneous)		0.71 (0.56, 0.89)		0.95 (0.65, 1.4)
Alogliptin	0.85 (0.66, 1.10)		0.77 (0.54, 1.09)	3.18 (0.46, 32.11)
Linagliptin		*Not estimable*	0.96 (0.76, 1.26)	0.98 (0.82, 1.17)
Saxagliptin				1.03 (0.87, 1.22)
Sitagliptin	1.03 (0.89, 1.19)			1.22 (0.7, 2.14)
Vildagliptin			1.80 (0.54, 7.15)	1.21 (0.21, 8.08)
Gliclazide				6.54 (0.18, 738.69)
Insulin				1.3 (0.65, 2.55)
Pioglitazone	0.94 (0.74, 1.20)			0.99 (0.09, 8.58)
Metformin				1.58 (0.26, 10.63)

(a) Figures obtained from Table 19 of document F9: subsequent NMA comorbidities
(b) Figures obtained from Table 5 of document F9: subsequent NMA comorbidities, except for subcutaneous semaglutide, which was taken from Perkovic 2024
(c) Figures obtained from Table 12 of document F9: subsequent NMA comorbidities
(d) Figures obtained from Table 11 of document F10: subsequent NMA higher risk

Table 91. Risk of IHD versus placebo (hazard ratios)

	ASCVD[a]	CKD	HF	High risk of CVD[b]
Canagliflozin				
Dapagliflozin	0.40 (0.08, 1.50)			1.02 (0.85, 1.22)
Empagliflozin	0.97 (0.73, 1.30)			0.11 (0, 4.85)
Ertugliflozin	0.81 (0.63, 1.07)			
Dulaglutide				1.12 (0.83, 1.5)
Exenatide				1.14 (0.92, 1.42)
Liraglutide				0.96 (0.75, 1.23)
Semaglutide (oral)				1.92 (0.84, 4.38)
Semaglutide (subcutaneous)				0.83 (0.48, 1.44)
Alogliptin	0.90 (0.60, 1.37)			
Linagliptin				0.88 (0.58, 1.34)
Saxagliptin				1.18 (0.88, 1.6)
Sitagliptin	0.90 (0.70, 1.16)			1.54 (0.73, 3.42)
Vildagliptin				
Gliclazide				
Insulin				1.18 (0.51, 2.74)
Pioglitazone				14.96 (0.55, 964.6)
Metformin				0.45 (0, 44.74)

(a) Figures obtained from Table 24 of document F9: subsequent NMA comorbidities
(b) Figures obtained from Table 19 of document F10: subsequent NMA higher risk

Table 92. Risk of HHF versus placebo (hazard ratios)

	ASCVD[(a)]	CKD[(b)]	HF[(c)]	High risk of CVD[(d)]
Canagliflozin	0.68 (0.51, 0.90)	0.61 (0.47, 0.79)	0.61 (0.45, 0.84)	0.67 (0.52, 0.87)
Dapagliflozin	0.79 (0.64, 0.98)	0.72 (0.57, 0.91)	0.73 (0.55, 0.96)	0.73 (0.61, 0.88)
Empagliflozin	0.65 (0.50, 0.85)	0.61 (0.42, 0.88)		0.45 (0.03, 5.1)
Ertugliflozin	0.70 (0.54, 0.91)	*Not estimable*	0.63 (0.44, 0.90)	
Dulaglutide				0.93 (0.77, 1.12)
Exenatide				0.94 (0.79, 1.14)
Liraglutide		0.82 (0.14, 4.74)	0.98 (0.75, 1.28)	0.87 (0.73, 1.04)
Semaglutide (oral)		*Not estimable*		0.91 (0.54, 1.54)
Semaglutide (subcutaneous)				1.08 (0.75, 1.54)
Alogliptin	1.19 (0.90, 1.58)		1.00 (0.71, 1.41)	6.53 (0.31, 721.77)
Linagliptin		0.84 (0.68, 1.04)	0.88 (0.68, 1.14)	0.9 (0.75, 1.08)
Saxagliptin				1.27 (1.07, 1.52)
Sitagliptin	1.00 (0.83, 1.20)	0.75 (0.13, 4.48)	1.05 (0.79, 1.39)	1.92 (1.08, 3.53)
Vildagliptin				
Gliclazide				
Insulin				1.7 (0.77, 3.65)
Pioglitazone	1.41 (1.10, 1.80)			2.1 (0.57, 9.49)
Metformin				0.75 (0.15, 3.27)

(a) Figures obtained from Table 20 of document F9: subsequent NMA comorbidities
(b) Figures obtained from Table 6 of document F9: subsequent NMA comorbidities
(c) Figures obtained from Table 13 of document F9: subsequent NMA comorbidities
(d) Figures obtained from Table 21 of document F10: subsequent NMA higher risk

Table 93. Risk of MI versus placebo (hazard ratios)

	ASCVD[(a)]	CKD[(b)]	HF[(c)]	High risk[(d)]
Canagliflozin	0.79 (0.63, 0.99)			0.85 (0.69, 1.05)
Dapagliflozin	0.88 (0.75, 1.03)		0.85 (0.61, 1.18)	0.89 (0.77, 1.02)
Empagliflozin	0.87 (0.70, 1.08)			
Ertugliflozin	1.04 (0.86, 1.26)			
Dulaglutide				0.96 (0.79, 1.17)
Exenatide				0.95 (0.83, 1.08)
Liraglutide		0.90 (0.01, 20.14)	0.74 (0.52, 1.06)	0.88 (0.769, 1.04)
Semaglutide (oral)				1.1 (0.7, 1.71)
Semaglutide (subcutaneous)		0.80 (0.55, 1.15)		0.73 (0.51, 1.04
Alogliptin	1.08 (0.88, 1.33)		1.04 (0.74, 1.46)	2.98 (0.25, 88.99)
Linagliptin		2.39 (0.50, 16.38)		1.15 (0.92, 1.46)
Saxagliptin				0.95 (0.81, 1.12)
Sitagliptin	0.96 (0.81, 1.13)	3.45 (0.29, 54.17)		1.58 (0.43, 5.75)
Vildagliptin	*Not estimable*			
Gliclazide				2.04 (0.2, 34.38)
Insulin				0.99 (0.23, 4.57)
Pioglitazone	0.84 (0.66, 1.07)			0.75 (0.25, 2.11)
Metformin				

(a) Figures obtained from Table 23 of document F9: subsequent NMA comorbidities
(b) Figures obtained from Table 9 of document F9: subsequent NMA comorbidities, except for subcutaneous semaglutide, which was taken from Perkovic 2024
(c) Figures obtained from Table 16 of document F9: subsequent NMA comorbidities
(d) Figures obtained from Table 17 of document F10: subsequent NMA higher risk

Table 94. Risk of stroke versus placebo (hazard ratios)

	ASCVD[(a)]	CKD[(b)]	HF[(c)]	High risk of CVD[(d)]
Canagliflozin	0.88 (0.67, 1.16)			0.9 (0.71, 1.15)
Dapagliflozin	0.97 (0.76, 1.22)	<0.01 (<0.01, 4.30)	1.21 (0.76, 1.90)	1.01 (0.85, 1.21)
Empagliflozin	1.24 (0.92, 1.65)			0.72 (0.04, 13.16)
Ertugliflozin	1.00 (0.76, 1.32)			
Dulaglutide				0.78 (0.63, 0.97)
Exenatide				0.86 (0.7, 1.06)
Liraglutide		*Not estimable*	0.89 (0.53, 1.50)	0.88 (0.71, 1.09)
Semaglutide (oral)				0.77 (0.41, 1.44)
Semaglutide (subcutaneous)		1.22 (0.84, 1.77)		0.62 (0.39, 0.98)
Alogliptin	0.92 (0.56, 1.51)		1.85 (0.70, 5.56)	
Linagliptin		0.84 (0.01, 28.75)		0.89 (0.65, 1.25)
Saxagliptin				1.11 (0.89, 1.39)
Sitagliptin				0.35 (0.06, 1.55)
Vildagliptin			0.04 (<0.01, 1.12)	0.33 (0.05, 1.62)
Gliclazide				0.09 (0, 3.92)
Insulin				0.26 (0.06, 0.96)
Pioglitazone	0.81 (0.61, 1.07)			0.87 (0.2, 3.53)
Metformin				

(a) Figures obtained from Table 22 of document F9: subsequent NMA comorbidities
(b) Figures obtained from Table 8 of document F9: subsequent NMA comorbidities, except for subcutaneous semaglutide, which was taken from Perkovic 2024
(c) Figures obtained from Table 15 of document F9: subsequent NMA comorbidities
(d) Figures obtained from Table 18 of document F10: subsequent NMA higher risk

Table 95. Risk of established kidney disease versus placebo (hazard ratios)

	ASCVD	CKD[(a)]	HF	High risk of CVD[(b)]
Canagliflozin		0.68 (0.54, 0.86)		0.77 (0.31, 1.96)
Dapagliflozin		0.48 (0.05, 4.37)		0.35 (0.15, 0.83)
Empagliflozin				
Ertugliflozin				
Dulaglutide				0.5 (0.11, 1.87)
Exenatide				0.86 (0.59, 1.2)
Liraglutide				0.89 (0.62, 1.24)
Semaglutide (oral)				
Semaglutide (subcutaneous)		0.84 (0.63, 1.12)		
Alogliptin				
Linagliptin				0.98 (0.68, 1.39)
Saxagliptin		0.0006 (<0.0001, 0.64)		0.9 (0.62, 1.32)
Sitagliptin				
Vildagliptin				
Gliclazide				
Insulin				
Pioglitazone				
Metformin				

(a) Figures obtained from Table 10 of document F9: subsequent NMA comorbidities, except for subcutaneous semaglutide, which was taken from Perkovic 2024
(b) Figures obtained from Table 22 of document F10: subsequent NMA higher risk

1 Appendix B: Code lists for ASCVD and HF

2 **Table 96. Terms used to define ASCVD in SNOMED**

MedCode ID	Term
2534664018	Ischaemic heart disease
299757012	Angina pectoris
94884017	Acute myocardial infarction
2537480011	IHD - Ischaemic heart disease
405339016	Cerebrovascular accident
395783012	Transient ischaemic attack
395788015	Transient cerebral ischaemia
235911000006116	Peripheral vascular disease
1780501013	Acute non-ST segment elevation myocardial infarction
105536013	Intermittent claudication
605501000006117	CVA unspecified
219531000000117	MI - acute myocardial infarction
2536395017	Coronary artery disease
1780491019	Acute ST segment elevation myocardial infarction
1488382011	Acute coronary syndrome
299835014	Ischaemic heart disease NOS
395780010	Cerebral infarction
605491000006113	CVA - Cerebrovascular accident
7845011	Unstable angina
299714019	Acute myocardial infarction of inferior wall
300515011	Peripheral vascular disease NOS
605461000006117	CVA - cerebrovascular accident due to cerebral artery occlusion
1222398015	Cerebral arterial occlusion
122401000006115	Stroke unspecified
395791015	Other peripheral vascular disease
744901000006114	Intracerebral haemorrhage (ICH)
350348018	Stable angina
300370010	Left sided CVA
5010981000006119	Stroke

MedCode ID	Term
251692018	H/O: TIA
216185010	Peripheral vascular disease monitoring
299721019	Acute myocardial infarction NOS
4031011	Old myocardial infarction
72571000006115	Unstable angina
411512011	Claudication
300371014	Right sided CVA
482941000006119	Angina pectoris NOS
497559016	Arteriosclerotic dementia
299765010	Angina pectoris NOS
350346019	Triple vessel disease of the heart
595731000006114	Coronary atherosclerosis
605471000006112	Cerebral hemorrhage
741131000000114	Peripheral vascular disease monitoring first letter
696161000006115	Multi-infarct dementia
451133011	Left sided cerebral infarction
158118014	Cerebellar infarction
299782012	Single coronary vessel disease
299709018	Anterior myocardial infarction NOS
742481000006118	Ischaemic leg
122361000006113	Stroke due to cerebral arterial occlusion
118689010	Cerebral thrombosis
122371000006118	Cerebral haemorrhage
451134017	Right sided cerebral infarction
810821000006112	H/O: myocardial infarct at greater than 60
299796018	Ischaemic cardiomyopathy
299776014	Chronic ischaemic heart disease
455641000006112	Acute anterolateral myocardial infarction
810811000006116	H/O: myocardial infarct at less than 60
299783019	Double coronary vessel disease
442204010	Angina on effort

MedCode ID	Term
13944841000006117	Peripheral arterial disease
299342019	Lacunar infarction
218511000000117	Infarction - cerebral
95931000006111	Transient cerebral ischaemia NOS
67511000006117	Vertebro-basilar insufficiency
299745015	Acute coronary insufficiency
37443015	Heart attack
457531000006110	Acute inferolateral myocardial infarction
116992017	Acute subendocardial infarction
1227364015	History of coronary artery bypass grafting
299741012	Preinfarction syndrome
350535018	Peripheral ischaemic vascular disease
443199013	Ischaemic foot
450665015	Ischaemic toe
2474651019	Infarction of basal ganglia
399031000006111	[X]Multi-infarct dementia
502878012	Cerebellar haemorrhage
7847015	Crescendo angina
350533013	Peripheral ischaemia
3414251000006112	VAD - Vascular dementia
524511000006116	Brainstem stroke syndrome
300366019	Cerebellar stroke syndrome
451132018	[V]Presence of coronary artery bypass graft
2160096015	Coronary artery bypass graft occlusion
494261017	Worsening angina
299707016	Acute anterior myocardial infarction
884611000006112	Peripheral vasc. disease NOS
230021000006115	Personal history of myocardial infarction
884151000006119	Myocardial Infarction
338974012	Ischaemic chest pain
459859010	Asymptomatic coronary heart disease

MedCode ID	Term
5058071000006110	Lower limb ischaemia
300362017	Middle cerebral artery syndrome
363791000006112	[X]Arteriosclerotic dementia
4778181000006119	Left sided cerebral hemisphere cerebrovascular accident
125470015	Cerebral embolism
300349016	Transient cerebral ischaemia NOS
106394016	Vertebrobasilar insufficiency
741071000000112	Peripheral vascular disease monitoring invitation
2855301000006112	Myocardial infarction
7844010	Preinfarction syndrome
1847121000006114	Peripheral arterial disease
4778201000006118	Right sided cerebral hemisphere cerebrovascular accident
256452010	ECG: myocardial infarction
299710011	Acute posterior myocardial infarction
498328016	Angina at rest
455651000006114	Acute anteroseptal myocardial infarction
299834013	Other specified ischaemic heart disease
300514010	Other specified peripheral vascular disease NOS
302011	Diabetic peripheral angiopathy
543141000006110	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
350350014	New onset angina
450322013	Acute non-Q wave infarction
1234005010	Acute inferoposterior infarction
6632221000006112	Peripheral arterial occlusive disease
300277011	Intracerebral haemorrhage, intraventricular
300321011	Cerebral infarction due to thrombosis of cerebral arteries
524541000006117	Brain stem infarction
300287010	Intracerebral haemorrhage NOS
884621000006116	Peripheral vasc. disease NOS
4776121000006117	Generalised ischaemic myocardial dysfunction
1786197015	Coronary thrombosis

MedCode ID	Term
1738171000006114	History of myocardial infarction
2534674015	Chronic myocardial ischaemia
350376014	Silent myocardial infarction
39111000006114	Other acute and subacute ischaemic heart disease
3371411000006113	CHD - Coronary heart disease
3371421000006117	Coronary heart disease
299711010	Acute lateral myocardial infarction
5058111000006119	Critical lower limb ischaemia
300312010	Cerebral infarct due to thrombosis of precerebral arteries
300941014	[X]Other cerebral infarction
503469016	Pontine haemorrhage
503791000006114	Basal ganglia haemorrhage
300364016	Posterior cerebral artery syndrome
5011091000006110	Partial anterior cerebral circulation infarction
6990981000006114	Ischaemic stroke
25897016	Subclavian steal syndrome
499739014	Insufficiency - basilar artery
67501000006115	Vertebrobasilar artery syndrome
350354017	Silent myocardial ischaemia
5058231000006119	Coronary artery stenosis
451369010	H/O: Myocardial infarction in last year
299805019	Other chronic ischaemic heart disease NOS
299718016	Other acute myocardial infarction
98087016	Angina decubitus
1654891000000110	Coronary angioplasty planned
1550991000000116	Coronary artery bypass graft operation planned
4005601000006116	Calcific coronary arteriosclerosis
394541000006112	[X]Ischaemic heart diseases
89332015	Atherosclerotic heart disease
3600701000006114	Coronary artery atheroma
2115181000000110	Coronary microvascular disease

MedCode ID	Term
13930051000006117	Dressler's syndrome
8453031000006117	Haemorrhagic stroke
5011131000006112	Posterior cerebral circulation infarction
5582311000006110	Occipital cerebral infarction
294656010	Arteriosclerotic dementia NOS
8044481000006118	Ischaemic stroke without coma
300322016	Cerebral infarction due to embolism of cerebral arteries
300363010	Anterior cerebral artery syndrome
300943012	Cerebral artery occlusion
345655015	Pure motor lacunar syndrome
106392017	Basilar artery syndrome
4775971000006114	Angina
219521000000119	Attack - heart
459487012	Refractory angina
482811000006113	Angina at rest
2609111000000119	Non-obstructive coronary atherosclerosis
5887611000006117	Exercise-induced angina
458410010	Post infarct angina
459488019	Transient myocardial ischaemia
6651391000006114	NSTEMI - Non-ST segment elevation MI
2536393012	Arteriosclerotic heart disease
300510018	Other specified peripheral vascular disease
1715241000006112	Vascular claudication
2377871000000112	Ischaemic foot pain at rest
542261000006114	Cerebral infarction due to occlusion of precerebral artery
9912271000006112	Cerebellar stroke
163261000006119	Right sided intracerebral haemorrhage, unspecified
300313017	Cerebral infarction due to embolism of precerebral arteries
345675012	Lobar cerebral haemorrhage
496232015	Internal capsule haemorrhage
5011051000006116	Total anterior cerebral circulation infarction

MedCode ID	Term
300939013	Cerebral haemorrhage
748941000006115	Left sided intracerebral haemorrhage, unspecified
884421000006119	Cerebral haemorrhage
130375018	Lateral medullary syndrome
345684012	Carotid territory transient ischaemic attack
300348012	Other transient cerebral ischaemia
416991000006112	Transient cerebral ischemia
58046010	Vertebral artery syndrome
6360391000006118	Atypical angina
542251000006112	Cerebral infarction due to cerebral venous thrombosis, non-pyogenic
345650013	Brainstem infarction NOS
256460011	ECG: myocardial infarct NOS
208365015	Postoperative myocardial infarction
2537483013	Chronic coronary insufficiency
299808017	Subsequent myocardial infarction
59952018	Nocturnal angina
495394013	Cortical haemorrhage
300344014	Carotid artery syndrome hemispheric
1667741000000110	[V]Personal history of transient ischaemic attack
1234306015	Acute septal infarction
4032016	Healed myocardial infarction
345658018	Pure sensory lacunar syndrome
5492171000006112	TIA
905351000006113	[RFC] Myocardial infarction (MI)
299712015	True posterior myocardial infarction
299719012	Acute atrial infarction
447324018	Acute Q-wave infarct
6360351000006112	Multi vessel coronary artery disease
6651221000006117	STEMI - ST elevation myocardial infarction
299720018	Other acute myocardial infarction NOS
460681000006116	Acute transmural myocardial infarction of unspecif site

MedCode ID	Term
884141000006116	Coronary thrombosis
7571581000006113	Acute anterior ST segment elevation myocardial infarction
5011471000006116	Posterior circulation stroke of uncertain pathology
7054171000006115	Acute lacunar infarction
744921000006116	Intracerebral haemorrhage in hemisphere, unspecified
12223101000006118	Intracerebral haemorrhage
14068071000006114	History of transient ischaemic attack
300353019	Intermittent cerebral ischaemia
8231151000006110	Personal history of transient ischaemic attack
1786198013	Thrombosis - coronary
299723016	Other acute and subacute ischaemic heart disease
7572321000006112	Acute ST segment elevation myocardial infarction of inferior wall
5886711000006111	Ischaemia of feet
5011041000006118	Anterior cerebral circulation infarction
5011411000006113	Thalamic haemorrhage
1212072018	Occlusive stroke
6348301000006119	Embolic stroke
682481000006118	Myocardial infarction aborted
216351000006118	Post infarction pericarditis
7105241000006116	Typical angina
494438016	Subendocardial ischaemia
6864781000006110	Myocardial ischaemia
109915012	Post-myocardial infarction syndrome
14130101000006118	Stenosis of anterior descending branch of left coronary artery
6021731000006115	Critical ischaemia of foot
5967391000006111	Multiple lacunar infarcts
423221000006117	[X]Predominantly cortical dementia
370701000006118	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
300956017	[X]Intracerebral haemorrhage in hemisphere, unspecified
542831000006116	Cerebral embolus
906771000006113	[RFC] Peripheral vascular disease

MedCode ID	Term
299742017	Coronary thrombosis not resulting in myocardial infarction
300874013	[X]Other forms of angina pectoris
299800012	Other specified chronic ischaemic heart disease
299804015	Other specified chronic ischaemic heart disease NOS
299708014	Acute anteroapical infarction
967931000006114	Acute myocardial infarction of posterolateral wall
6850801000006111	Disorder of coronary artery
3381601000006117	Acute myocardial infarction of anterior wall
300963017	[X]Other specified peripheral vascular diseases
459308015	Type 2 diabetes mellitus with peripheral angiopathy
3515794015	Acute cerebral ischaemia
5011291000006119	Haemorrhagic cerebral infarction
5011461000006111	Anterior circulation stroke of uncertain pathology
57341000006119	Wallenberg's syndrome
5011491000006115	Anterior circulation transient ischaemic attack
5492221000006118	Transient ischemic attack
2476647018	Vertebral artery compression syndrome
4354151000006115	Right coronary artery occlusion
931961000006117	Acute coronary syndrome
100681000006116	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
537751000006115	Cardiac rupture after acute myocardial infarction
299763015	Angina decubitus NOS
14130061000006116	Stenosis of right coronary artery
8036721000006118	Chronic total occlusion of coronary artery
299812011	Subsequent myocardial infarction of inferior wall
5887631000006111	Exertional angina
6546111000006118	ACS - Acute coronary syndrome
460686018	[V]Presence of aortocoronary bypass graft
299750014	Other acute and subacute ischaemic heart disease NOS
6860251000006115	Ischemic heart disease
3371381000006110	CAD - Coronary artery disease

MedCode ID	Term
7571601000006115	Acute STEMI (ST elevation myocardial infarction) of anterior wall
7572331000006110	Acute STEMI (ST elevation myocardial infarction) of inferior wall
14132941000006118	Myocardial infarction with non-obstructive coronary artery
370661000006114	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
3508964014	Cerebrovascular accident due to thrombus of left middle cerebral artery
5011161000006115	Lacunar stroke
605481000006110	CVA - cerebrovascular accident in the puerperium
6846141000006118	Cardioembolic stroke
746571000006116	Intracerebral haemorrhage, multiple localized
5011191000006111	Pure motor lacunar infarction
9868571000006116	Mural thrombus of left ventricle following acute myocardial infarction
813961000006116	Haemopericardium as current complication following acute myocardial infarction
498031000006112	Atrial septal defect as current complication following acute myocardial infarction
36036010	Syncope anginosa
5056201000006111	Triple vessel coronary artery disease
6601121000006118	Coronary artery thrombosis
362461000006119	[X]Acute transmural myocardial infarction of unspecif site
299811016	Subsequent myocardial infarction of anterior wall
455422014	Postoperative subendocardial myocardial infarction
6360361000006114	Left main coronary artery disease
13941171000006115	Occlusion of mid left anterior descending coronary artery
14130081000006114	Stenosis of left coronary artery main stem
8278561000006114	Ischaemic lower limb pain at rest
3508961018	Cerebrovascular accident due to thrombus of right middle cerebral artery
7855631000006111	Cerebral ischaemic stroke due to small artery occlusion
13909901000006119	Cerebral ischaemic stroke co-occurrent with subarachnoid haemorrhage
300276019	External capsule haemorrhage
4777881000006112	Intracerebral haemorrhage, multiple localised

MedCode ID	Term
345639010	Infarction - precerebral
5011451000006114	Stroke of uncertain pathology
3505637014	Occlusion of left middle cerebral artery
300352012	Impending cerebral ischaemia
5492201000006111	TIA - Transient ischaemic attack
7289121000006119	Recurrent transient cerebral ischaemic attack
2729671000000118	Acute transmural myocardial infarction
455423016	Postoperative myocardial infarction, unspecified
4776071000006117	Two coronary vessel disease
6860261000006118	IHD - Ischemic heart disease
109916013	Dressler's syndrome
14130091000006112	Stenosis of circumflex branch of left coronary artery
5011141000006119	Posterior cerebral circulation stroke
6990991000006112	Ischemic stroke
14194801000006111	Acute cerebrovascular accident due to ischaemia
3166141000006114	Angina, class II
7475751000006117	Ischaemic dilated cardiomyopathy due to coronary artery disease
3536581000006113	Coronary occlusion
13930031000006112	Delayed postmyocardial infarction pericarditis
13941121000006116	Occlusion of proximal left anterior descending coronary artery
280561000006111	Non-insulin-dependent diabetes mellitus with peripheral angiopathy
13919651000006113	Ulcer of heel due to atherosclerosis of artery of lower limb
6348291000006115	Thrombotic stroke
7839991000006115	Silent cerebral infarct
3511959014	Thrombosis of left middle cerebral artery
3509794017	Cerebrovascular accident due to occlusion of left middle cerebral artery
14014251000006116	Cerebrovascular accident due to occlusion of bilateral pontine arteries
5011111000006118	Partial anterior cerebral circulation stroke
5011211000006112	Pure sensory lacunar infarction

MedCode ID	Term
12122331000006116	Acute ST segment elevation myocardial infarction of inferolateral wall
2619484018	MI - Myocardial infarction aborted
300879015	[X]Other forms of chronic ischaemic heart disease
12122341000006114	Acute ST segment elevation myocardial infarction of inferoposterior wall
5056421000006119	Old inferior myocardial infarction
67081000006119	Ventricular septal defect as current complication following acute myocardial infarction
300511019	Peripheral angiopathic disease EC NOS
3511955015	Thrombosis of right middle cerebral artery
14492731000006117	Cerebrovascular accident of thalamus
13909881000006116	Cerebral ischaemic stroke due to global hypoperfusion with watershed infarct
4056931000006116	Brain stem haemorrhage
3509810017	Cerebrovascular accident due to occlusion of right middle cerebral artery
5011121000006114	PACS - Partial anterior cerebral circulation stroke
2901571000006113	Completed stroke
12223121000006111	ICH - intracerebral haemorrhage
3508955016	Cerebrovascular accident due to thrombus of basilar artery
118831000006118	Subsequent myocardial infarction of unspecified site
6546751000006118	First myocardial infarction
300876010	[X]Other forms of acute ischaemic heart disease
3371361000006117	Coronary arteriosclerosis
5058121000006110	Critical lower limb ischemia
459306016	Type II diabetes mellitus with peripheral angiopathy
7067291000006113	Infarction of medulla oblongata
2729571000000119	Cerebral infarction due to stenosis of cerebral artery
3505639012	Occlusion of right middle cerebral artery
32122016	Status anginosus
543291000006110	Myocardial infarction with complication
6841231000006113	Acute ischaemic heart disease

MedCode ID	Term
7510331000006117	History of non-ST segment elevation myocardial infarction
3641641000006116	Acute myocardial infarction of anterolateral wall
13941191000006119	Occlusion of distal left anterior descending coronary artery
14015031000006119	Myocardial infarction due to demand ischaemia
7574481000006111	Subsequent non-ST segment elevation myocardial infarction
5589641000006112	Intracerebellar and posterior fossa haemorrhage
3507383012	Spontaneous haemorrhage of cortical intracerebral hemisphere
483988011	Bulbar haemorrhage
2729551000000111	Cerebral infarction due to occlusion of cerebral artery
14182621000006113	Cryptogenic stroke
5011521000006118	Vertebrobasilar territory transient ischaemic attack
299758019	Stenocardia
4776031000006115	Ischaemic heart disease - angina
4776141000006112	Ischemic cardiomyopathy
2855351000006111	Myocardial infarct
5056411000006110	Old anterior myocardial infarction
5056941000006119	Post-infarction pericarditis
8087751000006116	Acute ST segment elevation myocardial infarction involving left anterior descending coronary artery
6841391000006118	Acute myocardial ischaemia
1229885017	Microinfarction of heart
3565871000006113	Acute myocardial infarction of inferolateral wall
7502661000006117	Microvascular ischaemia of myocardium
4354131000006110	Left coronary artery occlusion
13945191000006117	Occlusion of anterior descending branch of left coronary artery
14130111000006115	LAD (left anterior descending) coronary artery stenosis
7848701000006116	Acute occlusion of artery of lower limb co-occurrent and due to thromboembolus
13718621000006117	History of cerebrovascular accident due to ischaemia
5011071000006114	Total anterior cerebral circulation stroke
5011241000006111	Lacunar ataxic hemiparesis
14194811000006114	Acute ischaemic stroke

MedCode ID	Term
9843961000006118	Acute ST segment elevation myocardial infarction of anterolateral wall
9868461000006110	Unstable angina co-occurrent and due to coronary arteriosclerosis
7065281000006117	Ischaemic congestive cardiomyopathy
3499001000006116	Angina, class I
7508021000006119	CABG (coronary artery bypass graft) operation planned
7572351000006115	Silent coronary vasospastic disease
13941141000006111	Acute ST segment elevation myocardial infarction due to mid left anterior descending coronary artery occlusion
5294511000006117	Coronary graft stenosis
6043771000006118	Non-Q wave myocardial infarction
616081000006113	Diabetes mellitus insulin-glucose infusion in acute myocardial infarction
3452181000006112	Acute myocardial infarction of lateral wall
14145381000006119	Occlusion of circumflex branch of left coronary artery
913931000006116	Type 1 diabetes mellitus with peripheral angiopathy
300970017	[X]Peripheral angiopathy in diseases classified elsewhere
6633851000006110	PVD-peripheral vascular disease
5967911000006119	Trash foot
3508962013	Stroke due to thrombus of right middle cerebral artery
2832651000006111	Subcortical haemorrhage
5011351000006119	Posterior cerebral circulation haemorrhagic infarction
3512176011	Embolus of left middle cerebral artery
2622631000006114	Intrapontine haemorrhage
13909861000006114	Cerebral ischaemic stroke due to dissection of artery
5011081000006112	TACS - Total anterior cerebral circulation stroke
12223111000006115	Intracerebral hemorrhage
14194611000006113	Acute cerebrovascular accident of basal ganglia
14518481000006115	Cerebrovascular accident of basal ganglia
14518501000006113	Cerebrovascular accident of brainstem
3778021000006116	LMS - Lateral medullary syndrome
11920121000006117	Transient cerebral ischemia
300345010	Multiple and bilateral precerebral artery syndromes

MedCode ID	Term
9844011000006119	Acute ST segment elevation myocardial infarction of posterior wall
4776051000006110	Single vessel coronary artery disease
5935321000006111	Acute Q wave myocardial infarction
13935211000006117	Acute myocardial infarction of inferolateral wall with posterior extension
3886751000006118	Angina, class III
14130071000006111	RCA (right coronary artery) stenosis
2515471000006117	Septal infarction by electrocardiogram
8041051000006118	History of placement of stent in coronary artery bypass graft
299813018	Subsequent myocardial infarction of other sites
300882013	[X]Subsequent myocardial infarction of unspecified site
5647291000006110	Ischaemic myocardial dysfunction
212061000006119	Postoperative transmural myocardial infarction of anterior wall
212071000006114	Postoperative transmural myocardial infarction of inferior wall
7093091000006111	Recent myocardial infarction
3536601000006115	Coronary artery occluded
7574491000006114	Subsequent NSTEMI (non-ST segment elevation myocardial infarction)
3699921000006110	Acute inferior myocardial infarction
3745741000006117	Acute myocardial infarction of inferoposterior wall
13944861000006118	Peripheral artery disease
4392221000006118	Peripheral angiopathy due to diabetes mellitus
84961000006116	Type II diabetes mellitus with peripheral angiopathy
4193641000006111	Nonparalytic stroke
3509799010	Cerebrovascular accident due to occlusion of left posterior cerebral artery
3509790014	Cerebrovascular accident due to occlusion of right posterior cerebral artery
3508965010	Stroke due to thrombus of left middle cerebral artery
5011171000006110	LACI - Lacunar infarction
5011431000006119	Lacunar haemorrhage
3510963013	Lacunar ataxic hemiparesis of left dominant side
3505651014	Occlusion of left posterior cerebral artery

MedCode ID	Term
14194191000006114	Acute cerebrovascular accident due to stenosis of left carotid artery
3511086012	Thrombosis of right vertebral artery
5011101000006116	PACI - Partial anterior cerebral circulation infarction
3507370011	Spontaneous haemorrhage of cerebral hemisphere
14194211000006110	Acute cerebrovascular accident due to occlusion of left middle cerebral artery
14194641000006112	Acute cerebrovascular accident of brainstem
3512178012	Embolus of right middle cerebral artery
3777981000006119	Posterior inferior cerebellar artery syndrome
5011501000006111	Anterior circulation transient ischemic attack
5011551000006110	Posterior circulation transient ischaemic attack
212091000006110	Postoperative transmural myocardial infarction unspec site
9843981000006111	Acute ST segment elevation myocardial infarction of lateral wall
9843991000006114	Acute ST segment elevation myocardial infarction of anteroseptal wall
6360421000006114	Recurrent angina after coronary stent placement
3459561000006119	Acute myocardial infarction of apical-lateral wall
4776081000006119	Double vessel coronary artery disease
158601000006116	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction
8011041000006111	Acute myocardial infarction due to right coronary artery occlusion
5056501000006113	Post-infarction ventricular septal defect
7084801000006112	Mixed myocardial ischaemia and infarction
2571561000006118	Pre-infarction syndrome
3576371000006117	Postmyocardial infarction syndrome
7572341000006117	Acute inferior ST segment elevation myocardial infarction
13919691000006119	Ulcer of ankle due to atherosclerosis of artery of lower limb
3510961010	Lacunar ataxic hemiparesis of right dominant side
3508952018	Cerebrovascular accident due to thrombus of left carotid artery
14194491000006118	Acute cerebrovascular accident due to occlusion of right carotid artery
14492571000006113	Cerebrovascular accident due to occlusion of right anterior cerebral artery

MedCode ID	Term
14194741000006118	Acute cerebrovascular accident due to occlusion of right cerebellar artery
14492751000006112	Thalamic stroke
14493231000006118	Cerebrovascular accident due to embolism of bilateral middle cerebral arteries
9875951000006117	Cerebrovascular accident due to right carotid artery stenosis
13717171000006112	Cerebrovascular accident due to stenosis of bilateral carotid arteries
5011061000006119	TACI - Total anterior cerebral circulation infarction
13967201000006117	Occlusion of branch of basilar artery
5011541000006113	Posterior circulation transient ischemic attack
988951000006117	Transient Ischaemic Attacks
3551171000006114	Acute myocardial infarction of high lateral wall
7574041000006111	Mitral valve regurgitation due to acute myocardial infarction
13961321000006113	Occlusion of proximal portion of right coronary artery
13961461000006113	Acute ST segment elevation myocardial infarction due to occlusion of posterior lateral branch of right coronary artery
9844051000006118	Acute ST segment elevation myocardial infarction due to right coronary artery occlusion
6837051000006119	Basal ganglion stroke
5011261000006110	Multi-infarct state
7855711000006113	Stroke co-occurrent with migraine
2855341000006114	MI - Myocardial infarction
7966931000006114	Angina associated with type 2 diabetes mellitus
13945211000006116	Acute ST segment elevation myocardial infarction due to occlusion of anterior descending branch of left coronary artery
159001000006119	Rupture of papillary muscle as current complication following acute myocardial infarction
3024781000006112	Past myocardial infarction diagnosed on ECG AND/OR other special investigation, but currently presenting no symptoms
12276271000006112	Progressive angina
6360401000006116	Recurrent angina after percutaneous transluminal coronary angioplasty
3842391000006115	Ischaemic contracture of left ventricle syndrome
13947581000006115	Occlusion of diagonal branch of anterior descending branch of left coronary artery

MedCode ID	Term
5898341000006114	Ischemic foot
6021741000006113	Critical ischemia of foot
84591000006119	Type 2 diabetes mellitus with peripheral angiopathy
14457701000006115	Left posterior cerebral artery thrombosis
3505653012	Occlusion of right posterior cerebral artery
4777811000006117	Basal ganglia hemorrhage
3508958019	Cerebrovascular accident due to thrombus of right carotid artery
14194941000006115	Acute cerebrovascular accident due to embolism of right middle cerebral artery
14194971000006111	Acute cerebrovascular accident due to embolism of left middle cerebral artery
4775931000006111	Aborted myocardial infarction
4776001000006111	Anginal syndrome
5056431000006116	Old lateral myocardial infarction
13945981000006117	Acute ST segment elevation myocardial infarction due to occlusion of septal branch of anterior descending branch of left coronary artery
494260016	Impending infarction
7298951000006115	Arteriosclerosis of coronary artery bypass graft of transplanted heart
3512174014	Embolus of right posterior cerebral artery
14492741000006110	Stroke of thalamus
2726591000006119	Anterior choroidal artery syndrome
4540591000006113	History of transient ischemic attack
6969941000006114	Coronary artery stent thrombosis
5056311000006117	Acute Q wave infarction - inferior
3526080018	Mural thrombus of right ventricle following acute myocardial infarction
300881018	[X]Subsequent myocardial infarction of other sites
8087551000006113	History of acute ST segment elevation myocardial infarction
6360371000006119	Significant coronary bypass graft disease
7571611000006117	Acute ST segment elevation myocardial infarction of anterior wall involving right ventricle
14194831000006115	History of type 2 myocardial infarction

MedCode ID	Term
13941211000006118	Acute ST segment elevation myocardial infarction due to distal left anterior descending coronary artery occlusion
13961331000006111	Occlusion of distal portion of right coronary artery
13961361000006119	Occlusion of mid portion of right coronary artery
13961451000006111	Acute STEMI (ST elevation myocardial infarction) due to PDA (posterior descending artery) branch of RCA (right coronary artery) occlusion
14132951000006116	MINOCA - myocardial infarction with non-obstructive coronary artery
14452831000006118	Bilateral embolism of middle cerebral arteries
14457721000006113	Right posterior cerebral artery thrombosis
4777861000006119	Intracerebral haemorrhage with intraventricular haemorrhage
5011331000006114	Anterior cerebral circulation haemorrhagic infarction
411416011	Stroke in the puerperium
14194661000006111	Acute cerebrovascular accident due to stenosis of right carotid artery
5011231000006118	Pure sensorimotor lacunar infarction
12223131000006114	ICH - intracerebral hemorrhage
7064691000006118	Transient cerebral ischaemia due to atrial fibrillation
1218860015	Acute papillary muscle infarction
6847761000006118	Chronic ischemic heart disease
7703511000006110	Subacute ischaemic heart disease
13941091000006115	Acute ST segment elevation myocardial infarction due to proximal left anterior descending coronary artery occlusion
5887641000006118	Angina of effort
6360441000006119	Recurrent angina after coronary artery bypass graft
7278491000006111	Atherosclerosis of coronary artery
7572221000006117	Subsequent ST segment elevation myocardial infarction of inferior wall
7696501000006114	Resting ischaemia
13961441000006114	Acute ST segment elevation myocardial infarction due to occlusion of posterior descending branch of right coronary artery
14145391000006116	Acute ST segment elevation myocardial infarction due to occlusion of circumflex branch of left coronary artery
5058081000006113	Lower limb ischemia

MedCode ID	Term
6632271000006113	Peripheral artery occlusive disease
3509792018	Cerebrovascular accident due to occlusion of left carotid artery
5649201000006113	Extension of cerebrovascular accident
3509817019	Left hemispheric cerebellar artery embolism with stroke
3636969013	Occlusion of right middle cerebral artery by embolus
9875961000006115	Cerebrovascular accident due to left carotid artery stenosis
13718601000006110	History of embolic cerebrovascular accident
14492321000006119	Cerebrovascular accident due to embolism of left anterior cerebral artery
3508956015	Stroke due to basilar artery thrombus
14489491000006119	Cerebrovascular accident due to thrombosis of right posterior cerebral artery
14194571000006115	Acute cerebrovascular accident due to occlusion of left carotid artery
13966821000006114	Occlusion of distal basilar artery
9844071000006111	Acute ST segment elevation myocardial infarction of septum
6946631000006113	Obliterative coronary artery disease
7572301000006119	Acute myocardial infarction during procedure
7572881000006117	Acute ST segment elevation myocardial infarction of inferior wall involving right ventricle
14194701000006115	Myocardial infarction due to atherothrombotic coronary artery disease
9353781000006114	Coronary arteriosclerosis after percutaneous coronary angioplasty
14742011000006111	Acute anterior non-ST segment elevation myocardial infarction
9843951000006115	Acute ST segment elevation myocardial infarction of posterolateral wall
5056441000006114	Old posterior myocardial infarction
14057221000006111	Rupture of ventricle due to acute myocardial infarction
3191111000006116	Congenital coronary artery sclerosis
13961431000006116	Acute STEMI (ST elevation myocardial infarction) due to AM (acute marginal) branch of RCA (right coronary artery) occlusion
14145371000006117	Acute myocardial infarction due to occlusion of circumflex branch of left coronary artery
13944851000006115	Peripheral arterial vascular disease
14861611000006117	Ischaemic foot with rest pain

MedCode ID	Term
4270361000006116	Paralytic stroke
5011251000006113	Dysarthria-clumsy hand syndrome
5011421000006117	Thalamic hemorrhage
6837061000006117	Basal ganglion infarct
3441831000006111	Progressing stroke
14194721000006113	Acute cerebrovascular accident due to thrombosis of right middle cerebral artery
14492871000006111	Stroke due to thrombosis of left posterior cerebral artery
14457741000006118	Left cerebellar artery thrombosis
14492191000006119	Cerebrovascular accident due to occlusion of left anterior cerebral artery
5582351000006111	Top of basilar syndrome
7295961000006113	Superior cerebellar artery syndrome
7289131000006116	Recurrent transient cerebral ischemic attack
212081000006112	Postoperative transmural myocardial infarction other sites
8014911000006110	Sequela of cardioembolic stroke
14509111000006110	Dilated cardiomyopathy of ischaemic origin
7106991000006111	Coronary arteriosclerosis of coronary artery bypass graft
3458791000006114	Anginal chest pain at rest
7572291000006115	Subsequent STEMI (ST elevation myocardial infarction)
7572861000006110	Acute myocardial infarction of anterior wall involving right ventricle
7789771000006114	Non-obstructive atherosclerosis of coronary artery
13941161000006110	Acute STEMI (ST elevation myocardial infarction) due to mid LAD (left anterior descending) coronary artery occlusion
13945971000006115	Occlusion of septal branch of anterior descending branch of left coronary artery
158611000006118	Rupture of chordae tendinae as current complication following acute myocardial infarction
5056271000006117	Acute Q wave infarction - anteroseptal
5056471000006118	Accelerated coronary artery disease in transplanted heart
7572251000006114	Subsequent ST segment elevation myocardial infarction of anterior wall
7848541000006112	Arrhythmia as current complication following acute myocardial infarction

MedCode ID	Term
13935161000006114	Acute myocardial infarction of right ventricle
13945201000006119	Occlusion of left anterior descending coronary artery
13961401000006112	Occlusion of posterior descending branch of right coronary artery
9837051000006111	Gangrene of right lower limb due to atherosclerosis
5058091000006111	Ischemic leg
13919631000006118	Limb pain at rest due to atherosclerosis of artery of lower limb
3532661000006118	IC - Intermittent claudication
14014281000006112	Cerebrovascular accident due to stenosis of bilateral vertebral arteries
3507359016	Spontaneous haemorrhage of brain stem
3636133016	Cerebrovascular accident due to occlusion of right middle cerebral artery by embolus
3636141016	Cerebrovascular accident due to occlusion of right cerebellar artery by embolus
3636143018	Cerebrovascular accident due to occlusion of left cerebellar artery by embolus
3505881015	Right middle cerebral artery thrombosis
14194841000006113	Acute cerebrovascular accident due to occlusion of left cerebellar artery
13905301000006116	Bilateral occlusion of pontine arteries
14492841000006115	Cerebrovascular accident due to occlusion of right posterior communicating artery
14492861000006116	Cerebrovascular accident due to thrombosis of left posterior cerebral artery
4056951000006111	Brainstem haemorrhage
4057031000006117	Brain stem infarct
14194281000006115	Acute cerebrovascular accident due to occlusion of right posterior cerebral artery
14194331000006112	Acute cerebrovascular accident due to occlusion of right middle cerebral artery
14492471000006114	Cerebrovascular accident due to thrombosis of right cerebellar artery
14194621000006117	Acute stroke of basal ganglia
14493261000006110	Cerebrovascular accident due to thrombosis of left cerebellar artery
14179491000006111	Unstable angina due to arteriosclerosis of coronary artery bypass graft of transplanted heart

MedCode ID	Term
12125971000006114	Unstable angina co-occurrent and due to arteriosclerosis of coronary artery bypass graft
4775981000006112	Cardiac angina
4776021000006118	Ischemic heart disease - angina
5056261000006112	Asymptomatic ischaemia
7572281000006118	Subsequent ST segment elevation myocardial infarction
14194711000006117	Type 1 myocardial infarction
13961381000006112	Acute STEMI (ST elevation myocardial infarction) due to mid RCA (right coronary artery) occlusion
13961391000006110	Occlusion of marginal branch of right coronary artery
14145451000006115	Acute STEMI (ST segment elevation myocardial infarction) of apex of heart
8032161000006112	Coronary arteriosclerosis in patient with history of previous myocardial infarction
14752451000006117	Ventricular thrombus following acute myocardial infarction
14015311000006110	Coronary artery disease due to type 2 diabetes mellitus
5056321000006113	Acute non-Q wave infarction - inferior
5056331000006111	Acute Q wave infarction - inferolateral
5056341000006118	Acute non-Q wave infarction - inferolateral
5056461000006113	MI - Silent myocardial infarction
6864791000006113	Myocardial ischemia
7574081000006117	Mitral valve regurgitation due to acute myocardial infarction without papillary muscle and chordal rupture
3655161000006110	Pericarditis secondary to acute myocardial infarction
14194821000006118	History of myocardial infarction due to demand ischaemia
9478171000006111	Pain at rest of left lower limb co-occurrent and due to atherosclerosis
84781000006112	Type I diabetes mellitus with peripheral angiopathy
913941000006114	Peripheral angiopathy due to type 1 diabetes mellitus
6632231000006110	PAOD - Peripheral arterial occlusive disease
6632251000006115	Peripheral angiopathy
14180191000006115	Bilateral intermittent claudication of lower limbs due to atherosclerosis of nonbiological bypass graft
3509769018	Cerebrovascular accident due to occlusion of left cerebellar artery

MedCode ID	Term
2832661000006113	Subcortical hemorrhage
2893541000006113	Weber-Gubler syndrome
14172901000006118	Bilateral occlusion of middle cerebral arteries
14172931000006114	Bilateral occlusion of anterior cerebral arteries
3414261000006114	Multi infarct dementia
7951271000006116	Haemorrhage of medulla oblongata
3512170017	Embolus of left posterior cerebral artery
14492701000006113	Cerebrovascular accident due to thrombosis of left vertebral artery
14518541000006110	Cerebrovascular accident due to embolism of basilar artery
4057041000006110	Brain stem stroke
4057051000006112	Infarction of brain stem
14457901000006117	Cerebral venous sinus thrombosis in puerperium
9875641000006111	Cerebrovascular accident due to right carotid artery occlusion
14492231000006112	Cerebrovascular accident due to occlusion of basilar artery
5582321000006119	Foville syndrome
3507363011	Spontaneous haemorrhage of deep cerebral hemisphere
3636136012	Cerebrovascular accident due to occlusion of left middle cerebral artery by embolus
14194151000006115	Acute cerebrovascular accident due to occlusion of left posterior cerebral artery
14194161000006118	Acute stroke due to occlusion of left posterior cerebral artery
14194651000006114	Acute stroke of brainstem
3719851000006116	Cerebellar hemorrhage
13909891000006118	Cerebral ischaemic stroke due to hypercoagulable state
5011531000006115	Vertebrobasilar territory transient ischemic attack
8032061000006113	Gangrene due to peripheral vascular disease
2729631000000115	Acute nontransmural myocardial infarction
14741971000006110	Acute inferior non-ST segment elevation myocardial infarction
9844021000006110	Acute ST segment elevation myocardial infarction due to left coronary artery occlusion
14488861000006119	Supraventricular tachycardia following acute myocardial infarction
6601131000006115	CT - Coronary thrombosis

MedCode ID	Term
6619191000006115	Past history of myocardial infarction
7100421000006116	Recurrent coronary arteriosclerosis after percutaneous transluminal coronary angioplasty
3427201000006111	AMI - Acute myocardial infarction
3494951000006115	Aortocoronary artery bypass graft repeated
7508011000006110	Coronary artery bypass grafting planned
7848501000006110	Ventricular aneurysm as current complication following acute myocardial infarction
7855741000006112	Atherosclerosis of autologous coronary artery bypass graft
8024001000006117	Acute coronary artery occlusion not resulting in myocardial infarction
13941111000006112	Acute STEMI (ST elevation myocardial infarction) due to proximal LAD (left anterior descending) coronary artery occlusion
13947721000006111	Acute ST segment elevation myocardial infarction due to occlusion of intermediate artery
13961471000006118	Acute STEMI (ST elevation myocardial infarction) due to PL (posterolateral) branch of RCA (right coronary artery) occlusion
3951991000006119	Angina, class IV
14145431000006110	Acute ST segment elevation myocardial infarction of apex of heart
14546511000006116	Postmyocardial infarction pericardial effusion
9868481000006117	Angina co-occurrent and due to coronary arteriosclerosis
12125951000006116	Arteriosclerosis of autologous vein coronary artery bypass graft with angina
8004261000006118	Acute myocardial infarction due to left coronary artery occlusion
4776171000006116	Reinfarction of myocardium
5056301000006115	Acute non-Q wave infarction - anterolateral
5647321000006118	Hibernating myocardium
6914971000006118	Myocardial infarction in recovery phase
7080821000006111	Coronary arteriosclerosis due to radiation
2571531000006110	Intermediate coronary syndrome
3536591000006111	Coronary artery occlusion
7848521000006117	Pulmonary embolism as current complication following acute myocardial infarction
13935201000006115	Acute apical myocardial infarction of heart

MedCode ID	Term
13941231000006112	Acute STEMI (ST elevation myocardial infarction) due to distal LAD (left anterior descending) coronary artery occlusion
13961351000006116	Acute STEMI (ST elevation myocardial infarction) due to distal RCA (right coronary artery) occlusion
13961411000006110	Occlusion of posterior lateral branch of right coronary artery
13961421000006119	Acute ST segment elevation myocardial infarction due to occlusion of marginal branch of right coronary artery
12122231000006112	Bilateral lower limb atherosclerosis pain at rest co-occurrent and due to atherosclerosis
4392201000006111	Diabetic peripheral vascular disease
12125761000006117	Bilateral atherosclerosis of lower limbs with gangrene
5057981000006111	Peripheral ischemic vascular disease
5058001000006116	Peripheral ischemia
8015271000006112	Peripheral vascular disease associated with another disorder
14452791000006113	Embolism of left carotid artery
14457761000006119	Right cerebellar artery thrombosis
14790901000006117	Malignant middle cerebral artery syndrome
3510818013	Acute cerebral ischemia
4777871000006114	Intracerebral hemorrhage with intraventricular hemorrhage
5011371000006112	Massive supratentorial cerebral haemorrhage
2893551000006110	Weber syndrome
5589651000006114	Intracerebellar and posterior fossa hemorrhage
3506623013	Dysphagia due to and following non-traumatic intracerebral haemorrhage
3510959018	Lacunar ataxic hemiparesis of left nondominant side
3346051000006110	Internal capsule hemorrhage
3414231000006117	MID - Multi-infarct dementia
7855641000006118	Cerebral ischemic stroke due to small artery occlusion
2622651000006119	Pontine hemorrhage
13909871000006119	Cerebral ischaemic stroke due to aortic arch embolism
14492821000006110	Cerebrovascular accident due to embolism of right anterior cerebral artery
14492941000006113	Cerebrovascular accident due to occlusion of bilateral vertebral arteries

MedCode ID	Term
4056941000006114	Brain stem hemorrhage
8031281000006118	Cerebral infarction due to stenosis of carotid artery
14451981000006116	Occlusion of right anterior cerebral artery
14457851000006110	Cerebral venous sinus thrombosis in pregnancy
14492111000006112	Cerebrovascular accident due to occlusion of left posterior communicating artery
14742481000006110	Asymptomatic occlusion of intracranial vertebral artery
3509781019	Cerebrovascular accident due to occlusion of right cerebellar artery
13718611000006113	History of embolic stroke
13718641000006112	History of ischaemic stroke
5009091000006112	Infarction of optic radiation
5011301000006118	Hemorrhagic cerebral infarction
14492331000006116	Stroke due to embolism of left anterior cerebral artery
989201000006117	Cerebral haemorrhage
989211000006119	Cerebral haemorrhage NOS
5912811000006111	Infarction of visual cortex
3636139017	Cerebrovascular accident due to occlusion of left posterior cerebral artery by embolus
14492421000006113	Cerebrovascular accident due to embolism of right carotid artery
14802151000006119	Cerebrovascular accident with intracranial haemorrhage
7855721000006117	Stroke and migraine
3719861000006119	Haemorrhagic cerebellum
3728451000006116	Cerebral arterial embolism
14492921000006118	Stroke due to embolism of left carotid artery
14493271000006115	Stroke due to thrombosis of left cerebellar artery
5492181000006110	Temporary cerebral vascular dysfunction
7107851000006112	Anterior myocardial infarction on electrocardiogram

Table 97. Terms used to define ASCVD with ICD-10 codes

ICD-10 Code	Term
I20	Angina pectoris

ICD-10 Code	Term
I20.0	Unstable angina
I20.1	Angina pectoris with documented spasm
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I22	Subsequent myocardial infarction
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
I23	Certain current complications following acute myocardial infarction
I23.0	Haemopericardium as current complication following acute myocardial infarction
I23.1	Atrial septal defect as current complication following acute myocardial infarction
I23.2	Ventricular septal defect as current complication following acute myocardial infarction
I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction
I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
I23.8	Other current complications following acute myocardial infarction
I24	Other acute ischaemic heart diseases
I24.0	Coronary thrombosis not resulting in myocardial infarction

ICD-10 Code	Term
I24.1	Dressler syndrome
I24.8	Other forms of acute ischaemic heart disease
I24.9	Acute ischaemic heart disease, unspecified
I25	Chronic ischaemic heart disease
I25.0	Atherosclerotic cardiovascular disease, so describe
I25.1	Atherosclerotic heart disease
I25.2	Old myocardial infarction
I25.3	Aneurysm of heart
I25.4	Coronary artery aneurysm and dissection
I25.5	Ischaemic cardiomyopathy
I25.6	Silent myocardial ischaemia
I25.8	Other forms of chronic ischaemic heart disease
I25.9	Chronic ischaemic heart disease, unspecified
I60	Subarachnoid haemorrhage
I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation
I60.1	Subarachnoid haemorrhage from middle cerebral artery
I60.2	Subarachnoid haemorrhage from anterior communicating artery
I60.3	Subarachnoid haemorrhage from posterior communicating artery
I60.4	Subarachnoid haemorrhage from basilar artery
I60.5	Subarachnoid haemorrhage from vertebral artery
I60.6	Subarachnoid haemorrhage from other intracranial arteries
I60.7	Subarachnoid haemorrhage from intracranial artery, unspecified
I60.8	Other subarachnoid haemorrhage
I60.9	Subarachnoid haemorrhage, unspecified
I61	Intracerebral haemorrhage
I61.0	Intracerebral haemorrhage in hemisphere, subcortical
I61.1	Intracerebral haemorrhage in hemisphere, cortical
I61.2	Intracerebral haemorrhage in hemisphere, unspecified
I61.3	Intracerebral haemorrhage in brain stem
I61.4	Intracerebral haemorrhage in cerebellum
I61.5	Intracerebral haemorrhage, intraventricular

ICD-10 Code	Term
I61.6	Intracerebral haemorrhage, multiple localized
I61.8	Other intracerebral haemorrhage
I61.9	Intracerebral haemorrhage, unspecified
I62	Other nontraumatic intracranial haemorrhage
I62.0	Nontraumatic subdural haemorrhage
I62.1	Nontraumatic extradural haemorrhage
I62.9	Intracranial haemorrhage (nontraumatic), unspecified
I63	Cerebral infarction
I63.0	Cerebral infarction due to thrombosis of precerebral arteries
I63.1	Cerebral infarction due to embolism of precerebral arteries
I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I64	Stroke, not specified as haemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I65.0	Occlusion and stenosis of vertebral artery
I65.1	Occlusion and stenosis of basilar artery
I65.2	Occlusion and stenosis of carotid artery
I65.3	Occlusion and stenosis of multiple and bilateral precerebral arteries
I65.8	Occlusion and stenosis of other precerebral artery
I65.9	Occlusion and stenosis of unspecified precerebral artery
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I66.0	Occlusion and stenosis of middle cerebral artery
I66.1	Occlusion and stenosis of anterior cerebral artery
I66.2	Occlusion and stenosis of posterior cerebral artery

ICD-10 Code	Term
I66.3	Occlusion and stenosis of cerebellar arteries
I66.4	Occlusion and stenosis of multiple and bilateral cerebral arteries
I66.8	Occlusion and stenosis of other cerebral artery
I66.9	Occlusion and stenosis of unspecified cerebral artery
I73.9	Peripheral vascular disease, unspecified
I74.3	Embolism and thrombosis of arteries of lower extremities
I74.5	Embolism and thrombosis of iliac artery
E11.5	Type 2 diabetes mellitus with peripheral circulatory complications
E14.5	Unspecified diabetes mellitus with peripheral circulatory complications
I69.3	Sequelae of cerebral infarction
I69.4	Sequelae of stroke, not specified as haemorrhage or infarction
I70	Atherosclerosis
I70.0	Atherosclerosis of aorta

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2 **Table 98. Terms used to define HF in SNOMED**

MedCode Id	Term
139475013	Heart failure
70653017	Congestive heart failure
141306010	Left ventricular failure
493287011	Congestive cardiac failure
2616471011	New York Heart Association Classification - Class II
2616470012	New York Heart Association Classification - Class I
2616472016	New York Heart Association Classification - Class III

MedCode Id	Term
301694014	Pulmonary oedema
139482012	Cardiac failure
395772015	Heart failure NOS
216184014	Congestive heart failure monitoring
300179017	Decompensated cardiac failure
1647701000000118	Heart failure with normal ejection fraction
3886041000006118	Left heart failure
1488804017	Heart failure confirmed
7573171000006116	Heart failure with reduced ejection fraction
147247018	Chronic congestive heart failure
206703015	Right heart failure
510016018	Biventricular congestive heart failure
300190010	Acute left ventricular failure
1490256017	Acute pulmonary oedema
18472010	Acute congestive heart failure
2227501000000110	Heart failure with preserved ejection fraction

MedCode Id	Term
251680018	H/O: heart failure
12626351000006111	QOF (Quality and Outcomes Framework) heart failure quality indicator-related care invitation
253994013	O/E - pulmonary oedema
7025691000006110	Decompensated chronic heart failure
94251011	Acute heart failure
2616473014	New York Heart Association Classification - Class IV
1816101000006113	Right ventricular failure
301741013	Acute pulmonary oedema unspecified
223981000000118	Cardiac failure NOS
490972013	Right ventricular failure
301743011	Acute pulmonary oedema NOS
300180019	Compensated cardiac failure
3182541000006117	Congestive cardiac failure
3182551000006115	CCF - Congestive cardiac failure
7321121000006119	Heart failure with preserved ejection fraction

MedCode Id	Term
2675255018	Congestive heart failure due to valvular disease
453099015	H/O: Heart failure in last year
13910671000006110	Heart failure with mid range ejection fraction
494669012	Chronic pulmonary oedema
2664351000006113	Chronic right-sided heart failure
7251291000006119	Chronic diastolic heart failure
1661371000000112	HFNEF - heart failure with normal ejection fraction
504901000006118	Benign hypertensive heart disease with congestive cardiac failure
3283871000006117	Chronic heart failure
7056281000006118	Congestive heart failure due to left ventricular systolic dysfunction
72934016	Rheumatic left ventricular failure
12734351000006110	QOF (Quality and Outcomes Framework) heart failure quality indicator-related care invitation using preferred method of communication
139481017	Weak heart
1576321000006113	Cause of Death- Congestive Cardiac Failure

MedCode Id	Term
7573201000006117	Heart failure with reduced ejection fraction due to cardiomyopathy
350484012	Heart failure as a complication of care
741701000006114	Hypertensive heart and renal disease with (congestive) heart failure
7573181000006118	Heart failure with reduced ejection fraction due to coronary artery disease
3589241000006116	Chronic right-sided congestive heart failure
728681000006116	Malignant hypertensive heart disease without congestive heart failure
6212521000006115	Acute cardiac pulmonary oedema
7250571000006113	Chronic systolic heart failure
14015051000006114	Acute on chronic right-sided congestive heart failure
4193361000006119	Chronic left-sided heart failure
728671000006119	Malignant hypertensive heart disease with congestive cardiac failure
7573211000006119	Heart failure with reduced ejection fraction due to heart valve disease
3886071000006114	LVF - Left ventricular failure

MedCode Id	Term
6919191000006119	Diastolic heart failure
8030311000006111	Exacerbation of congestive heart failure
12623611000006114	Excepted from heart failure quality indicators - service unavailable
2585431000006117	Chronic left-sided congestive heart failure
789941000006117	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
14131371000006115	Telehealth monitoring for chronic heart failure
5054791000006119	Fluid overload pulmonary oedema
8048061000006111	Chronic combined systolic and diastolic heart failure
4005301000006110	Biventricular failure
2660881000006116	High output heart failure
6204381000006117	Acute right-sided heart failure
6914191000006115	Systolic heart failure
7052811000006113	Right heart failure due to pulmonary hypertension
7475721000006114	Heart failure due to end stage congenital heart disease
3244761000006113	Hypertensive heart failure

MedCode Id	Term
7507301000006110	Acute exacerbation of chronic congestive heart failure
6043761000006113	Refractory heart failure
8011111000006111	Congestive heart failure with right heart failure
7573191000006115	Heart failure with reduced ejection fraction due to myocarditis
3182531000006110	Congestive heart disease
5054671000006113	High altitude pulmonary oedema
7510341000006110	Symptomatic congestive heart failure
3182561000006118	CHF - Congestive heart failure
14151151000006111	Heart failure due to thyrotoxicosis
3974561000006115	Pleural effusion due to congestive heart failure
3842421000006111	Congestive rheumatic heart failure
14742661000006115	Left ventricular failure with normal ejection fraction due to valvular heart disease
3886061000006119	Left-sided heart failure
2504341000006116	Acute left heart failure
3213831000006118	Right heart failure secondary to left heart failure

MedCode Id	Term
3868341000006118	HF - Heart failure
13971301000006111	Low output heart failure due to and following Fontan operation
2581861000006110	Hypertensive heart disease with congestive heart failure
3809001000006112	Acute right-sided congestive heart failure
3489281000006119	Hypertensive heart disease without congestive heart failure
7275961000006118	Acute on chronic diastolic heart failure
14171441000006118	Heart failure management programme

Table 99. Terms used to define HF with ICD-10 codes

ICD-10 code	Description
I50	Heart failure
I50.0	Congestive heart failure
I50.1	Left ventricular failure
I50.9	Heart failure, unspecified
I11.0	Hypertensive heart disease with (congestive) heart failure

Appendix C: Events at 3, 5 and 10 years predicted by model

Table 100. Cumulative percentage of people incurring each event at 3, 5 and 10 years as predicted by the model: ASCVD population

	Heart Failure(%)			Stroke(%)			MI(%)			ESRF(%)			Angina(%)			All cause mortality(%)		
Years	3	5	10	3	5	10	3	5	10	3	5	10	3	5	10	3	5	10
Metformin	7.13	10.26	14.82	7.60	11.54	18.01	7.78	11.84	18.72	0.61	0.95	1.67	1.21	1.93	3.20	29.06	43.61	68.71
SGLT-2 Class	5.13	7.35	11.09	7.74	11.88	19.06	6.81	10.52	17.02	0.48	0.77	1.36	1.15	1.85	3.11	27.05	41.05	66.22
Dulaglutide	6.52	9.28	13.79	5.80	8.88	14.14	7.19	11.02	17.71	0.63	0.99	1.71	1.36	2.16	3.59	28.17	42.51	67.81
Exenatide	6.64	9.57	13.91	6.43	9.87	15.78	7.23	11.13	17.91	0.55	0.86	1.53	1.37	2.20	3.68	27.68	41.84	66.88
Liraglutide	6.22	8.95	13.30	6.62	10.22	16.58	6.68	10.37	16.95	0.57	0.90	1.63	1.17	1.90	3.22	26.32	40.06	65.16
Semaglutide; Oral	7.08	10.25	15.76	7.76	12.20	20.40	7.89	12.47	20.94	0.65	1.07	2.02	1.27	2.09	3.66	22.49	35.23	59.94
Semaglutide; Subcutaneous	7.20	10.19	14.94	4.54	6.95	11.07	5.41	8.31	13.34	0.53	0.84	1.46	1.21	1.91	3.19	28.65	42.88	67.87
Alogliptin	8.33	11.99	17.40	7.53	11.50	18.27	8.33	12.85	20.65	0.62	0.96	1.73	1.24	2.00	3.36	27.49	41.62	66.73
Linagliptin	6.57	9.49	13.78	6.72	10.23	16.09	8.69	13.27	21.07	0.60	0.94	1.64	1.20	1.92	3.18	28.77	43.30	68.54
Saxagliptin	8.69	12.38	17.70	8.28	12.46	19.40	7.30	11.13	17.70	0.55	0.85	1.48	1.43	2.28	3.76	29.31	43.84	68.85
Sitagliptin	12.02	16.87	23.78	7.31	11.01	17.18	7.44	11.37	18.07	0.61	0.94	1.65	1.11	1.79	3.00	29.58	43.98	68.83
Vildagliptin	7.18	10.33	14.92	7.44	11.30	17.72	7.59	11.60	18.43	0.61	0.94	1.64	1.20	1.92	3.19	28.97	43.48	68.67
Gliclazide	7.22	10.39	14.99	7.45	11.30	17.71	7.56	11.53	18.35	0.60	0.93	1.64	1.21	1.93	3.19	28.98	43.53	68.68
Insulin	7.37	10.63	15.39	7.42	11.27	17.68	7.57	11.56	18.42	0.60	0.92	1.61	1.21	1.93	3.20	29.02	43.52	68.70
Pioglitazone	9.91	14.22	20.46	6.08	9.26	14.63	6.50	10.01	16.11	0.59	0.91	1.61	1.23	1.99	3.33	28.36	42.59	67.55
SGLT-2i + Dulaglutide	5.08	7.30	11.17	6.20	9.60	15.67	6.33	9.82	16.07	0.38	0.61	1.09	1.37	2.19	3.69	26.10	39.82	65.02
SGLT-2i + Exenatide	5.20	7.59	11.30	6.93	10.77	17.56	6.37	9.92	16.31	0.33	0.52	0.98	1.40	2.24	3.82	25.54	39.14	64.12
SGLT-2i + Liraglutide	4.82	7.06	10.84	7.13	11.17	18.52	5.95	9.31	15.53	0.35	0.56	1.06	1.18	1.93	3.32	24.14	37.20	62.08
SGLT-2i + Semaglutide; Oral	5.53	8.19	13.12	8.31	13.29	22.86	6.95	11.15	19.24	0.40	0.67	1.32	1.27	2.12	3.81	20.03	31.92	56.15
SGLT-2i + Semaglutide; Subcutaneous	5.59	8.03	12.03	4.87	7.53	12.23	4.74	7.35	11.97	0.33	0.52	0.93	1.20	1.93	3.25	27.00	40.91	65.91

Table 101. Cumulative percentage of people incurring each event at 3, 5 and 10 years as predicted by the model: HF population

	Heart Failure(%)[(a)]			Stroke(%)			MI(%)			ESRF(%)			Angina(%)			All cause mortality(%)		
Years	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**
Metformin	N/A	N/A	N/A	10.86	14.86	19.93	12.19	16.99	23.12	1.12	1.44	1.96	2.69	3.87	5.51	45.46	62.48	85.11
SGLT-2 Class	N/A	N/A	N/A	11.13	15.44	21.15	10.90	15.43	21.49	0.88	1.16	1.61	2.59	3.76	5.44	43.26	60.10	83.42
Dulaglutide	N/A	N/A	N/A	8.30	11.52	15.74	11.33	15.96	22.04	1.15	1.50	2.03	3.03	4.38	6.26	44.45	61.49	84.55
Exenatide	N/A	N/A	N/A	9.23	12.81	17.53	11.34	15.98	22.14	0.99	1.29	1.79	3.07	4.48	6.40	44.04	61.02	84.19
Liraglutide	N/A	N/A	N/A	9.43	13.12	17.99	8.93	12.69	17.75	1.04	1.35	1.86	2.61	3.80	5.49	43.60	60.50	83.80
Semaglutide; Oral	N/A	N/A	N/A	10.90	15.42	21.85	12.21	17.51	24.94	1.20	1.60	2.31	2.76	4.08	6.01	39.54	55.97	80.26
Semaglutide; Subcutaneous	N/A	N/A	N/A	6.62	9.26	12.78	8.63	12.24	17.12	0.97	1.26	1.72	2.70	3.93	5.66	44.05	61.04	84.29
Alogliptin	N/A	N/A	N/A	10.83	15.03	20.56	12.54	17.64	24.44	1.15	1.49	2.07	2.72	3.97	5.72	43.35	60.15	83.47
Linagliptin	N/A	N/A	N/A	9.51	13.08	17.67	13.58	18.93	25.82	1.11	1.42	1.93	2.69	3.89	5.56	45.17	62.23	84.96
Saxagliptin	N/A	N/A	N/A	11.78	16.13	21.65	11.36	15.88	21.71	1.03	1.31	1.77	3.16	4.54	6.41	45.54	62.62	85.31
Sitagliptin	N/A	N/A	N/A	10.63	14.58	19.65	11.39	15.94	21.81	1.12	1.43	1.94	2.43	3.51	5.01	45.41	62.45	85.17
Vildagliptin	N/A	N/A	N/A	10.58	14.53	19.61	11.82	16.56	22.67	1.13	1.44	1.96	2.69	3.90	5.56	45.27	62.29	85.05
Gliclazide	N/A	N/A	N/A	10.58	14.54	19.63	11.82	16.56	22.71	1.11	1.43	1.95	2.69	3.91	5.56	45.24	62.29	85.13
Insulin	N/A	N/A	N/A	10.56	14.52	19.62	11.82	16.54	22.67	1.11	1.41	1.92	2.68	3.88	5.53	45.17	62.18	84.99
Pioglitazone	N/A	N/A	N/A	8.68	12.05	16.46	10.09	14.24	19.72	1.11	1.42	1.93	2.71	3.93	5.65	44.45	61.44	84.49

(c) The UKPDS Global beta model does not output event rates for heart failure in individuals with pre-existing heart failure, since it is viewed as a state rather than an event. Since the clinical review NMA captures heart failure events (hospitalisation for heart failure), we assumed that event rates of heart failure were the same as those in the ASCVD population (see Table 100).

Table 102. Cumulative percentage of people incurring each event at 3, 5 and 10 years as predicted by the model: (high risk of CVD and living with overweight)

	Heart Failure(%)			Stroke(%)			MI(%)			ESRF(%)			Angina(%)			All cause mortality(%)		
Years	3	5	10	3	5	10	3	5	10	3	5	10	3	5	10	3	5	10
Metformin	1.48	2.65	5.65	2.23	3.99	8.50	3.53	6.11	12.26	0.29	0.55	1.31	2.13	3.73	7.42	10.89	19.19	41.15
SGLT-2 Class	0.99	1.73	3.82	2.20	3.99	8.76	3.11	5.38	10.93	0.23	0.44	1.04	2.04	3.55	7.07	10.43	18.35	39.60
Dulaglutide	1.34	2.33	5.13	1.60	2.92	6.37	3.21	5.58	11.40	0.29	0.56	1.32	2.40	4.16	8.27	10.62	18.68	40.20
Exenatide	1.37	2.42	5.08	1.82	3.29	7.19	3.24	5.61	11.46	0.26	0.48	1.16	2.44	4.25	8.48	10.51	18.54	40.18
Liraglutide	1.25	2.21	4.74	1.83	3.34	7.34	2.96	5.13	10.54	0.27	0.51	1.23	2.07	3.61	7.22	10.25	18.06	39.18
Semaglutide; Oral	1.44	2.51	5.45	2.10	3.85	8.62	3.39	5.93	12.37	0.30	0.58	1.40	2.15	3.75	7.59	9.64	17.10	37.83
Semaglutide; Subcutaneous	1.52	2.62	5.61	1.25	2.26	4.97	2.41	4.15	8.53	0.26	0.49	1.16	2.16	3.74	7.49	10.52	18.38	39.58
Alogliptin	1.78	3.17	6.74	2.15	3.89	8.46	3.76	6.51	13.22	0.28	0.53	1.29	2.14	3.73	7.50	10.58	18.68	40.58
Linagliptin	1.38	2.44	5.19	1.89	3.42	7.39	3.97	6.88	13.88	0.27	0.52	1.26	2.16	3.74	7.40	10.85	19.07	40.98
Saxagliptin	1.90	3.39	7.08	2.36	4.28	9.27	3.28	5.69	11.54	0.25	0.49	1.16	2.53	4.40	8.76	10.97	19.33	41.62
Sitagliptin	2.84	4.98	10.21	2.12	3.82	8.19	3.31	5.73	11.63	0.28	0.53	1.29	1.95	3.41	6.81	11.01	19.43	41.90
Vildagliptin	1.51	2.69	5.69	2.10	3.80	8.28	3.42	5.91	11.98	0.29	0.54	1.29	2.14	3.73	7.47	10.83	19.06	41.03
Gliclazide	1.52	2.72	5.78	2.11	3.82	8.27	3.42	5.92	11.99	0.28	0.53	1.28	2.13	3.73	7.42	10.84	19.07	41.04
Insulin	1.56	2.80	5.92	2.09	3.80	8.29	3.43	5.90	11.95	0.28	0.52	1.25	2.15	3.74	7.44	10.92	19.15	41.03
Pioglitazone	2.22	3.99	8.37	1.71	3.08	6.69	2.90	5.03	10.21	0.29	0.54	1.25	2.16	3.76	7.57	10.64	18.76	40.54

Table 103. Cumulative percentage of people incurring each event at 3, 5 and 10 years as predicted by the model: (high risk of CVD and living with obesity)

	Heart Failure(%)			Stroke(%)			MI(%)			ESRF(%)			Angina(%)			All cause mortality(%)		
Years	3	5	10	3	5	10	3	5	10	3	5	10	3	5	10	3	5	10
Metformin	2.51	4.52	9.70	1.81	3.34	7.50	3.27	5.68	11.80	0.17	0.33	0.81	2.00	3.53	7.28	8.65	15.57	35.46
SGLT-2 Class	1.63	2.88	6.60	1.83	3.37	7.76	2.84	4.95	10.46	0.14	0.27	0.64	1.89	3.34	6.90	8.21	14.69	33.59
Dulaglutide	2.22	3.87	8.69	1.35	2.49	5.70	2.95	5.16	10.99	0.18	0.35	0.83	2.24	3.94	8.10	8.45	15.09	34.50
Exenatide	2.28	4.06	8.56	1.48	2.76	6.33	2.96	5.19	10.99	0.15	0.29	0.72	2.29	4.01	8.25	8.35	15.00	34.24
Liraglutide	2.05	3.64	7.99	1.53	2.83	6.53	2.71	4.74	10.14	0.16	0.31	0.75	1.90	3.37	7.00	8.07	14.46	33.19
Semaglutide; Oral	2.35	4.12	9.11	1.75	3.28	7.74	3.11	5.55	12.06	0.18	0.36	0.88	2.00	3.56	7.49	7.22	13.06	30.84
Semaglutide; Subcutaneous	2.47	4.29	9.26	1.02	1.90	4.37	2.19	3.85	8.20	0.16	0.30	0.73	1.99	3.52	7.29	8.42	15.01	33.95
Alogliptin	2.97	5.33	11.30	1.78	3.28	7.47	3.44	6.05	12.85	0.17	0.33	0.81	2.01	3.56	7.40	8.27	14.97	34.63
Linagliptin	2.28	4.12	8.88	1.56	2.90	6.60	3.65	6.38	13.33	0.17	0.32	0.79	1.99	3.50	7.24	8.61	15.47	35.26
Saxagliptin	3.16	5.63	11.83	1.97	3.64	8.18	3.01	5.30	11.11	0.15	0.29	0.72	2.36	4.17	8.62	8.77	15.82	36.15
Sitagliptin	4.62	8.08	16.45	1.75	3.24	7.26	3.07	5.39	11.41	0.17	0.33	0.80	1.83	3.26	6.78	8.76	15.89	36.44
Vildagliptin	2.51	4.51	9.65	1.75	3.22	7.33	3.13	5.48	11.50	0.17	0.32	0.79	2.02	3.54	7.28	8.67	15.60	35.45
Gliclazide	2.55	4.59	9.79	1.76	3.23	7.34	3.13	5.49	11.51	0.17	0.33	0.79	1.99	3.52	7.26	8.66	15.55	35.45
Insulin	2.62	4.75	10.21	1.74	3.22	7.31	3.12	5.48	11.54	0.17	0.32	0.78	1.99	3.51	7.25	8.69	15.61	35.57
Pioglitazone	3.67	6.59	13.82	1.41	2.60	5.94	2.64	4.66	9.94	0.17	0.32	0.77	2.00	3.57	7.44	8.50	15.38	35.28

Table 104. Cumulative percentage of people incurring each event at 3, 5 and 10 years as predicted by the model: Under 40 population

	Heart Failure(%)			Stroke(%)			MI(%)			ESRF(%)			Angina(%)			All cause mortality(%)		
Years	3	5	10	3	5	10	3	5	10	3	5	10	3	5	10	3	5	10
Metformin	0.49	0.93	2.37	0.32	0.60	1.52	1.54	2.64	5.86	0.03	0.07	0.21	1.43	2.61	5.89	0.79	1.50	4.33
SGLT-2 Class	0.31	0.57	1.53	0.32	0.59	1.55	1.35	2.31	5.15	0.03	0.06	0.16	1.37	2.48	5.58	0.73	1.39	3.94
Dulaglutide	0.42	0.77	2.09	0.24	0.45	1.15	1.42	2.42	5.44	0.04	0.08	0.22	1.61	2.91	6.56	0.75	1.42	4.08
Exenatide	0.43	0.81	2.15	0.27	0.50	1.29	1.40	2.41	5.41	0.03	0.06	0.18	1.64	2.96	6.67	0.75	1.42	4.09
Liraglutide	0.40	0.74	1.98	0.27	0.50	1.31	1.30	2.23	4.97	0.03	0.07	0.19	1.39	2.50	5.66	0.71	1.33	3.82
Semaglutide; Oral	0.44	0.82	2.25	0.30	0.57	1.49	1.46	2.52	5.70	0.03	0.08	0.22	1.43	2.59	5.88	0.60	1.15	3.34
Semaglutide; Subcutaneous	0.47	0.87	2.37	0.18	0.34	0.90	1.03	1.77	3.97	0.03	0.07	0.18	1.43	2.59	5.87	0.77	1.45	4.17
Alogliptin	0.57	1.10	2.78	0.30	0.57	1.49	1.64	2.82	6.33	0.03	0.07	0.21	1.44	2.62	5.93	0.75	1.42	4.13
Linagliptin	0.42	0.83	2.14	0.28	0.52	1.34	1.76	3.01	6.72	0.03	0.07	0.20	1.45	2.61	5.91	0.78	1.48	4.25
Saxagliptin	0.61	1.17	2.98	0.34	0.65	1.68	1.45	2.48	5.52	0.03	0.06	0.18	1.72	3.07	6.94	0.81	1.53	4.42
Sitagliptin	0.91	1.73	4.35	0.31	0.57	1.48	1.42	2.43	5.50	0.03	0.07	0.21	1.30	2.36	5.37	0.80	1.53	4.47
Vildagliptin	0.47	0.91	2.35	0.31	0.57	1.49	1.49	2.57	5.73	0.04	0.07	0.21	1.43	2.60	5.87	0.80	1.51	4.33
Gliclazide	0.48	0.94	2.39	0.30	0.56	1.50	1.48	2.54	5.70	0.03	0.07	0.20	1.45	2.63	5.93	0.79	1.50	4.33
Insulin	0.51	0.97	2.48	0.31	0.57	1.49	1.49	2.55	5.70	0.03	0.07	0.20	1.44	2.60	5.90	0.80	1.51	4.35
Pioglitazone	0.72	1.40	3.54	0.25	0.46	1.19	1.24	2.12	4.78	0.03	0.07	0.20	1.45	2.62	5.95	0.76	1.45	4.21
SGLT-2i + Dulaglutide	0.28	0.52	1.44	0.26	0.49	1.27	1.24	2.11	4.74	0.02	0.05	0.14	1.63	2.93	6.58	0.63	1.19	3.41
SGLT-2i + Exenatide	0.29	0.54	1.48	0.28	0.53	1.40	1.22	2.08	4.69	0.02	0.04	0.12	1.65	2.98	6.68	0.63	1.17	3.36
SGLT-2i + Liraglutide	0.27	0.53	1.40	0.30	0.55	1.44	1.15	1.95	4.33	0.02	0.04	0.12	1.38	2.52	5.66	0.61	1.14	3.17
SGLT-2i + Semaglutide; Oral	0.31	0.58	1.58	0.33	0.63	1.64	1.30	2.23	5.02	0.02	0.05	0.14	1.43	2.60	5.90	0.53	1.00	2.84
SGLT-2i + Semaglutide; Subcutaneous	0.33	0.62	1.69	0.20	0.39	1.00	0.93	1.59	3.54	0.02	0.04	0.11	1.43	2.58	5.87	0.64	1.20	3.39

Table 105. Cumulative percentage of people incurring each event at 3, 5 and 10 years as predicted by the model: CKD 1-3

	Heart Failure(%)			Stroke(%)			MI(%)			ESRF(%)			Angina(%)			All cause mortality(%)		
Years	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**
Metformin	7.89	11.14	16.20	7.12	10.64	16.56	6.35	9.80	15.92	1.18	1.70	2.87	1.90	3.08	5.43	24.59	37.34	61.08
SGLT-2 Class	5.56	7.72	11.61	7.31	11.07	17.73	5.60	8.74	14.52	0.93	1.37	2.32	1.81	2.95	5.22	22.89	35.19	58.68
Dulaglutide	7.31	10.09	15.04	5.38	8.08	12.84	5.77	8.96	14.84	1.21	1.78	2.97	2.12	3.45	6.08	24.00	36.61	60.32
Exenatide	7.43	10.43	15.19	6.02	9.12	14.50	5.86	9.14	15.12	1.05	1.52	2.62	2.19	3.56	6.30	23.31	35.81	59.55
Liraglutide	6.98	9.75	14.51	6.22	9.46	15.27	5.44	8.54	14.35	1.09	1.61	2.79	1.85	3.04	5.45	22.21	34.29	57.77
Semaglutide; Oral	7.83	11.07	16.92	7.37	11.43	19.07	6.48	10.40	18.01	1.25	1.87	3.31	2.01	3.35	6.12	18.87	30.20	53.40
Semaglutide; Subcutaneous	8.03	11.18	16.65	8.58	13.03	21.10	4.97	7.92	13.47	1.05	1.56	2.69	1.98	3.23	5.79	21.54	33.42	56.93
Alogliptin	9.12	12.88	18.88	7.12	10.73	17.02	6.83	10.72	17.77	1.20	1.73	2.96	1.95	3.19	5.71	22.96	35.36	59.15
Linagliptin	6.96	9.82	14.38	6.21	9.35	14.74	7.04	10.90	17.81	1.17	1.70	2.84	1.90	3.08	5.42	24.31	37.01	60.83
Saxagliptin	9.48	13.31	19.23	7.67	11.45	17.89	5.94	9.21	15.06	1.07	1.55	2.60	2.27	3.70	6.46	24.71	37.49	61.38
Sitagliptin	12.78	17.81	25.33	6.87	10.19	15.87	6.06	9.42	15.47	1.19	1.71	2.88	1.78	2.89	5.14	24.84	37.63	61.49
Vildagliptin	7.89	11.13	16.21	6.93	10.37	16.24	6.13	9.51	15.57	1.18	1.70	2.87	1.88	3.08	5.43	24.51	37.22	61.07
Gliclazide	7.93	11.20	16.32	6.92	10.33	16.21	6.11	9.46	15.52	1.16	1.68	2.83	1.92	3.12	5.43	24.52	37.22	61.07
Insulin	8.17	11.54	16.84	6.93	10.35	16.18	6.12	9.51	15.56	1.17	1.67	2.81	1.93	3.12	5.46	24.55	37.28	61.12
Pioglitazone	10.70	15.16	22.01	5.66	8.51	13.40	5.31	8.30	13.75	1.16	1.65	2.81	1.95	3.20	5.68	23.84	36.44	60.20

Table 106. Cumulative percentage of people incurring each event at 3, 5 and 10 years as predicted by the model: CKD 4

	Heart Failure(%)			Stroke(%)			MI(%)			ESRF(%)			Angina(%)			All cause mortality(%)		
Years	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**	**3**	**5**	**10**
Standard Care	13.64	17.11	21.48	12.64	16.64	22.07	7.64	10.53	14.75	7.76	8.52	9.76	1.26	1.94	3.08	42.93	58.28	80.96
SGLT-2 Class	9.54	11.99	15.55	13.12	17.60	23.99	6.83	9.53	13.64	6.09	6.77	7.83	1.20	1.87	3.00	39.85	55.21	78.84
Dulaglutide	12.65	15.77	20.21	9.65	12.88	17.43	7.11	9.85	14.01	7.85	8.69	9.99	1.40	2.16	3.46	41.59	56.78	79.99
Exenatide	12.84	16.17	20.44	10.80	14.41	19.49	7.14	9.92	14.11	6.87	7.58	8.80	1.45	2.25	3.60	41.02	56.39	79.54
Liraglutide	12.02	15.12	19.40	11.10	14.89	20.37	6.60	9.21	13.29	7.08	7.86	9.13	1.22	1.91	3.09	39.84	55.01	78.66
Semaglutide; Oral	13.85	17.60	23.03	13.30	18.26	25.77	8.09	11.64	17.36	8.02	9.00	10.69	1.40	2.23	3.70	33.79	49.26	74.48
Semaglutide; Subcutaneous	14.11	17.60	22.41	15.17	20.32	27.76	6.12	8.60	12.51	6.80	7.58	8.84	1.33	2.09	3.37	38.81	54.23	78.02
Alogliptin	15.73	19.73	24.81	12.56	16.66	22.38	8.30	11.53	16.36	7.74	8.54	9.84	1.31	2.04	3.24	41.30	56.73	79.95
Linagliptin	11.91	15.02	19.04	11.17	14.85	19.89	8.51	11.75	16.58	7.61	8.38	9.61	1.24	1.92	3.05	42.38	57.76	80.66
Saxagliptin	16.34	20.38	25.38	13.60	17.88	23.69	7.23	9.95	13.96	7.03	7.72	8.83	1.51	2.31	3.63	43.21	58.59	81.21
Sitagliptin	22.02	27.11	33.29	12.19	15.93	21.03	7.44	10.27	14.42	7.75	8.51	9.72	1.19	1.84	2.92	43.62	58.91	81.31
Vildagliptin	13.59	17.04	21.45	12.32	16.25	21.73	7.46	10.28	14.46	7.75	8.51	9.75	1.27	1.94	3.07	42.83	58.09	80.79
Gliclazide	13.65	17.17	21.62	12.32	16.26	21.73	7.45	10.25	14.44	7.73	8.49	9.73	1.25	1.94	3.08	42.72	58.01	80.78
Insulin	13.91	17.56	22.15	12.32	16.29	21.74	7.45	10.28	14.49	7.68	8.43	9.63	1.27	1.97	3.09	42.68	58.08	80.91
Pioglitazone	18.27	22.95	28.80	10.04	13.28	17.80	6.46	8.95	12.72	7.69	8.43	9.63	1.30	2.02	3.23	42.29	57.56	80.43

Appendix D: Model-predicted CVM odds ratios

Table 107. base case: model-predicted CVM odds ratios

	ASCVD	CKD1-3	CKD4	HF	hrCVD + obesity	hrCVD + overweight	hrCVD + under 40 years
Metformin	1.00	1.00	1.00	1.00	1.00	1.00	1.00
SGLT-2i Class	0.81	0.81	0.83	0.90	0.83	0.85	0.87
Dulaglutide	0.91	0.92	0.89	0.90	0.91	0.92	0.91
Exenatide	0.88	0.87	0.90	0.89	0.89	0.91	0.91
Liraglutide	0.77	0.74	0.82	0.82	0.79	0.80	0.78
Semaglutide; Oral	0.50	0.43	0.53	0.62	0.53	0.64	0.58
Semaglutide; Subcutaneous	0.91	0.67	0.81	0.79	0.89	0.85	0.92
Alogliptin	0.89	0.85	0.94	0.86	0.87	0.91	0.87
Linagliptin	0.98	0.98	0.96	0.99	0.99	1.00	0.95
Saxagliptin	1.05	1.04	1.08	1.02	1.03	1.04	1.03
Sitagliptin	1.09	1.06	1.12	0.98	1.04	1.04	1.02
Vildagliptin	0.99	1.00	0.99	0.99	1.00	0.99	1.00
Gliclazide	0.99	1.00	0.99	0.99	0.99	0.98	0.99
Insulin	1.00	1.00	1.00	0.99	0.99	0.99	1.00
Pioglitazone	0.95	0.94	0.98	NR	0.95	0.94	0.94
SGLT-2i + Dulaglutide	0.74						0.62
SGLT-2i + Exenatide	0.71						0.59
SGLT-2i + Liraglutide	0.60						0.52
SGLT-2i + Semaglutide; Oral	0.31						0.38
SGLT-2i + Semaglutide; Subcutaneous	0.77						0.59

Abbreviations: ASCVD= atherosclerotic cardiovascular disease, CKD= chronic kidney disease, CVM= cardiovascular mortality, HF= heart failure, hrCVD= high risk of cardiovascular disease, SGLT-2i= sodium- glucose co-transporter-2 inhibitor
Model-predicted CVM odds ratios exceeded +/-5% expected odds ratios with:
ASCVD= alogliptin (106%), sitagliptin (106%), SGLT-2i plus liraglutide (94%), SGLT-2i plus semaglutide; oral (72%)

CKD1-3= semaglutide; oral (82%)
CKD4= empagliflozin (112%), liraglutide (107%), semaglutide; subcutaneous (115%), alogliptin (111%), sitagliptin (108%)
HF= canagliflozin (107%), empagliflozin (121%), semaglutide,oral (119%), semaglutide; subcutaneous (83%), alogliptin (113%), pioglitazone (94%)
hrCVD plus living with obesity= semaglutide; subcutaneous (94%)
hrCVD plus living with overweight= empagliflozin (115%), semaglutide; oral (121%), semaglutide; subcutaneous (90%), alogliptin (108%)
hrCVD plus aged under 40 years= empagliflozin (106%), semaglutide; oral (110%), SGLT-2i plus dulaglutide (107%), SGLT-2i plus exenatide (107%), SGLT-2i plus liraglutide (106%), SGLT-2i plus semaglutide; oral (113%)

Table 108. Shi NMA sensitivity analysis: model-predicted CVM odds ratios

	ASCVD	CKD1-3	CKD4	HF	hrCVD + obesity	hrCVD + overweight	hrCVD + under 40 years
Metformin	1.00	1.00	1.00	1.00	1.00	1.00	1.00
SGLT-2 Class	0.86	0.87	0.85	0.90	0.86	0.87	0.87
Dulaglutide	0.86	0.88	0.88	0.87	0.87	0.87	0.86
Exenatide	0.87	0.88	0.88	0.87	0.87	0.87	0.87
Liraglutide	0.87	0.88	0.88	0.87	0.87	0.87	0.87
Semaglutide; Oral	0.87	0.88	0.88	0.87	0.87	0.87	0.89
Semaglutide; Subcutaneous	0.86	0.88	0.87	0.86	0.86	0.87	0.87
Alogliptin	0.99	0.99	0.98	0.98	0.99	0.99	1.00
Linagliptin	0.99	1.00	0.98	0.98	0.99	0.99	1.00
Saxagliptin	0.99	0.99	0.98	0.98	0.99	0.99	0.99
Sitagliptin	0.99	0.99	0.98	0.98	0.99	0.98	1.00
Vildagliptin	1.00	1.00	0.98	0.98	0.99	0.99	1.00
Gliclazide	1.01	1.01	1.01	0.99	0.99	0.99	0.99
Insulin	1.15	1.21	1.08	1.09	1.13	1.11	1.17
Pioglitazone	0.96	0.92	1.03	0.92	0.98	0.96	0.96

Abbreviations: ASCVD= atherosclerotic cardiovascular disease, CKD= chronic kidney disease, CVM= cardiovascular mortality, HF= heart failure, hrCVD= high risk of cardiovascular disease, SGLT-2i= sodium- glucose co-transporter-2 inhibitor
Model-predicted CVM odds ratios exceeded +/-5% expected odds ratios with:
ASCVD= insulin (92%)
CKD4= insulin (86%, pioglitazone (110%)
HF= insulin (86%)
hrCVD plus living with obesity= insulin (90%)
hrCVD plus living with overweight= insulin (89%)
hrCVD plus aged under 40 years= insulin (94%)

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