National Institute for Health and Care Excellence

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Draft for consultation

# Type 2 diabetes in adults: management

## [F10] Evidence reviews for subsequent pharmacological management of type 2 diabetes – network meta-analysis

*NICE guideline GID-NG10336*

*Evidence reviews underpinning recommendations 1.8.6-1.8.32, 1.8.34,1.8.38-1.8.60 and recommendations for research in the NICE guideline*

*August 2025*

*Draft for Consultation*

*This evidence review was developed by NICE*

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# 1. Introduction

Network meta-analysis (NMA) is a statistical technique that allows simultaneous pooling of data for three or more interventions when the available evidence forms a connected network of intervention comparisons from RCTs (for example: evidence from trials comparing interventions A vs B, trials of B vs C and trials of C vs A). This enables both direct evidence (for example A vs B trials for the AvB comparison) and indirect evidence (for example A vs C and B vs C trials provide an indirect estimate of AvB) to be pooled. NMA combines all the available data simultaneously into a single set of treatment effects that provide a unique ordering of intervention effectiveness, whilst respecting the randomisation in the included RCTs. The resulting estimates are therefore easier to interpret than a series of pairwise comparisons, enables ranking of the interventions, and because both direct and indirect evidence is pooled treatment effects are more precisely estimated (have greater statistical power).

NMA assumes that the included studies are similar in terms of factors that might interact with the intervention effects (effect modifiers). So, the relative effect of intervention B vs intervention A would be expected to be similar in all the studies (if they had included A and B interventions). This assumption is the same as that made in conventional pairwise meta-analysis, but we must be particularly careful that the studies making different comparisons do not differ in effect modifiers (the data are consistent). We can assess this assumption by measuring statistical heterogeneity, and by checking if the direct and indirect estimates agree when there are loops of evidence in the network (for example: an ABC triangle of evidence).

The analysis provides estimates of relative effects (with 95% credible intervals) for each intervention compared to a reference intervention. In this case the reference intervention was placebo. While placebo is not a therapy that every person with type 2 diabetes would receive, the committee agreed that is comparable to no treatment in this case and so could be used as a no treatment comparison making it a relevant reference intervention. The analysis also provides estimates of all pairwise comparisons. In addition, for a given assumed “baseline effect” on the reference intervention, we can obtain absolute effects for all interventions. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Having a single set of intervention effects that considers all the available evidence facilitates cost effectiveness analysis and decision making.

Many of the outcomes included in the reviews of this guideline update formed connected networks of RCT evidence and so NMA was considered. The topic was considered a high clinical priority for the guideline due to variations in practice and uncertainty about the most clinically and cost-effective strategy. It was also given high priority for new economic modelling. Given this, the committee agreed that NMA was warranted to facilitate cost effectiveness analysis and to help decision making in this area.

# 2. Study selection

Systematic reviews of RCTs comparing interventions for the management of type 2 diabetes was undertaken for the guideline. This included two reviews:

- Interventions for the initial management of type 2 diabetes
- Interventions for the subsequent management of type 2 diabetes

Studies identified in the reviews were considered for inclusion in the NMA. The full details for the evidence review can be found in the evidence review.

We performed NMAs that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence.

This report will discuss the results from the systematic review of subsequent management of type 2 diabetes.

## 2.1. Population

The population included adults (age at least 18 years) with type 2 diabetes mellitus. From this, studies were grouped into five population models:

- Model 1: People with type 2 diabetes mellitus and heart failure
- Model 2: People with type 2 diabetes mellitus and atherosclerotic cardiovascular disease
- Model 3: People with type 2 diabetes mellitus and chronic kidney disease
- Model 4: People with type 2 diabetes mellitus and lower risk of developing cardiovascular disease
- Model 5: People with type 2 diabetes mellitus and higher risk of developing cardiovascular disease

The aim of management is likely to be different for the different groups:

- For models 1, 2 and 3 – a main aim of treatment is likely to be to prevent future events from occurring (secondary prevention) while managing complications from their current health status,
- For models 4 and 5 – a main aim of treatment is to stop a first event from occurring (primary prevention) by trying to reduce their risk,

Higher risk of developing cardiovascular disease was defined by a QRISK3 score of at least 10% for people who were 40 or older, and people with cardiovascular risk factors (in addition to the presence of type 2 diabetes if they were under 40. No evidence was identified for the model 4 population.

For more information, see the main report sections protocols, summary tables, evidence tables, summary matrices and GRADE assessment tables.

## 2.2. Interventions and their comparability

The interventions included in the NMA were:

- Biguanides
    - Metformin hydrochloride standard release

    - Metformin hydrochloride slow release
        - Where it was not possible to classify the type metformin, this was classified as metformin hydrochloride (type unspecified) and included in the analysis. However, where this was the case, the committee considered that this was most likely reporting metformin hydrochloride standard release.
- DPP-4 inhibitors
    - Alogliptin (Vipidia)
    - Linagliptin (Trajenta)
    - Saxagliptin (Onglyza)
    - Sitagliptin (Januvia)
    - Vildagliptin (Galvus)
- GLP-1 receptor agonist
    - Dulaglutide (Trulicity)
    - Exenatide (Byetta)
    - Liraglutide (Victoza)
    - Lixisenatide (Lyxumia)
    - Semaglutide (Rybelsus, Ozempic)
- Dual GIP/GLP-1 receptor co-agonists
    - Tirzepatide (Mounjaro)
- SGLT2 inhibitors
    - Canagliflozin (Invokana)
    - Dapagliflozin (Forxiga)
    - Empagliflozin (Jardiance)
    - Ertugliflozin (Steglatro)
- Sulfonylureas
    - Gliclazide
    - Glimepiride
    - Glipizide
    - Tolbutamide
- Thiazolidinediones
    - Pioglitazone
- Combination of the therapies listed above (combinations may include medication being given separately or combination products – these combination products include combinations with insulin, such as Insulin degludec/Liraglutide and Insulin glargine/Lixisenatide)
- Insulin
- Placebo

The committee agreed that most of these interventions would be provided to people in the same or similar treatment contexts, limiting the inherent heterogeneity that would be present in comparing different comparisons together. Exceptions could be raised for metformin and insulin. Metformin is likely to be provided earlier in the treatment pathway, but still is used as an intervention throughout the treatment pathway so is not excluded based on this. On the contrary, insulin is likely to be provided later in the treatment pathway. In this review, insulin is only included to compare between the other interventions in the review. Therefore, it was noted that the studies where interventions were compared to insulin may reflect people who have received multiple different therapies before entering the trial and so reflect a different population to someone who is receiving their first subsequent therapy. However, it was agreed that this group represented a part of the population necessary for accessing these treatments and so this natural variation in progression would be seen throughout the different treatments, rather than favouring one specific treatment or class of treatments and

so was deemed reasonable for inclusion. Consistency between studies comparing insulin and those comparing other treatments will be assessed where possible to explore the validity of this assumption.

These interventions were compared on a drug level rather than a class level. This was agreed as the committee acknowledged that some interventions may show different effects within classes. All doses were combined. This was agreed by the committee as the strategy for the management for type 2 diabetes generally involves starting from a lower dose and increasing to a higher dose until the optimal effects are achieved while avoiding adverse effects. We are combining multiple populations in order to give a complete representation of the clinical reality that is seen in the NHS, and so make a more applicable population for the economic model. We aim to capture the variability introduced by this through between-study heterogeneity.

## 2.3. Outcome measures

The committee agreed that a subset of outcomes were most relevant for decision making and therefore for inclusion in an NMA:

- Binary/time-to-event outcomes:
  - Cardiovascular mortality
  - 3-item major adverse cardiovascular event (MACE)
  - 4-item MACE
  - 5-item MACE
  - Non-fatal myocardial infarction
  - Non-fatal stroke
  - Unstable angina
  - Hospitalisation for heart failure
  - Development of end-stage renal failure
- Continuous outcomes:
  - HbA1c change
  - Weight change

These were assessed at the end of follow-up reported in the trials. The minimum follow-up time in the trials included in the review was 6 months (24-26 weeks).

# 3. Statistical methods

## 3.1. Synthesis methods

A Bayesian framework is used to estimate all parameters, using Hamiltonian Monte Carlo simulation methods implemented in RStudio version 2023.09.0 Build 463, R version 4.3.3, (2024-02-29 ucrt) using the multinma package version 0.6.1.9003 for the model 5 binary/time-to-event outcomes. A generalised linear model was fitted that could combine studies reporting binary data at a single follow-up time with studies reporting hazard ratios (converted to log-hazard ratios). For all outcomes, studies reporting binary data were modelled using a binomial likelihood and a cloglog link function (this assumes an underlying exponential hazard function), whilst those reporting log-hazard ratios were modelled using a normal likelihood with an identity link function. Estimated pooled treatment effect parameters represent log-hazard ratios.

The correlation between arms in multi-arm (>2 arm) studies is automatically accounted for within multinma. In a random effects model, assuming a common heterogeneity variance parameter leads mathematically to 0.5 correlations between arms. To account for the correlation between contrasts in multi-arm (>2 arm) studies reporting log-hazard ratios it was necessary to include data on the baseline (arm 1) log-hazard. This was calculated using Woods et al. 2010[4].

We assessed the goodness of fit of the model by calculating the mean of the posterior distribution of the residual deviance. If this is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

For studies with zero or 100% events in one arm only, the data were analysed without continuity corrections. However, weakly informative priors were used to constrain the range of estimated log-HRs to be within a plausible (yet still very wide) range.

### 3.1.1. Priors

Non-informative Normal(0,100) priors were assigned to the trial-specific baseline and treatment effects parameters (log hazards ratio) have weakly informative Normal(0, 2.82), priors while a Half Normal(scale=5 prior was assigned in the random effects models. (Gunhan et al 2019[2]).

### 3.1.2. Convergence

Each analysis was run with 4 chains, each with a different set of initial values, to check that the model had converged through the mixing of chains via history plots. Convergence was also assessed using a Markov Chain Monte Carlo trace plot and was satisfactory by 8000 simulations for all outcomes with a target average acceptance probability (adapt delta) of no more than 0.999.

### 3.1.3. Methods of sensitivity analyses, subgroup analyses and meta-regression

Sensitivity analyses were conducted to investigate the effect of removing a study (Group 2022) where the dose of glimepiride was significantly above that used in clinical practice (8mg per day) and this contributed to inconsistency in the model. In the sensitivity analysis, the study was left in, while in the base case, the glimepiride arm of the study was removed.

This study was removed from the relevant outcomes (cardiovascular mortality, 3-item MACE, 4-item MACE, unstable angina and hospitalisation for heart failure) to investigate whether this had a significant effect on the results of the analysis.

There were insufficient studies to meaningfully explore the available data with subgroup analyses and meta-regression.

### 3.1.4. Between study heterogeneity

When considering models for NMA, there are several aspects of the data that will impact the choice of parameters included in the model. To assess the validity of an NMA it is essential to assess the extent of heterogeneity. Heterogeneity concerns the differences in treatment effects between trials within each treatment contrast, while consistency concerns the differences between the direct and indirect evidence informing the treatment contrasts.

A fixed effects NMA model is the simplest model available to estimate the effects of interventions separately while simultaneously synthesizing all available evidence. This model assumes no heterogeneity between trials within each treatment contrast. In other words, all trials are estimating the same treatment effect, regardless of any differences in the conduct of the trials, populations, or treatments (for example: administration method or dose). A random effects NMA model relaxes this assumption accounting for any differences in treatment effects between trials that are beyond chance by estimating and accounting for the between-study standard deviation. When critiquing NMA models, it is good practice to assess and compare the fit (using the posterior residual deviance) and deviance information criterion (DIC) of both fixed and random effects models, as a meaningful improvement observed in the random effects model of at least 3-5 points may provide evidence of potential between-study heterogeneity. The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed. A small difference in DIC between the fixed and random effects models (3–5 points) implies that the better fit obtained by adding random effects does not justify the additional complexity. Therefore, if the difference in DIC between a fixed-effect and random-effect model was smaller than 5 points, then we reported the fixed-effects model results as that makes fewer assumptions than the random-effect model, contains fewer parameters and is easier to interpret clinically. The data were insufficient to properly estimate random-effect models, which led to a reasonable preference for simpler fixed-effect models.

### 3.1.5. Baseline model and data

The baseline risk is defined as the (absolute) risk of achieving the outcome of interest for patients receiving the reference intervention (placebo) in the population of interest at a particular follow-up time. By calculating the survival function on the baseline at a particular follow-up time, hazard ratios estimated from the NMA can be applied to this to obtain absolute risks under each intervention in the population of interest (see section 2.1). This allows us to convert the results of the NMA, which are estimated as hazard ratios, into absolute risks for easier interpretation.

Baseline risk was estimated using a single representative population from the included studies. The studies are summarised and reported in full in Appendix B with the rationale of why each trial was selected as the representative study. Where trials reported zero events, these are excluded from the tables. The committee suggested that there could be

uncertainty where some effect may be seen at 1-2 years. Therefore, if a study had a follow up period of less than 1 year then it is not reported in the table, but if it had a follow up period of 1-2 years then it is included in the table.

For models 2 and 3, the studies selected were generally reporting data at earlier time points than those for models 1 and 5. This reduced the comparability between the 4 populations models. However, there was similarity between a pair of population models in each case (models 1 and 5 and models 2 and 3 respectively) which allows for somewhat easier comparison to be made in these circumstances. For model 3, the value was not estimable for non-fatal myocardial infarction and non-fatal stroke. In these instances, it was agreed that the values from model 2 would be used to inform model 3, as model 2 included people with atherosclerotic cardiovascular disease, of which chronic kidney disease would be considered a type of. Therefore, the committee agreed this was the most relevant population to use as an indirect risk for these outcomes.

**Table 1: Risk of events reported in trials that informed baseline risk in each population model**

| Event | Model 1 proportion | Model 2 proportion | Model 3 proportion | Model 5 proportion |
|---|---|---|---|---|
| Cardiovascular mortality | 10.6% at 46 weeks | 5.9% at 37 weeks | 8.6% at 37 weeks | 6.0% at 46 weeks |
| 3-item MACE | 19.3% at 38 weeks | 14.6% at 38 weeks | 11.5% at 31 weeks | 12.2% at 38 weeks |
| 4-item MACE | NA | NA | NA | 13.2% at 26 weeks |
| 5-item MACE | NA | NA | NA | 15.4% at 25 weeks |
| Non-fatal myocardial infarction | 8.5% at 46 weeks | 5.2% at 37 weeks | Not estimable (5.2% used) | 6.8% at 46 weeks |
| Non-fatal stroke | 3.6% at 46 weeks | 2.6% at 37 weeks | Not estimable (2.6% used) | 3.8% at 46 weeks |
| Unstable angina | 3.6% at 46 weeks | 2.8% at 37 weeks | NA | 2.7% at 46 weeks |
| Hospitalisation for heart failure | 13.0% at 46 weeks | 4.1% at 37 weeks | 7.1% at 37 weeks | 5.3% at 46 weeks |
| Development of end-stage renal failure | NA | NA | 7.5% at 31 weeks | 0.9% at 38 weeks |

## 3.2. Summary measures and reference treatment

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review of for different population subgroups, which individual and/or combinations of pharmacological therapies are most clinically and cost effective as subsequent treatment for the management of type 2 diabetes?

In the NMA, data were pooled as log-hazard ratios. To facilitate comparison with the results of the pairwise MA, we converted the log hazard ratios into absolute risks at a specific follow-up time. The absolute risk difference was calculated using the follow method where r0

is the baseline risk, $r1_k$ the risk on intervention k, and $HR_k$ the hazard ratio for intervention k versus the network reference treatment (estimated from the NMA) (Skoetz et al 2019)[3]:

$r1_k = 1 - \exp(\ln(1-r0) \times HR_k) = 1 - (1 - r0)^{HR_k}$

This approach has the advantage that baseline and relative effects are both modelled on the same log hazards scale. It also ensures that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

We also calculated the overall ranking of interventions according to their relative hazard compared to control group. Due to the skewness of the data, the NMA relative hazards and rank results are reported as medians rather than means to give a more accurate representation of the 'most likely' value.

In the cost effectiveness analysis, hazard ratios were used.

## 3.3. Methods of assessing inconsistency

A key assumption behind NMA is that the evidence in the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes relating to differences between the trials included in terms of their clinical or methodological characteristics that interact with the relative intervention effects (often called "effect modifiers").

Heterogeneity and inconsistency can be a problem for NMA, as they violate the similarity and transitivity assumptions. However, they can often be dealt with by subgroup analysis, meta-regression or by more narrowly defining inclusion criteria.

Inconsistency was assessed by comparing the chosen consistency model (fixed or random effects) to an "inconsistency", or unrelated mean effects, model (Dias, 2011[1]). The latter is equivalent to having separate, unrelated, meta-analyses for every pairwise contrast, with a common variance parameter assumed in the case of random effects models. Note that inconsistency can only be assessed when there are closed loops of direct evidence on 3 or more treatments that are informed by at least 2 distinct trials.

## 3.4. Model comparison

The posterior mean of the residual deviance, which measures the magnitude of the differences between the observed data and the model predictions of the data, was used to assess the goodness of fit of each model. Smaller values are preferred, and in a well-fitting model the posterior mean residual deviance should be close to the number of data points in the network (each study arm contributes 1 data point). In addition to comparing how well the models fit the data using the posterior mean of the residual deviance, models were compared using the DIC. This is equal to the sum of the posterior mean deviance and the effective number of parameters, and thus penalizes model fit with model complexity. Lower values are preferred and typically differences of at least 5 points are considered meaningful.

## 3.5. Assessing clinical importance

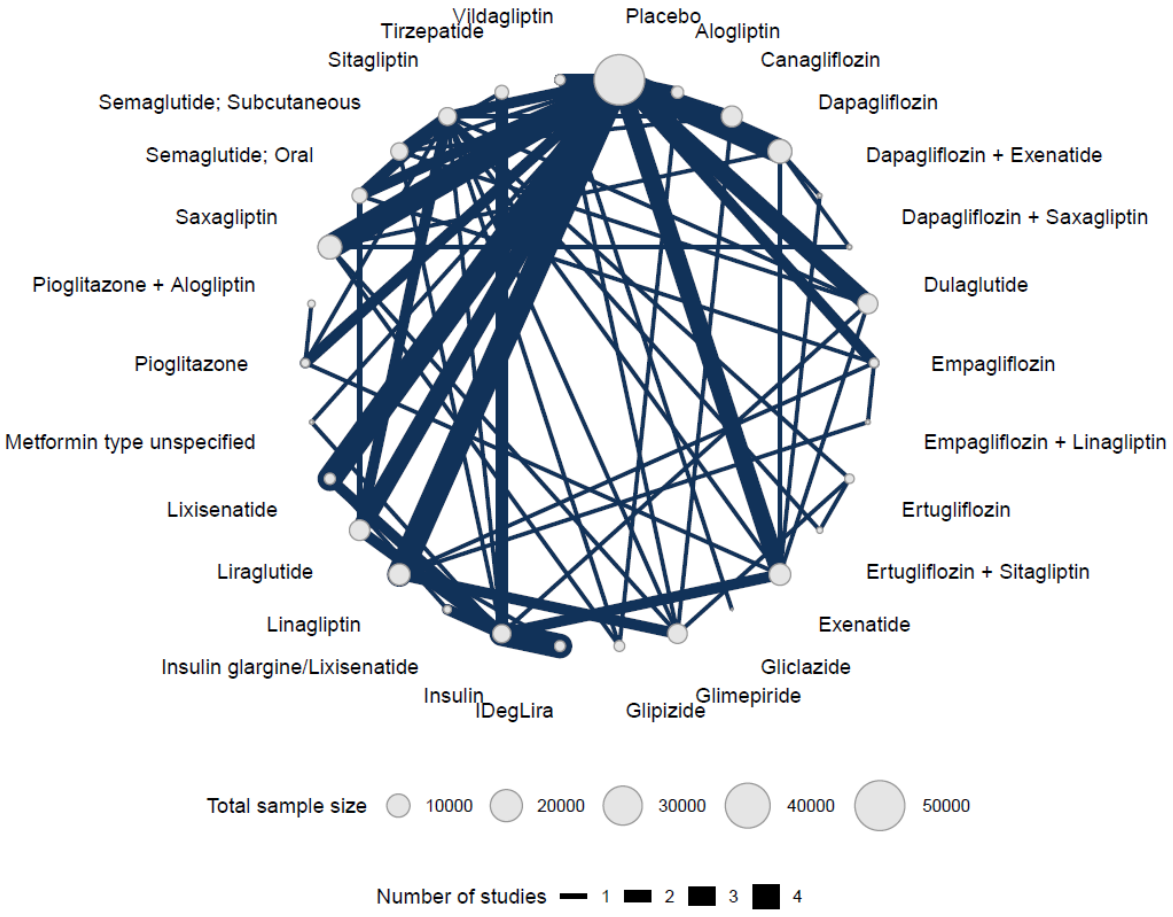
The credible intervals of the treatment effects were inspected to determine if there was statistical evidence of a difference between treatments, with no overlap in credible intervals indicating evidence of a difference between treatment effects. If a statistical difference was

identified, then the magnitude of the difference was considered meaningful if it was larger than the minimal important differences (MIDs) (more information in Methods chapter).

# 4. Outcomes – model 5 – high cardiovascular risk

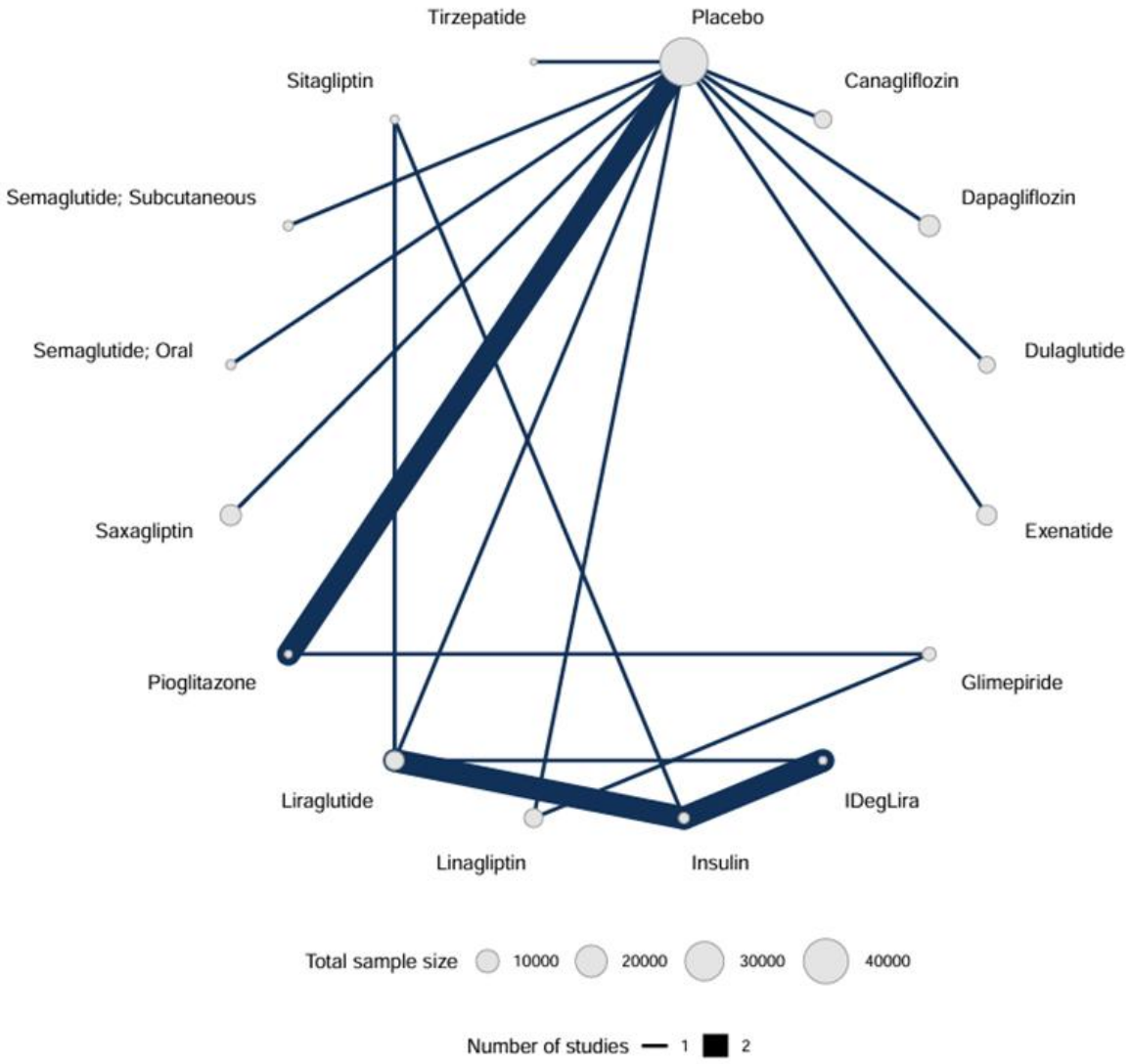
## 4.1. Cardiovascular mortality

**Figure 1: Network diagram. Line thickness indicates number of included trials reporting data for cardiovascular mortality for adults with type 2 diabetes in the base case analysis. Nodes are scaled to indicate number of individuals receiving each treatment.**



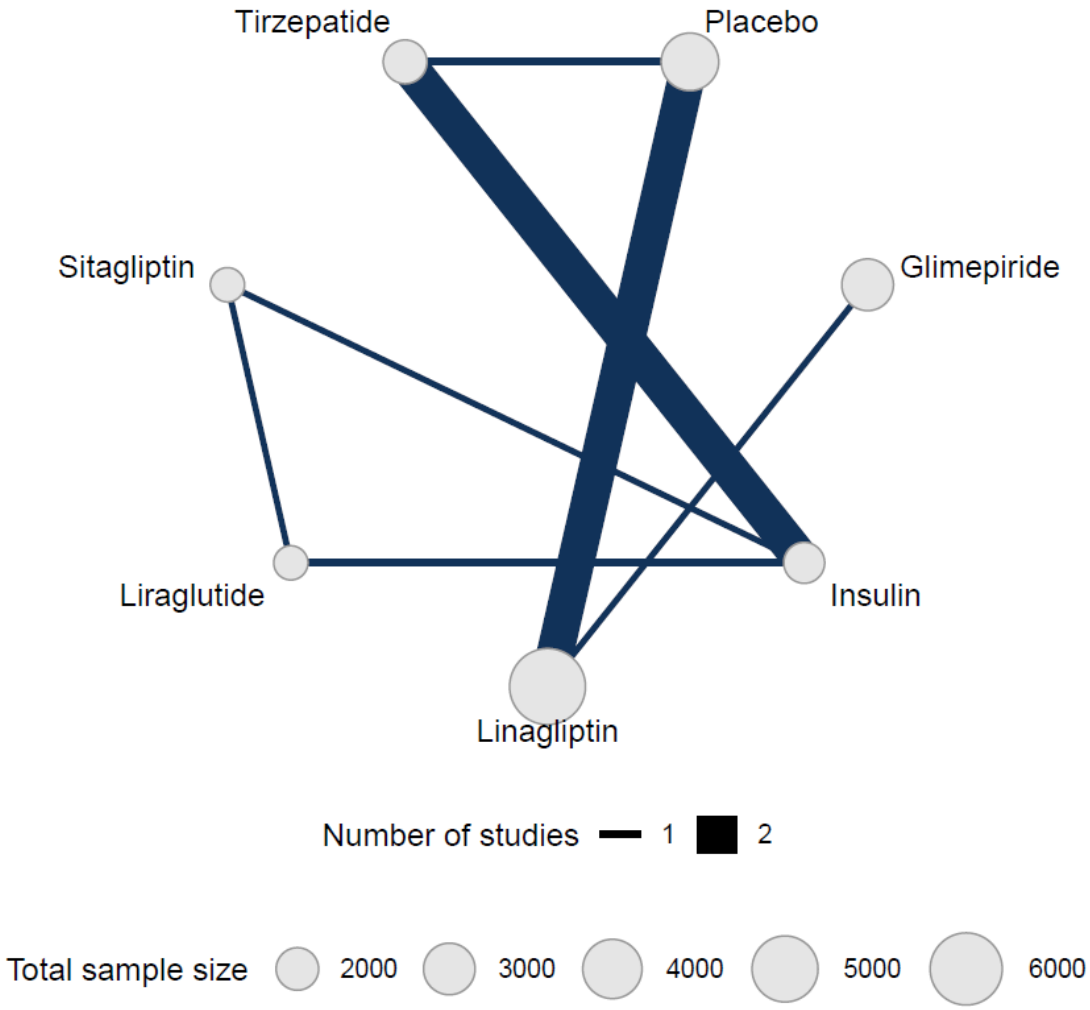
## 4.2. 3-item MACE

**Figure 2: Network diagram. Line thickness indicates number of included trials reporting data for 3-item MACE for adults with type 2 diabetes in the base case analysis. Nodes are scaled to indicate number of individuals receiving each treatment.**



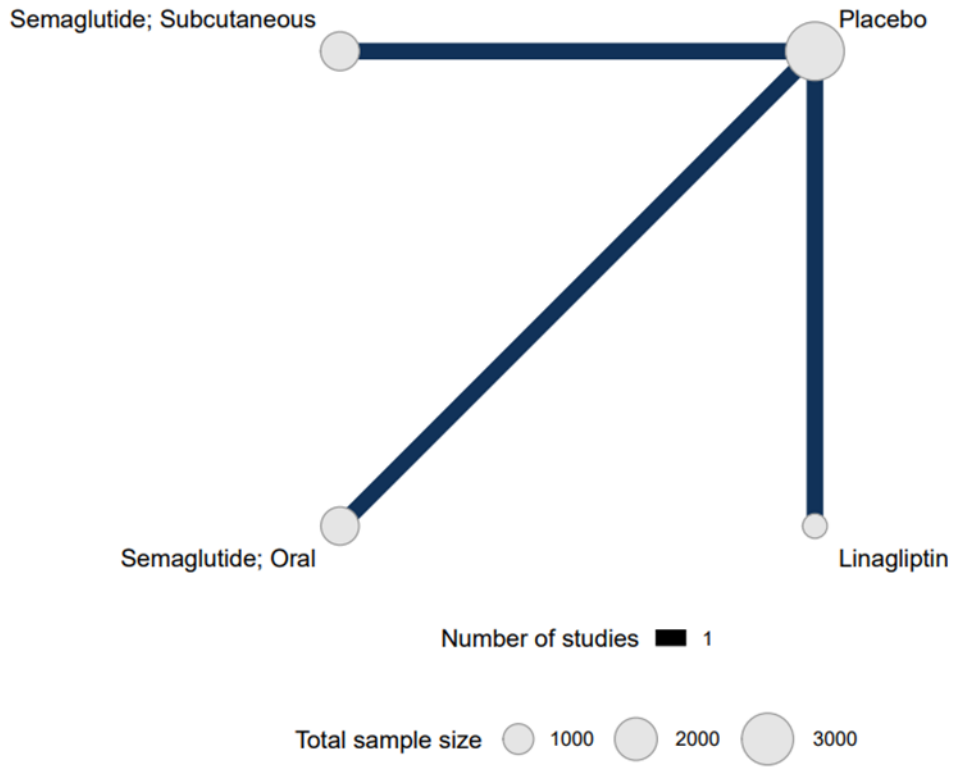
## 4.3. 4-item MACE

**Figure 3: Network diagram. Line thickness indicates number of included trials reporting data for 4-item MACE for adults with type 2 diabetes. Nodes are scaled to indicate number of individuals receiving each treatment.**



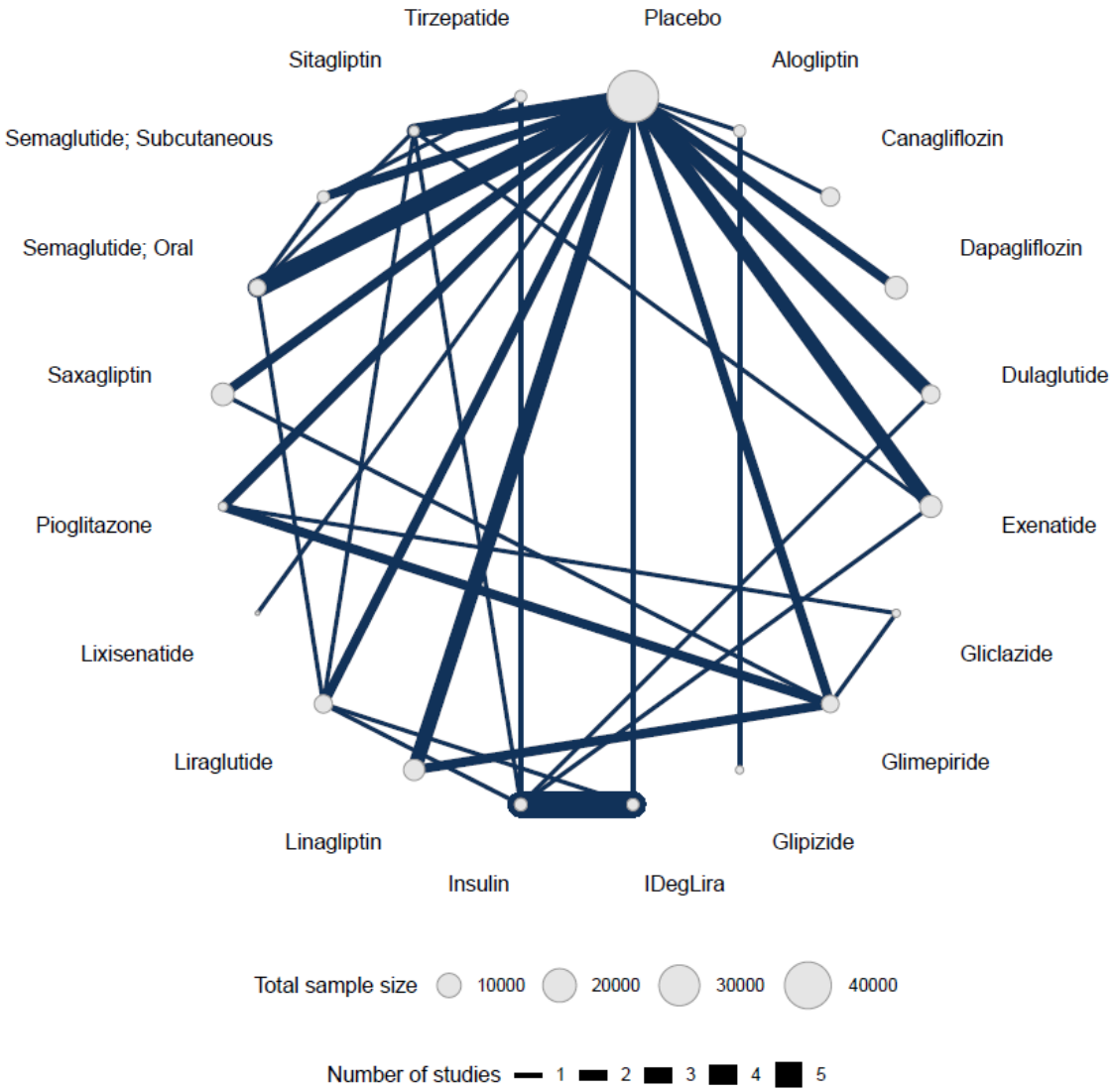
## 4.4. 5-item MACE

**Figure 4: Network diagram. Line thickness indicates number of included trials reporting data for 5-item MACE for adults with type 2 diabetes. Nodes are scaled to indicate number of individuals receiving each treatment.**



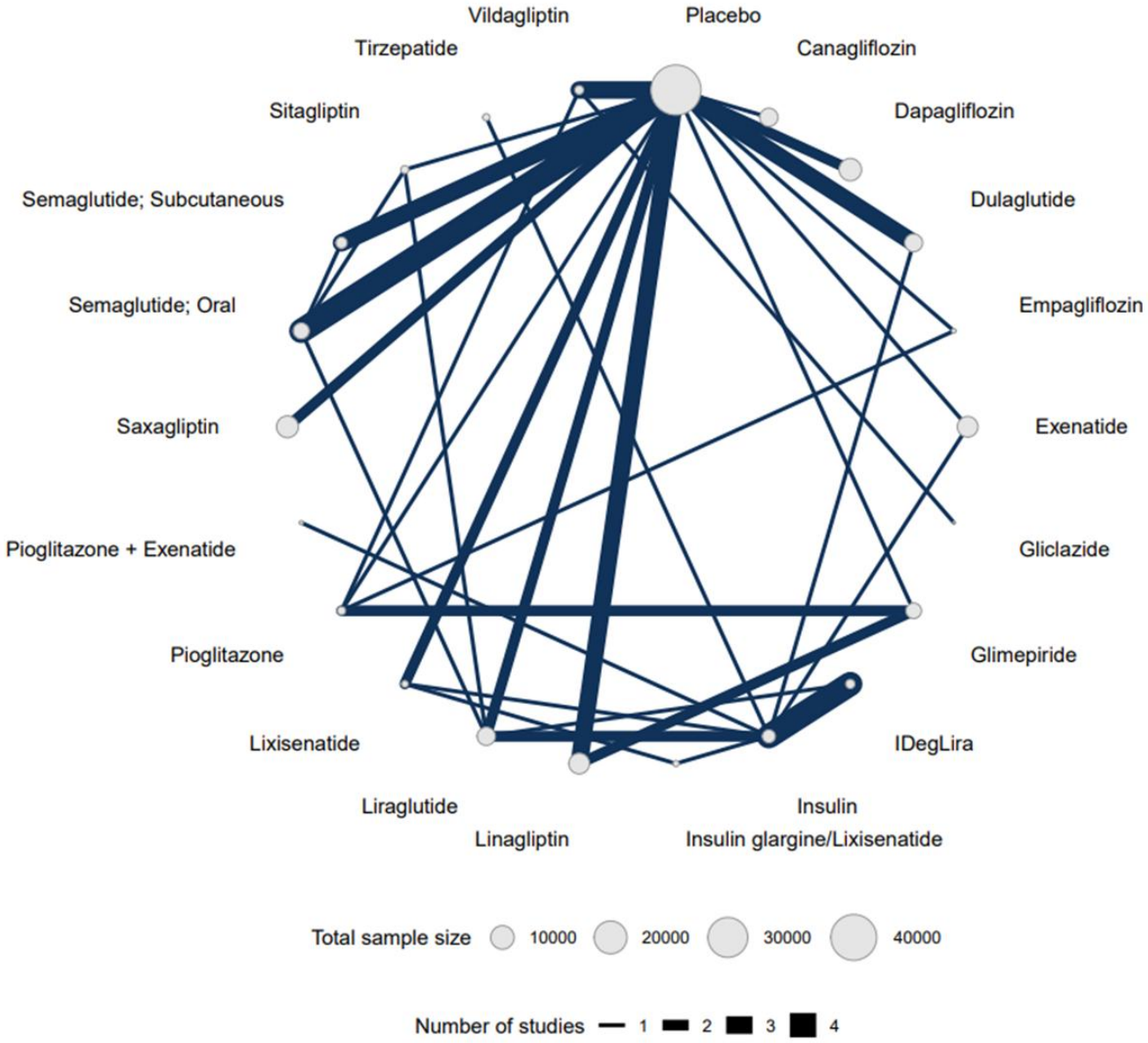
## 4.5. Non-fatal myocardial infarction

**Figure 5: Network diagram. Line thickness indicates number of included trials reporting data for non-fatal myocardial infarction for adults with type 2 diabetes. Nodes are scaled to indicate number of individuals receiving each treatment.**



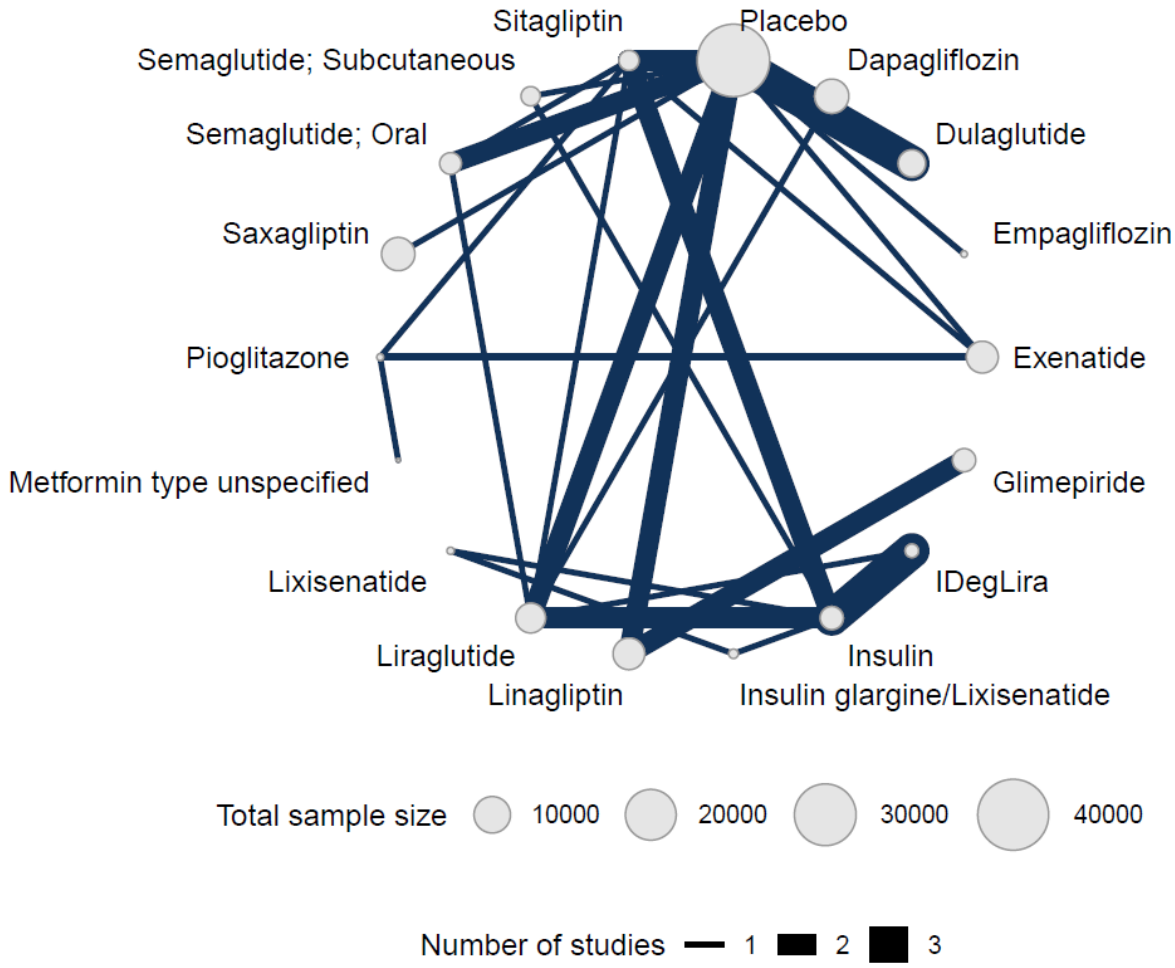
## 4.6. Non-fatal stroke

**Figure 6: Network diagram. Line thickness indicates number of included trials reporting data for non-fatal stroke for adults with type 2 diabetes. Nodes are scaled to indicate number of individuals receiving each treatment.**



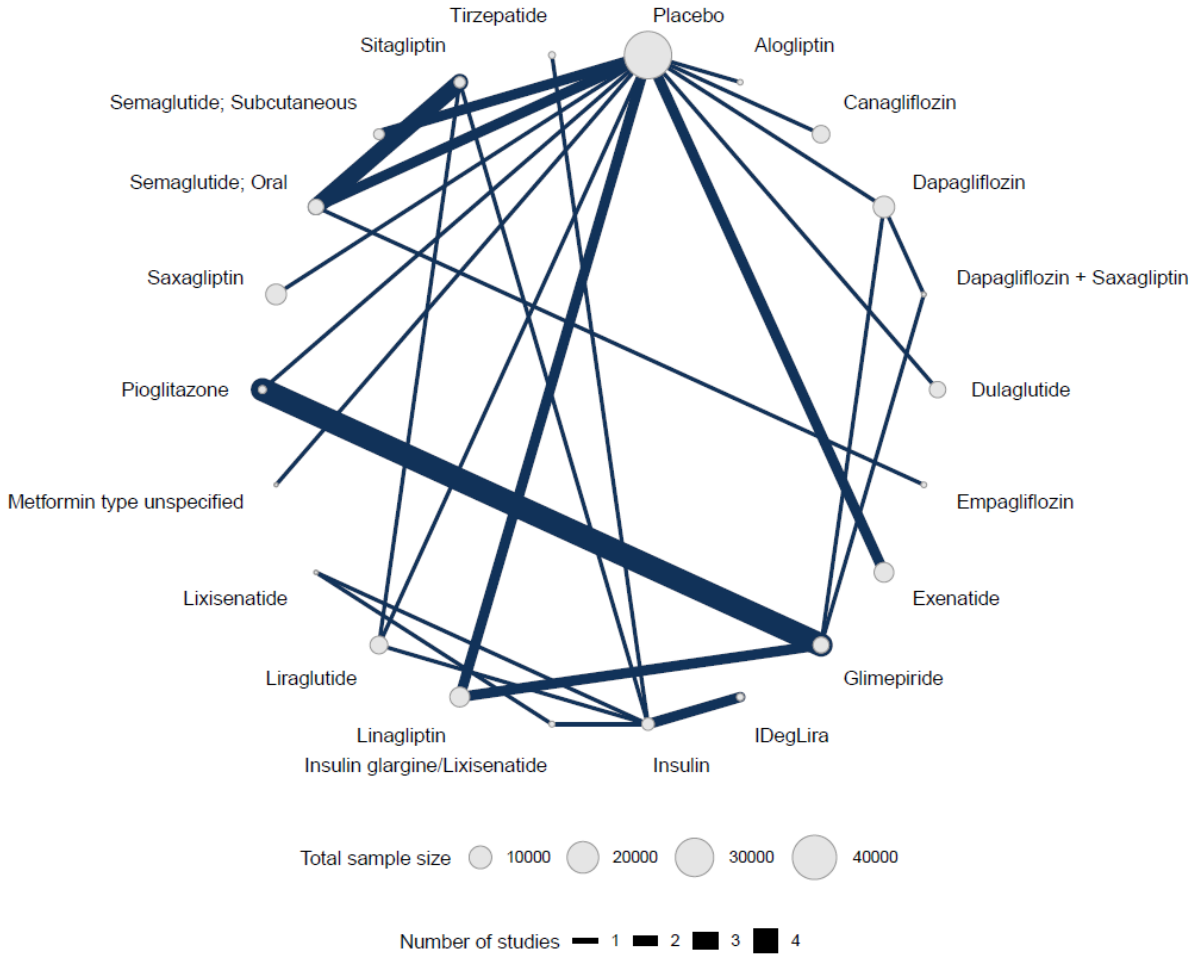
## 4.7. Unstable angina

**Figure 7: Network diagram. Line thickness indicates number of included trials reporting data for unstable angina for adults with type 2 diabetes. Nodes are scaled to indicate number of individuals receiving each treatment.**



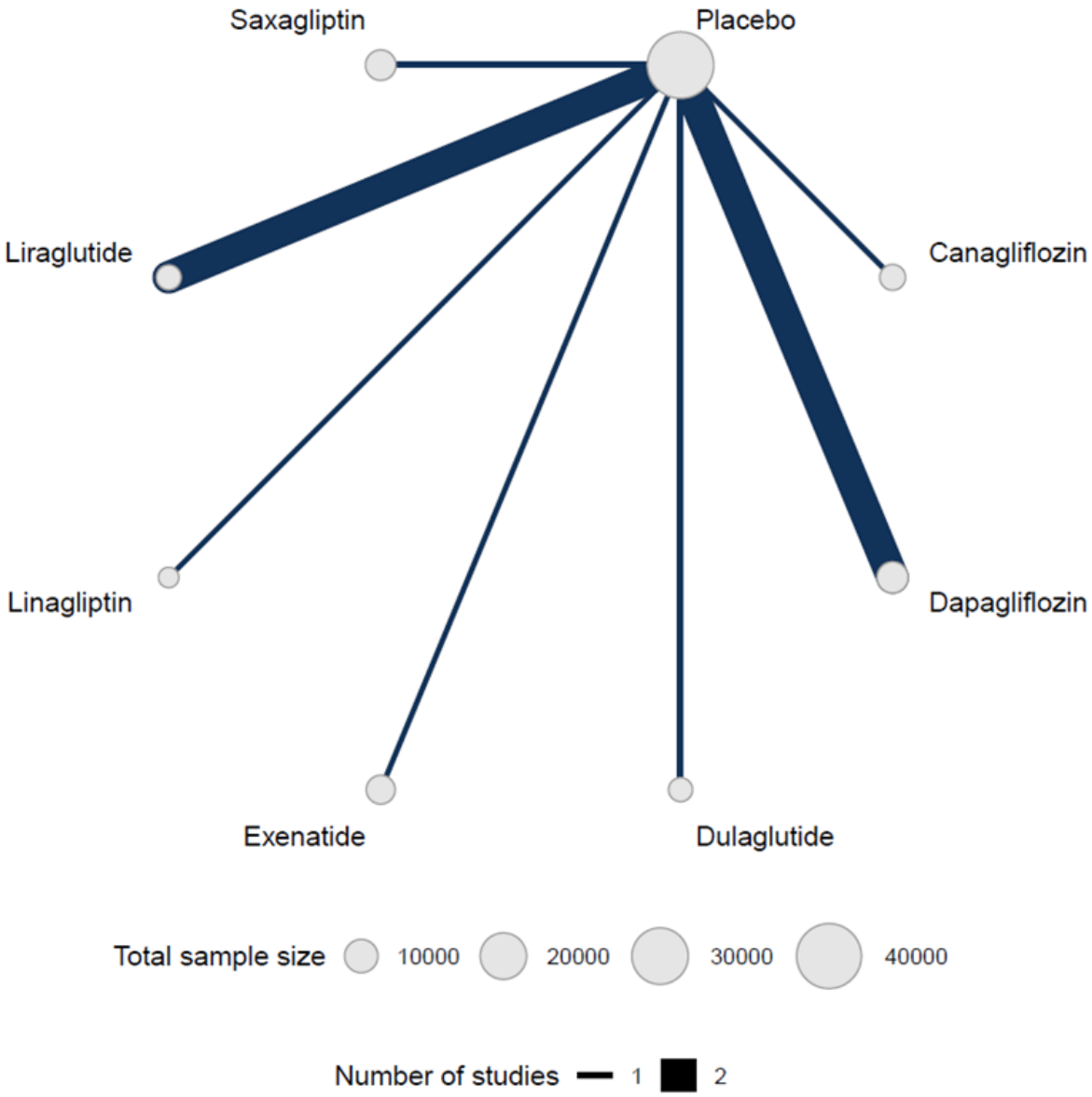
## 4.8. Hospitalisation for heart failure

**Figure 8: Network diagram. Line thickness indicates number of included trials reporting data for hospitalisation for heart failure for adults with type 2 diabetes in the base case analysis. Nodes are scaled to indicate number of individuals receiving each treatment.**



## 4.9. Development of end-stage renal failure

**Figure 9: Network diagram. Line thickness indicates number of included trials reporting data for development of end-stage renal failure for adults with type 2 diabetes. Nodes are scaled to indicate number of individuals receiving each treatment.**



# 5. Model fit – model 5 – high cardiovascular risk

The data were fitted to fixed and random-effects models, and the goodness of fit evaluated by calculating the total residual deviance (a calculation of the model's ability to predict the individual data points underlying it). Inconsistency was assessed by comparing the model fit statistics between the NMA (consistency) model and the unrelated mean effects (UME, inconsistency) model. Individual datapoints were also assessed by deviance contribution plot (dev-dev plot), by plotting contribution to the posterior mean residual deviance for the UME model against the NMA model. Plots of prior and posterior distributions for the treatment effects were compared to assess the degree to which the priors influenced the posterior results.

## 5.1. Cardiovascular mortality

**Table 2: Measures of goodness of fit of fixed- and random- effects models for cardiovascular mortality for the base case**

| Measure of goodness of fit | Fixed-effects model | Random-effects model | UME – fixed effects |
|---|---|---|---|
| **Total Residual deviance*** | 238.2 | 229.9 | 219.2 |
| **Posterior distribution (pD)** | 101.7 | 109.1 | 110.2 |
| **Deviance information criterion (DIC)** | 339.9 | 339.0 | 329.5 |
| **Between trial standard deviation (95% credible intervals)** | - | 0.35 (0.01, 1.05) | - |
| *Compared to 203 data points | | | |

A fixed-effects model was preferred for the analysis. Although the total residual deviance for the random-effects model was closer to the number of unconstrained data points, the deviance information criterion was similar for the fixed-effects model and random-effects model, and therefore the simpler fixed-effects model was deemed to be more appropriate. Subsequent results present data from the fixed-effects model only.

**Figure 10: Dev-dev plot for cardiovascular mortality for the base case**

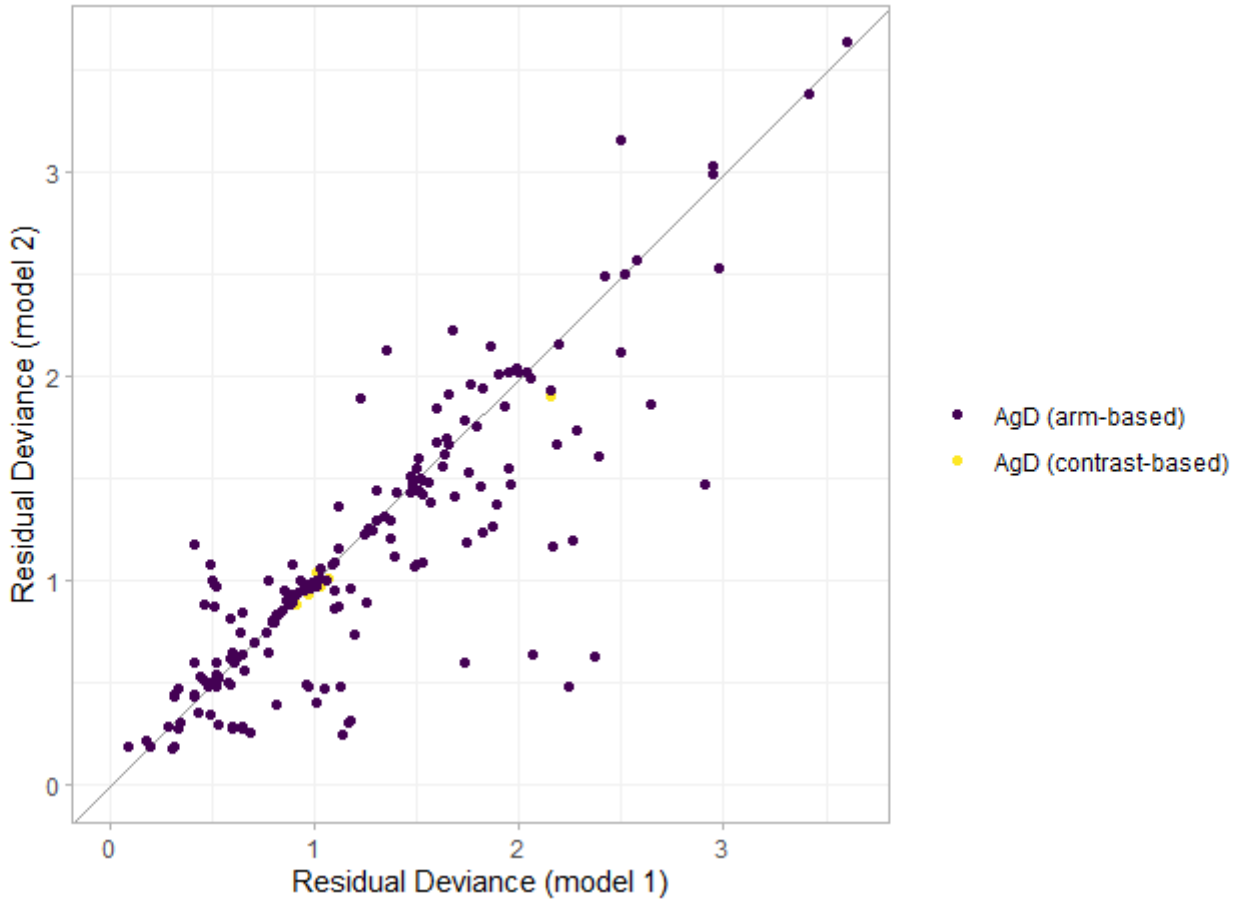
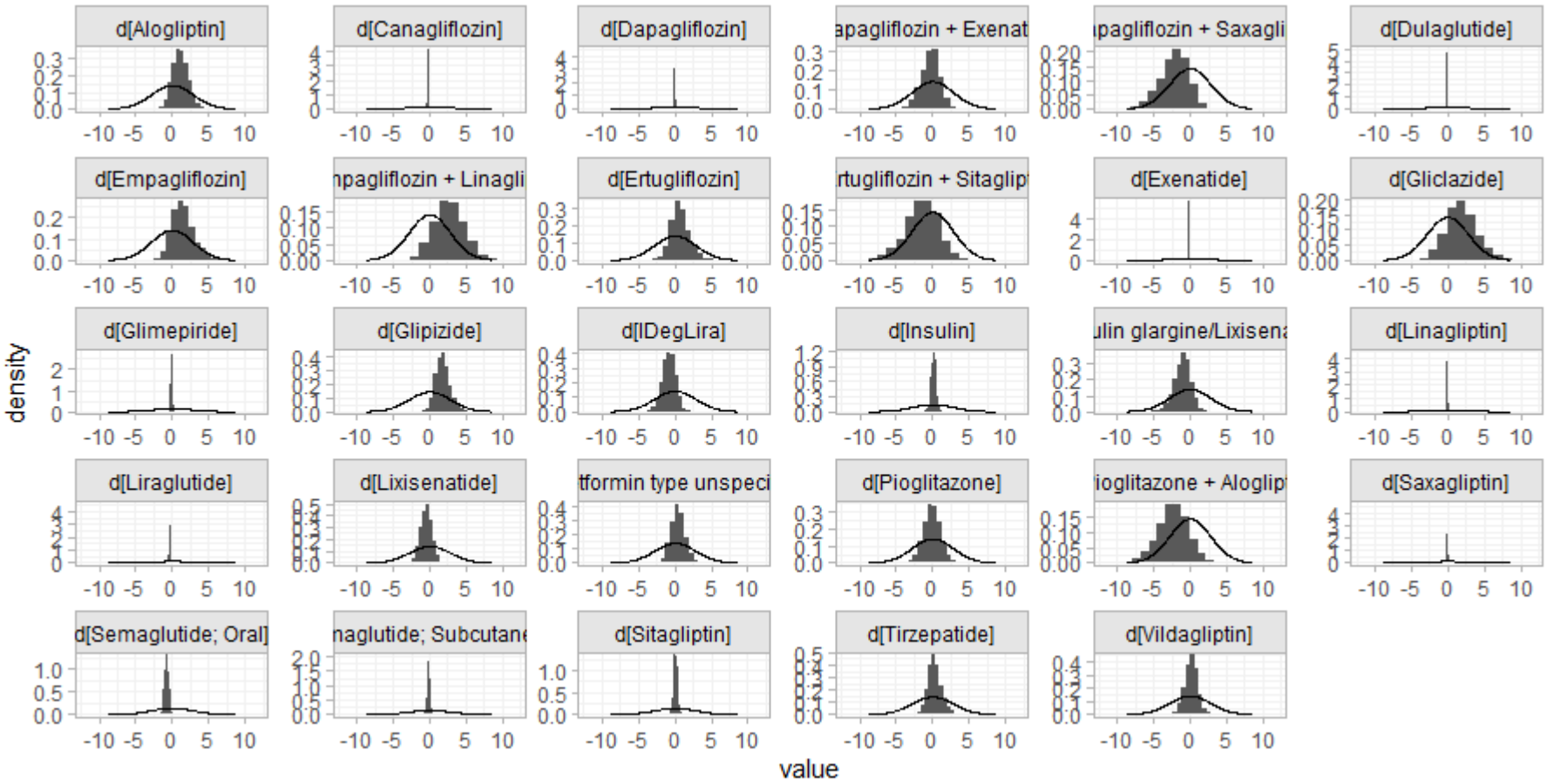


**Figure 11: Prior and posterior distributions for cardiovascular mortality for the base case**



## 5.2. 3-item MACE

**Table 3: Measures of goodness of fit of fixed- and random-effects models for 3-item MACE for the base case**

| Measure of goodness of fit | Fixed effect model | Random-effects model | UME – fixed effects |
|---|---|---|---|
| **Total Residual deviance*** | 28.1 | 26.8 | 26.4 |
| **Posterior distribution (pD)** | 22.2 | 23.3 | 23.3 |
| **Deviance information criterion (DIC)** | 50.2 | 50.1 | 49.7 |
| **Between trial standard deviation (95% credible intervals)** | - | 0.37 (0.02, 1.13) | - |
| *Compared to 27 data points | | | |

A fixed-effects model was preferred for the analysis. Although the total residual deviance for the random-effects model was closer to the number of unconstrained data points, the deviance information criterion was similar for the fixed-effects model and random-effects model, and therefore the simpler fixed-effects model was deemed to be more appropriate. Subsequent results present data from the fixed-effects model only.

**Figure 12: Dev-dev plot for 3-item MACE for the base case**

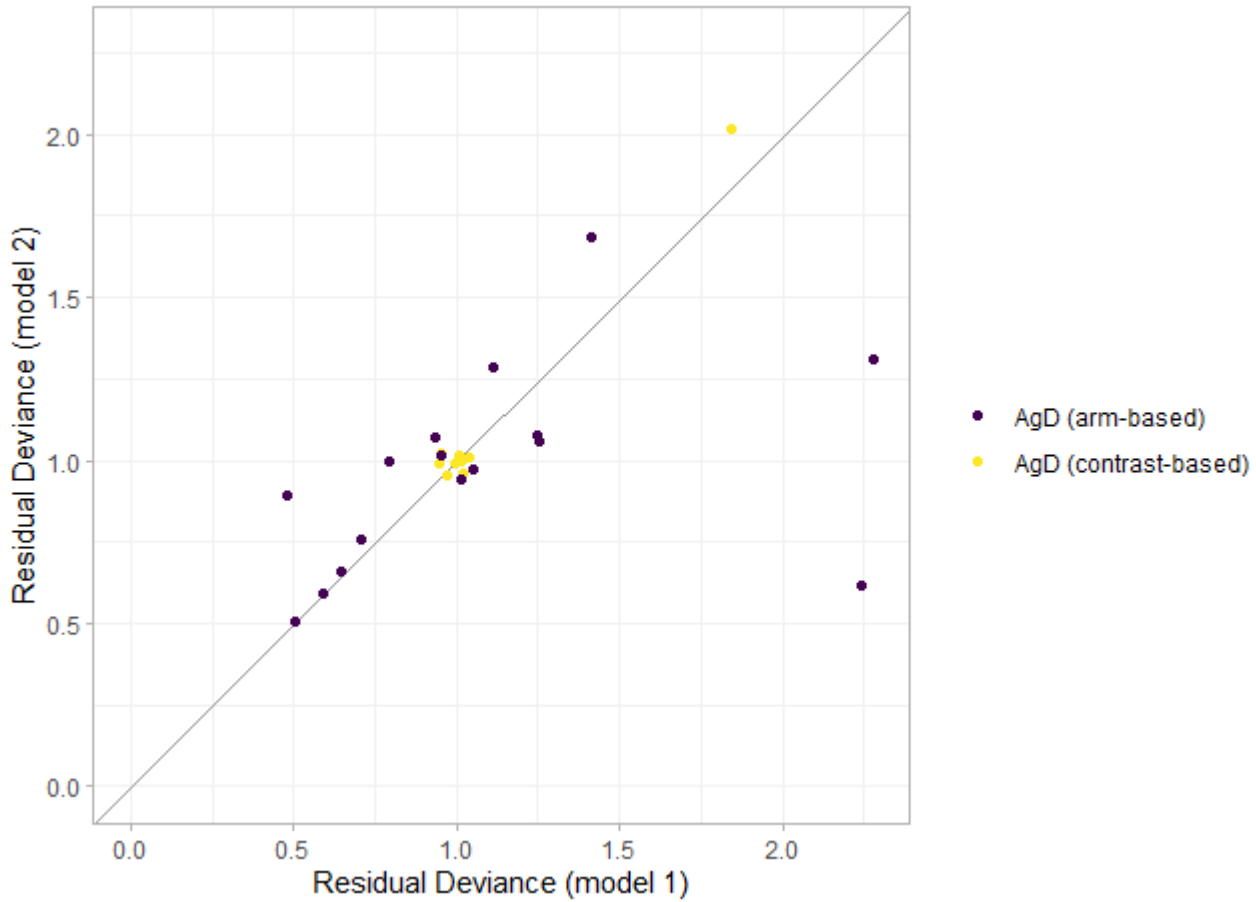
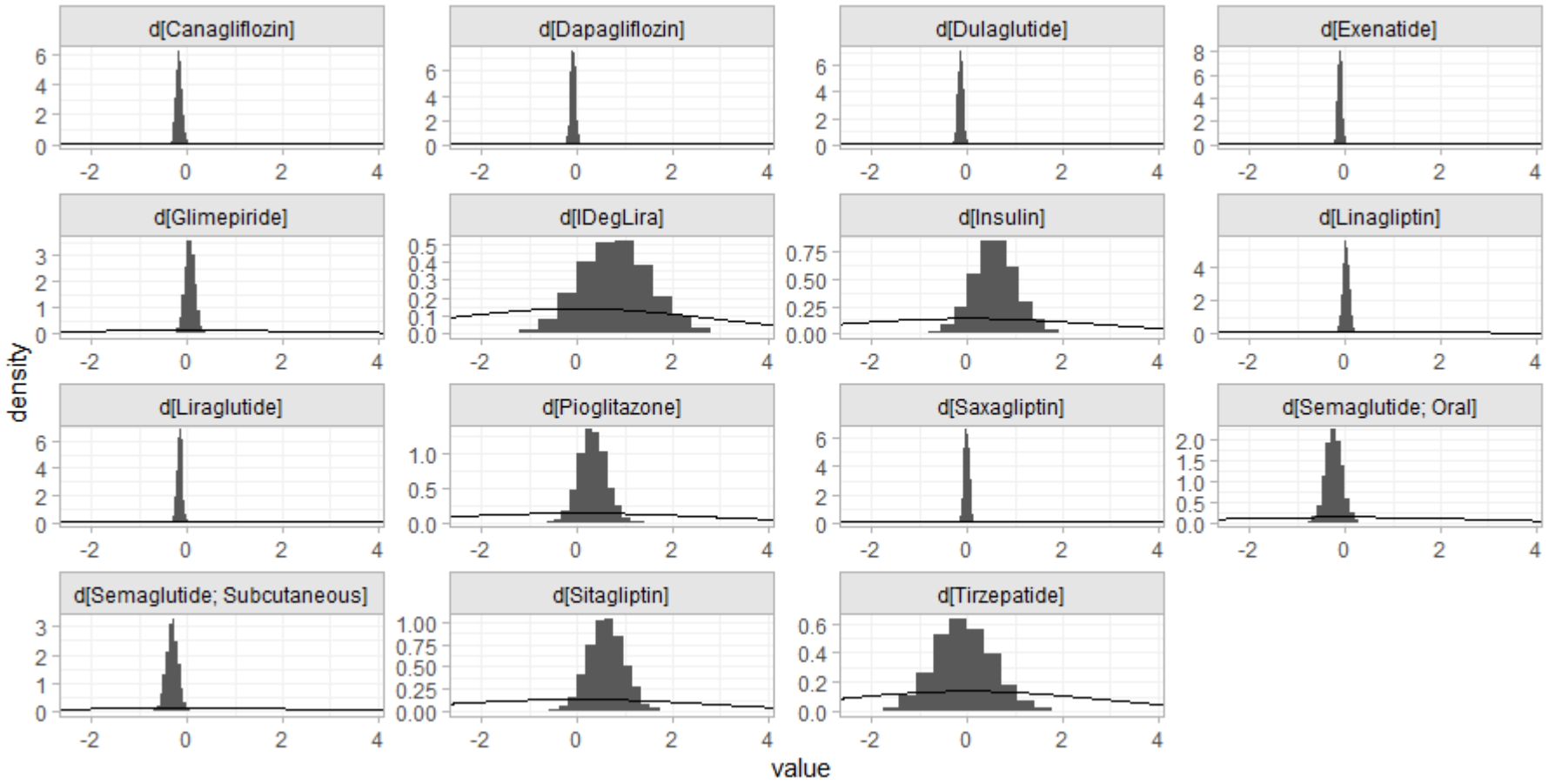


**Figure 13: Prior and posterior distributions for 3-item MACE for the base case**



## 5.3. 4-item MACE

**Table 4: Measures of goodness of fit of fixed- and random-effects models for 4-item MACE for the base case**

| Measure of goodness of fit | Fixed effect model | Random-effects model | UME – fixed effects |
|---|---|---|---|
| **Total Residual deviance*** | 17.7 | 17.3 | 17.9 |
| **Posterior distribution (pD)** | 10.7 | 12.1 | 10.9 |
| **Deviance information criterion (DIC)** | 28.4 | 29.5 | 28.8 |
| **Between trial standard deviation (95% credible intervals)** | - | 0.34 (0.02 to 1.20) | - |
| *Compared to 19 data points | | | |

A fixed-effects model was preferred for the analysis. The total residual deviance for the random-effects model was only marginally closer to the number of unconstrained data points and deviance information criterion was lower for the fixed-effects model. Subsequent results present data from the fixed-effects model only.

**Figure 14: Dev-dev plot for 4-item MACE for the base case**

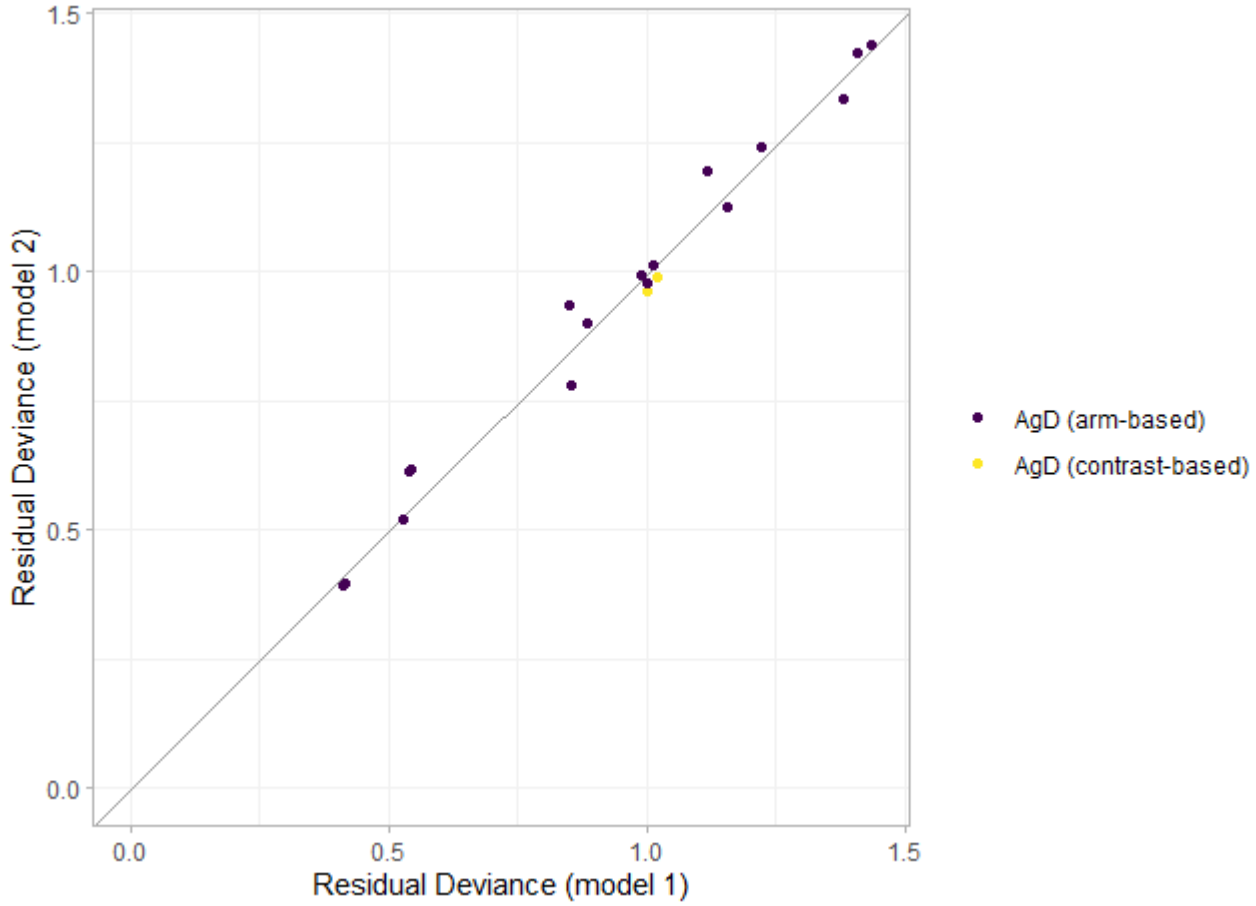
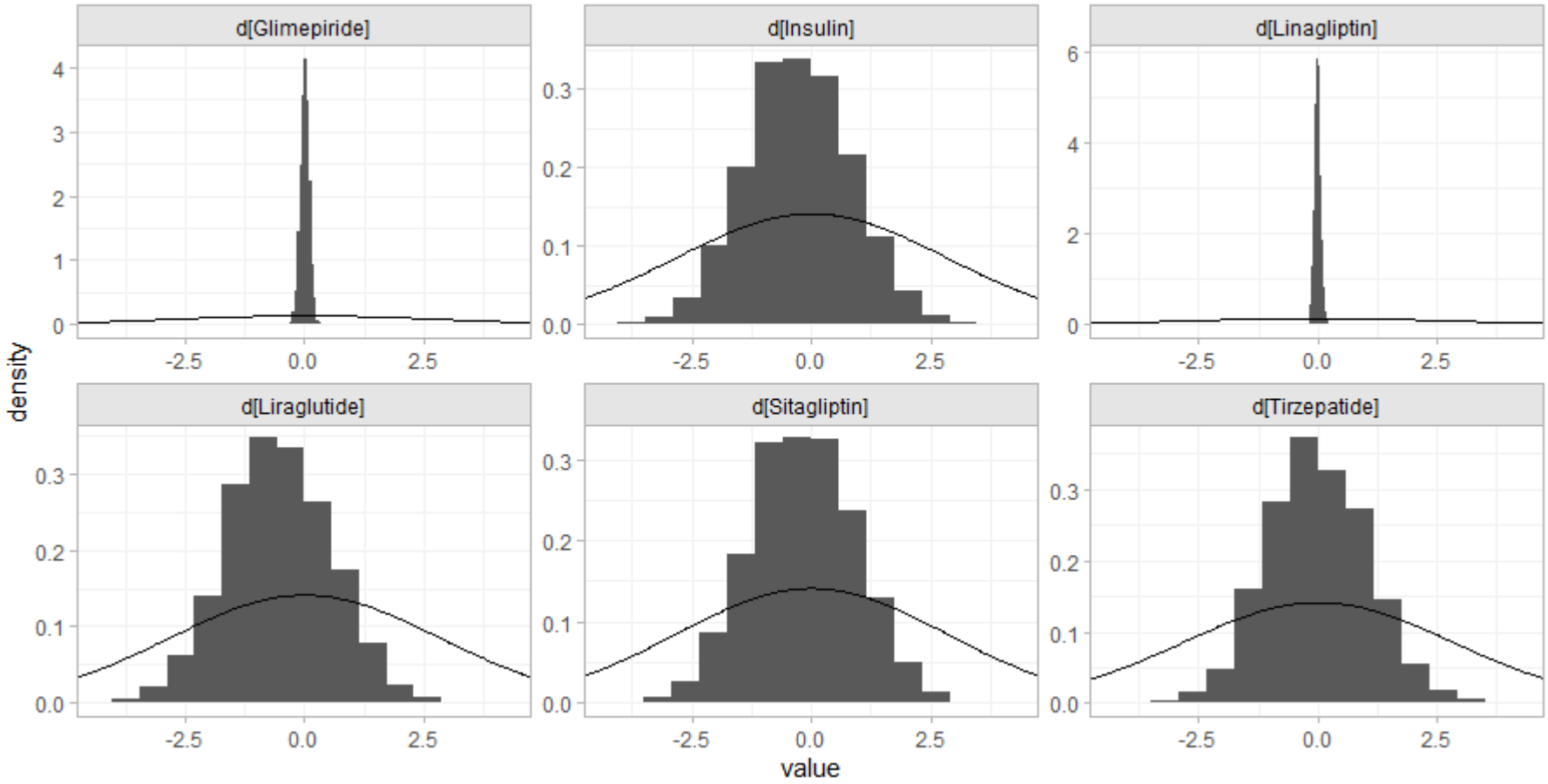


**Figure 15: Prior and posterior distributions for 4-item MACE for the base case**



## 5.4. 5-item MACE

**Table 5: Measures of goodness of fit of fixed- and random-effects models for 5-item MACE**

| Measure of goodness of fit | Fixed effect model | Random-effects model | UME – fixed effects |
|---|---|---|---|
| **Total Residual deviance*** | 3.9 | 4.0 | 3.9 |
| **Posterior distribution (pD)** | 3.9 | 4.0 | 3.9 |
| **Deviance information criterion (DIC)** | 7.9 | 8.0 | 7.8 |
| **Between-trial standard deviation (95% credible intervals)** | - | 1.36 (0.06, 5.92) | - |
| *Compared to 4 data points | | | |

A fixed-effects model was preferred for the analysis. The total residual deviance for the fixed-effects model was closer to the number of unconstrained data points, and the deviance information criterion was lower. Subsequent results present data from the fixed-effects model only.

**Figure 16: Dev-dev plot for 5-item MAC**

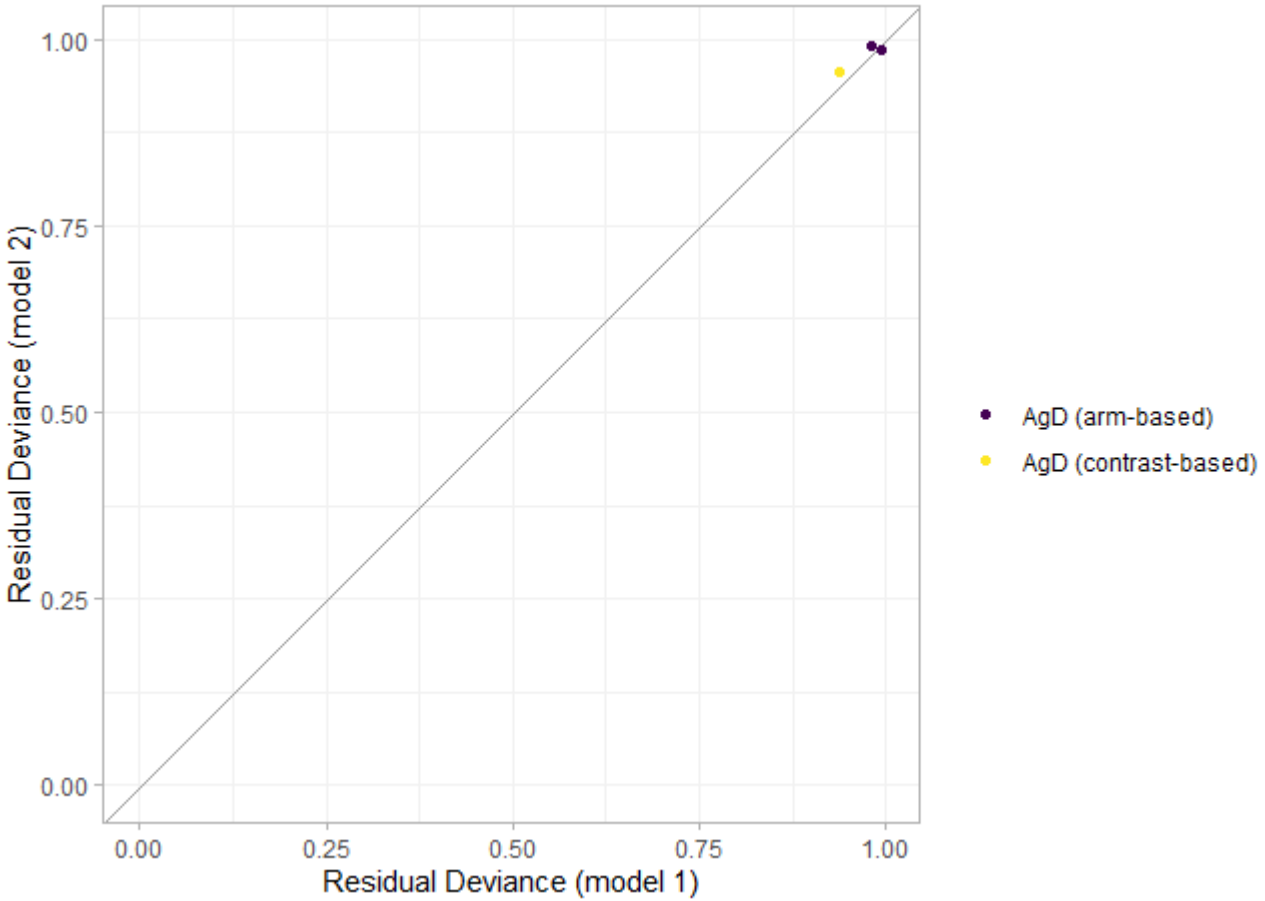
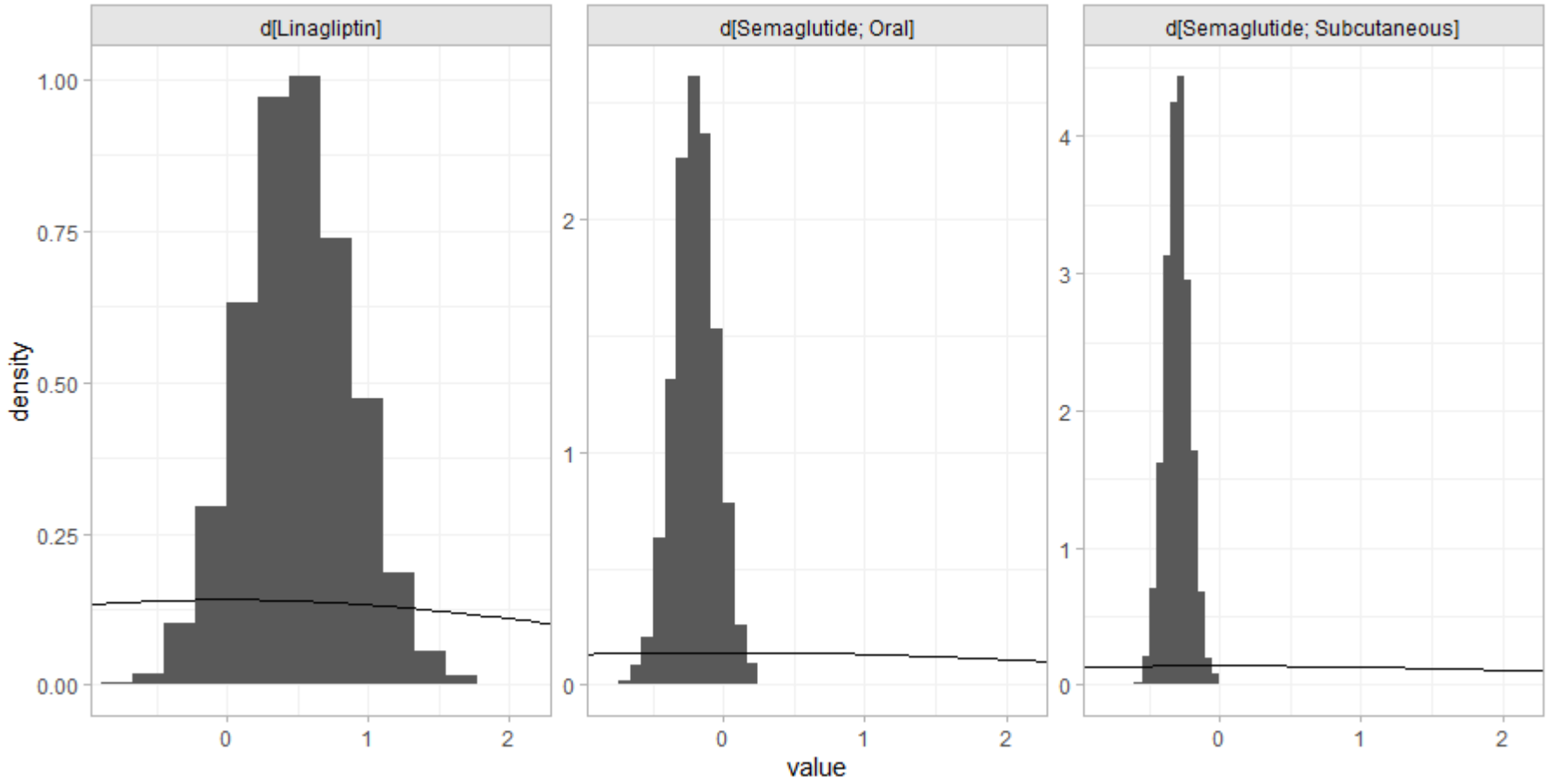


**Figure 17: Prior and posterior distributions for 5-item MACE**



## 5.5. Non-fatal myocardial infarction

**Table 6: Measures of goodness of fit of fixed- and random-effects models for non-fatal myocardial infarction**

| Measure of goodness of fit | Fixed-effects model | Random-effects model | UME – fixed effects |
|---|---|---|---|
| **Total Residual deviance*** | 125.3 | 123.8 | 117.7 |
| **Posterior distribution (pD)** | 59.0 | 62.3 | 62.4 |
| **Deviance information criterion (DIC)** | 184.3 | 186.2 | 180.1 |
| **Between trial standard deviation (95% credible intervals)** | - | 0.24 (0.01, 0.96) | - |
| *Compared to 110 data points | | | |

A fixed-effects model was preferred for the analysis. Although the total residual deviance for the random-effects model was closer to the number of unconstrained data points, the deviance information criterion was similar for the fixed-effects model and random-effects model, and therefore the simpler fixed-effects model was deemed to be more appropriate. Subsequent results present data from the fixed-effects model only.

**Figure 18: Dev-dev plot for non-fatal myocardial infarction**

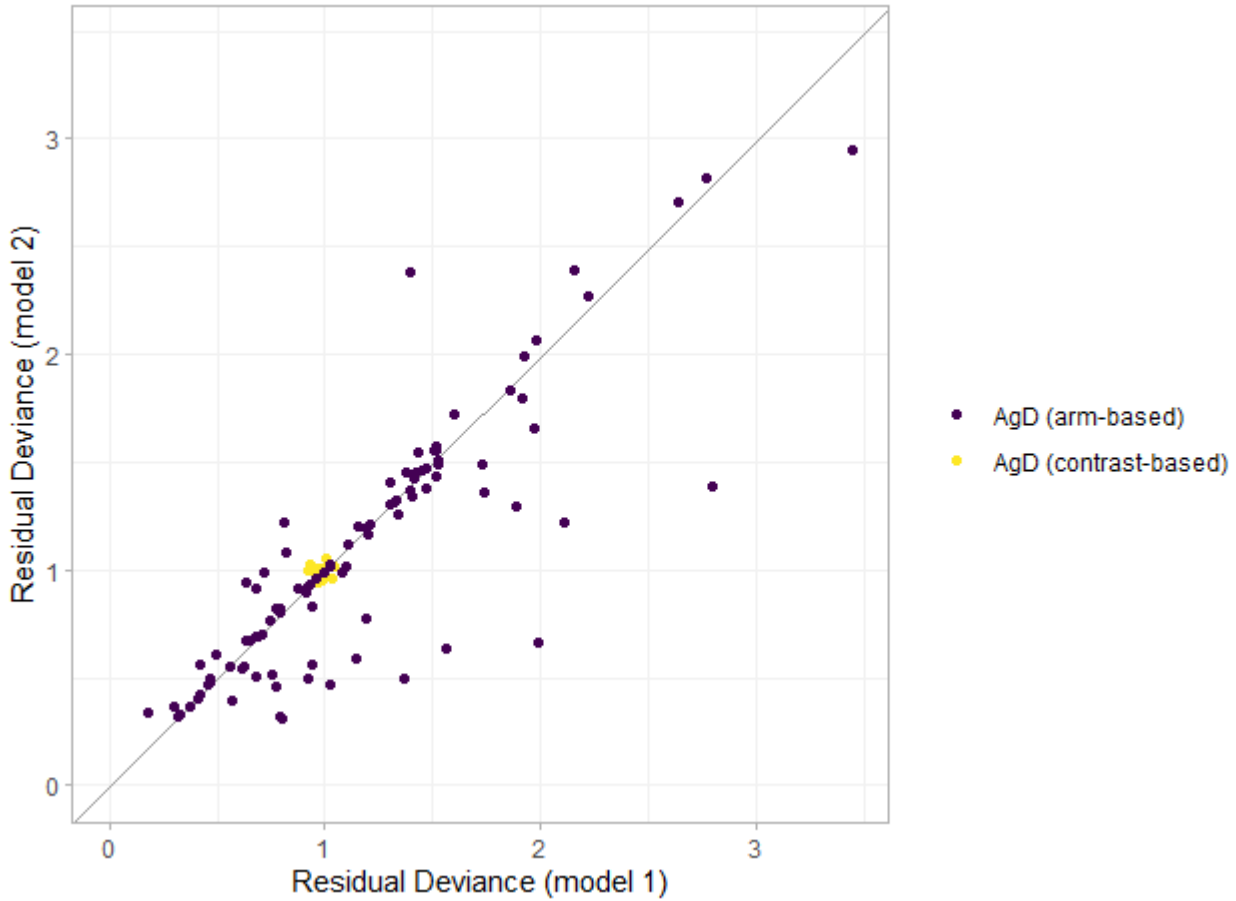
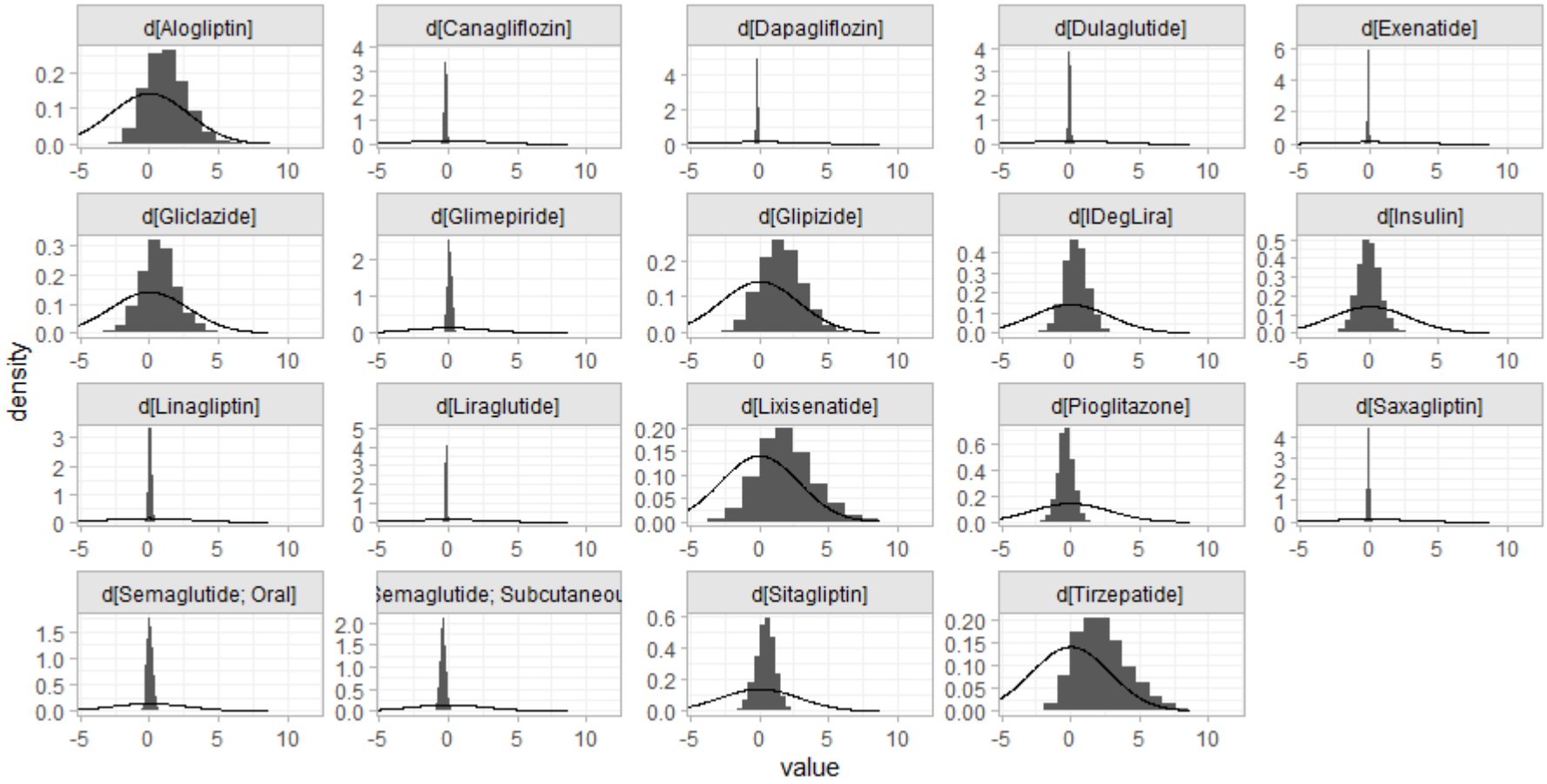


**Figure 19: Prior and posterior distributions for non-fatal myocardial infarction**



## 5.6. Non-fatal stroke

**Table 7: Measures of goodness of fit of fixed- and random-effects models for non-fatal stroke**

| Measure of goodness of fit | Fixed-effects model | Random-effects model | UME – fixed effects |
|---|---|---|---|
| **Total Residual deviance*** | 119.0 | 110.8 | 108.1 |
| **Posterior distribution (pD)** | 59.0 | 65.2 | 61 |
| **Deviance information criterion (DIC)** | 177.9.0 | 176.0 | 169.1 |
| **Between trial standard deviation (95% credible intervals)** | - | 0.55 (0.04 – 1.35) | - |
| *Compared to 105 data points | | | |

A fixed-effects model was preferred for the analysis. Although the total residual deviance for the random-effects model was closer to the number of unconstrained data points, the deviance information criterion was similar for the fixed-effects model and random-effects model, and therefore the simpler fixed-effects model was deemed to be more appropriate. Subsequent results present data from the fixed-effects model only.

**Figure 20: Dev-dev plot for non-fatal stroke**

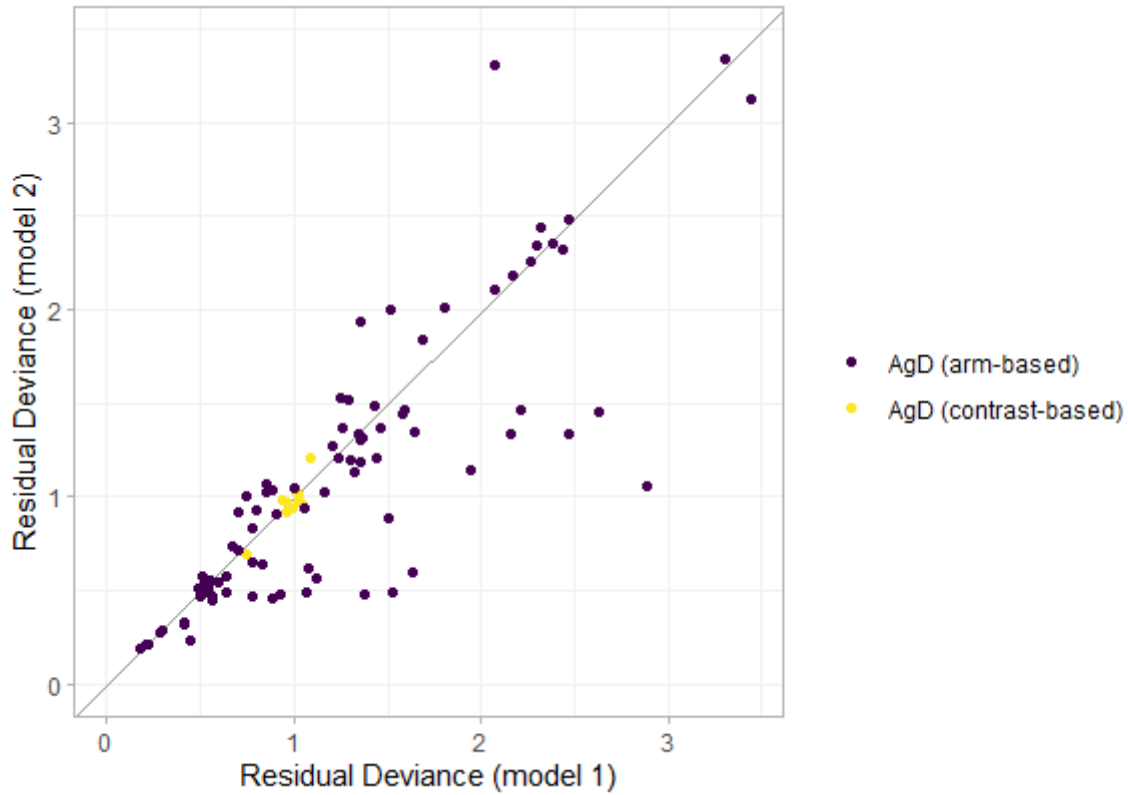
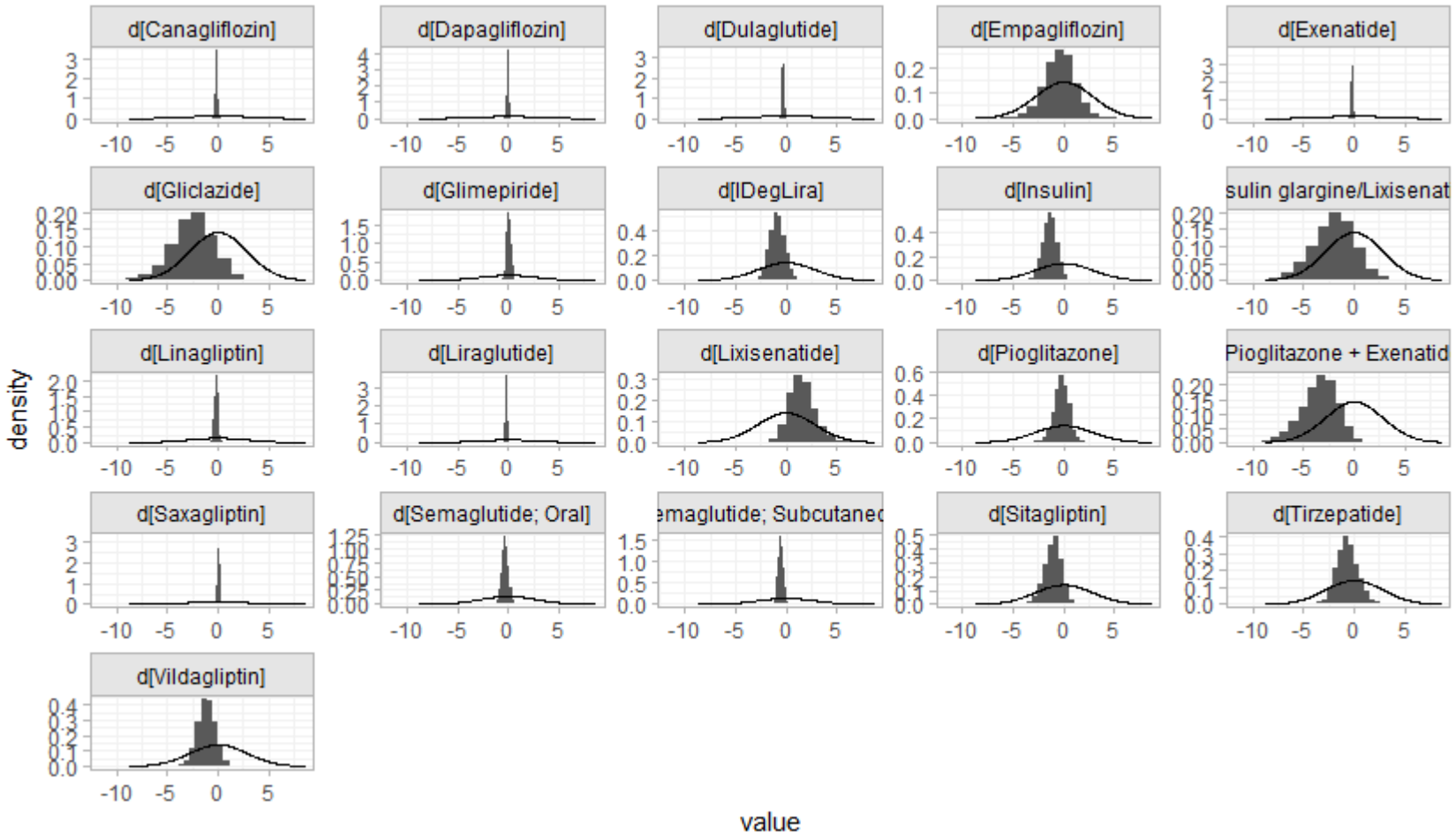


**Figure 21: Prior and posterior distributions for non-fatal stroke**



## 5.7. Unstable angina

**Table 8: Measures of goodness of fit of fixed- and random-effects models for unstable angina for the base case**

| Measure of goodness of fit | Fixed-effects model | Random-effects model | UME – fixed effects |
|---|---|---|---|
| **Total Residual deviance*** | 53.8 | 53.0 | 61.9 |
| **Posterior distribution (pD)** | 35.4 | 37.3 | 40.3 |
| **Deviance information criterion (DIC)** | 89.2 | 90.2 | 102.1 |
| **Between trial standard deviation (95% credible intervals)** | - | 0.29 (0.01 to 1.08) | - |
| *Compared to 58 data points | | | |

A fixed-effects model was preferred for the analysis. The total residual deviance for both models were similar to the number of unconstrained data points, and the deviance information criterion was lower for the fixed-effects model. Subsequent results present data from the fixed-effects model only.

**Figure 22: Dev-dev plot for unstable angina for the base case**

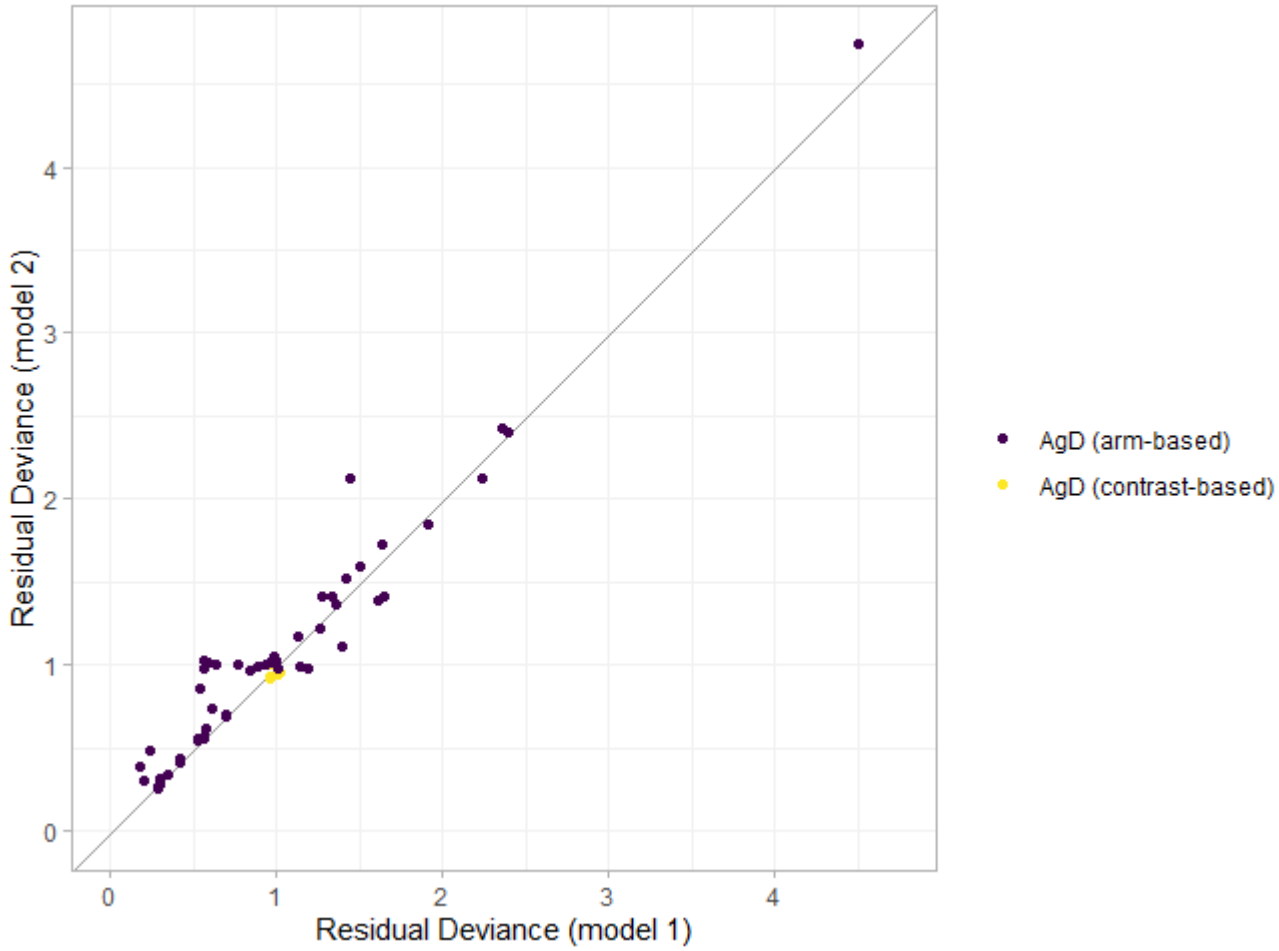


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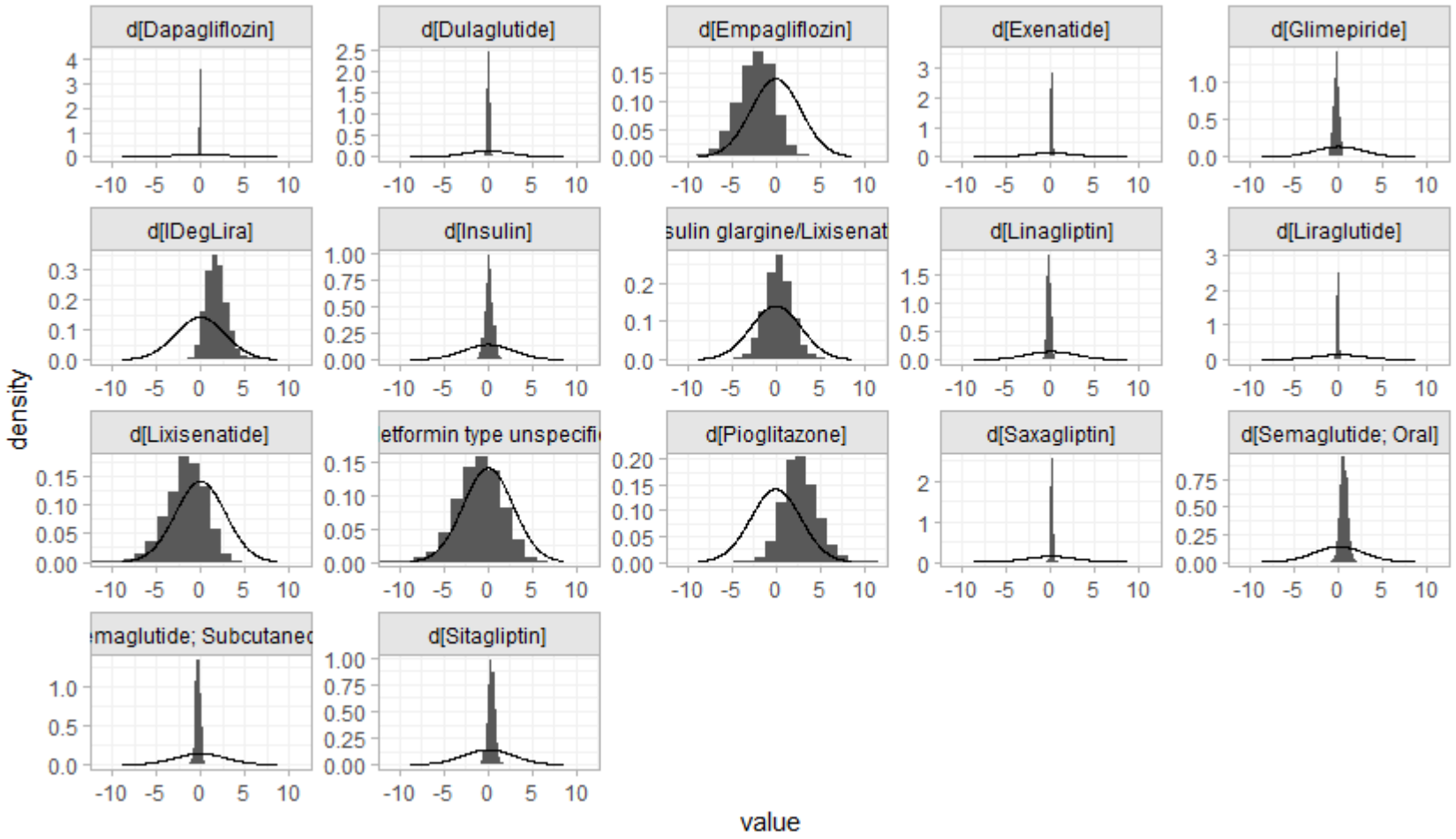
**Figure 23: Prior and posterior distributions for unstable angina for the base case**



## 5.8. Hospitalisation for heart failure

**Table 9: Measures of goodness of fit of fixed- and random-effects models for hospitalisation for heart failure for the base case**

| Measure of goodness of fit | Fixed-effects model | Random-effects model | UME – fixed effects |
|---|---|---|---|
| **Total Residual deviance*** | 77.7 | 74.2 | 78.3 |
| **Posterior distribution (pD)** | 39.3 | 41.8 | 40.8 |
| **Deviance information criterion (DIC)** | 117 | 116 | 119.1 |
| **Between trial standard deviation (95% credible intervals)** | - | 0.39 (0.02, 1.40) | - |
| *Compared to 64 data points | | | |

A fixed-effects model was preferred for the analysis. Although the total residual deviance for the random-effects model was closer to the number of unconstrained data points, the deviance information criterion was similar in both models. Subsequent results present data from the fixed-effects model only.

**Figure 24: Dev-dev plot for hospitalisation for heart failure for the base case**

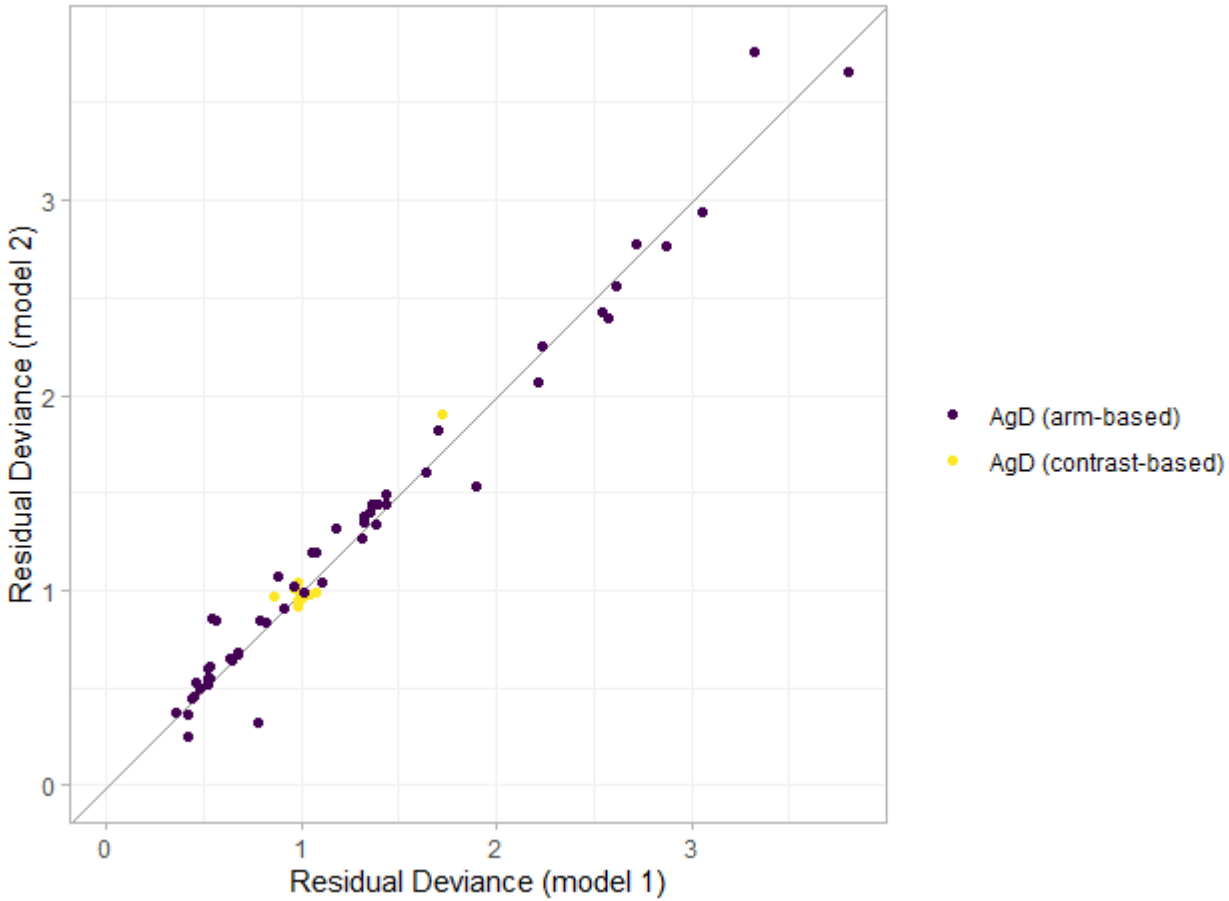
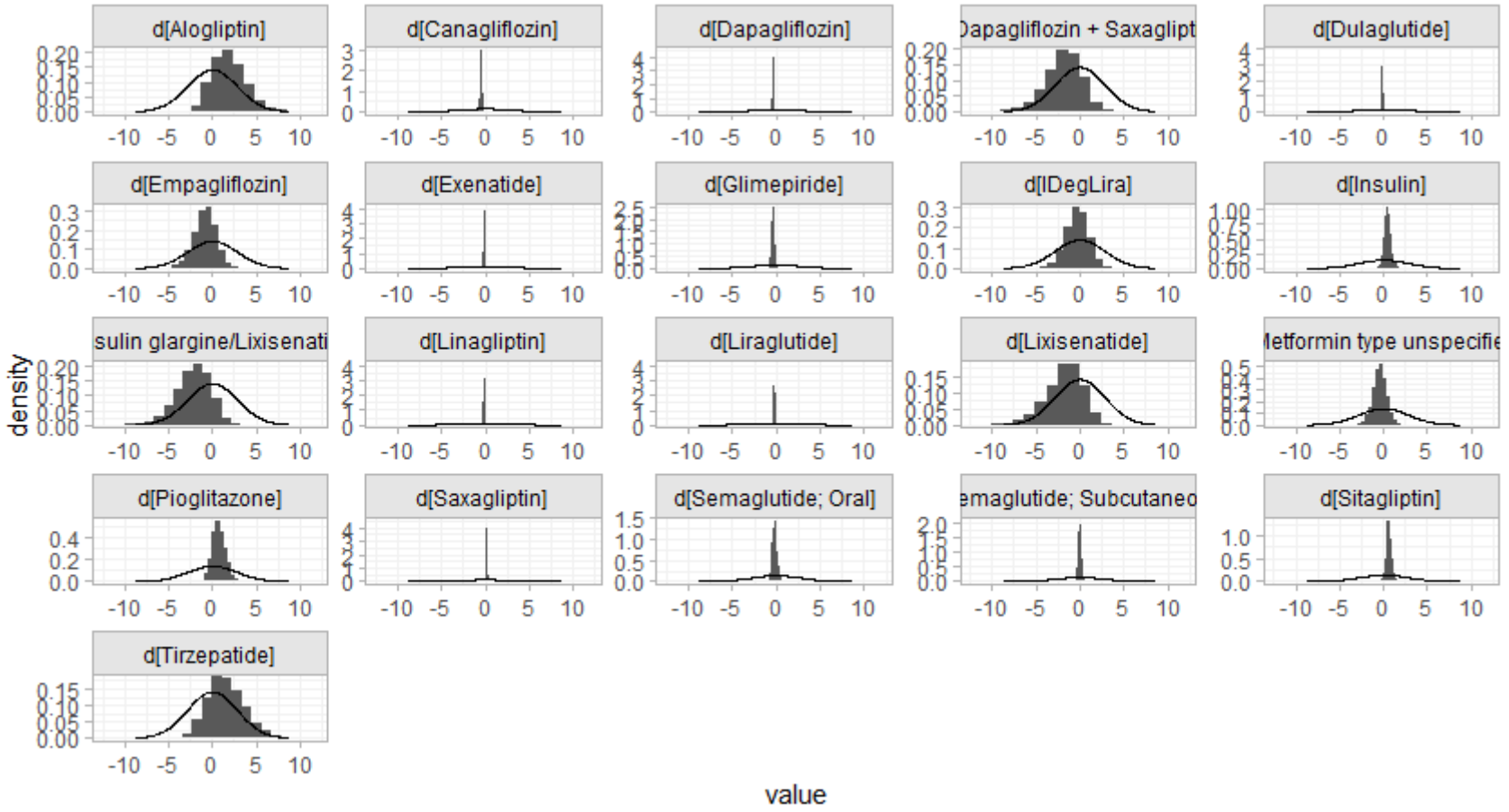


**Figure 25: Prior and posterior distributions for hospitalisation for heart failure for the base case**



## 5.9. Development of end-stage renal failure

**Table 10: Measures of goodness of fit of fixed- and random-effects models for end-stage renal failure**

| Measure of goodness of fit | Fixed-effects model | Random-effects model | UME – fixed effects |
|---|---|---|---|
| **Total Residual deviance*** | 14.1 | 14.3 | 14.1 |
| **Posterior distribution (pD)** | 12.2 | 12.8 | 12.1 |
| **Deviance information criterion (DIC)** | 26.3 | 27.1 | 26.2 |
| **Between trial standard deviation (95% credible intervals)** | - | 0.65 (0.03 – 2.60) | - |
| *Compared to 15 data points | | | |

A fixed-effects model was preferred for the analysis. The total residual deviance and the deviance information criterion were similar in both models. Therefore the simpler fixed-effects model was deemed to be more appropriate. Subsequent results present data from the fixed-effects model only.

**Figure 26: Dev-dev plot for the development of end-stage renal failure**

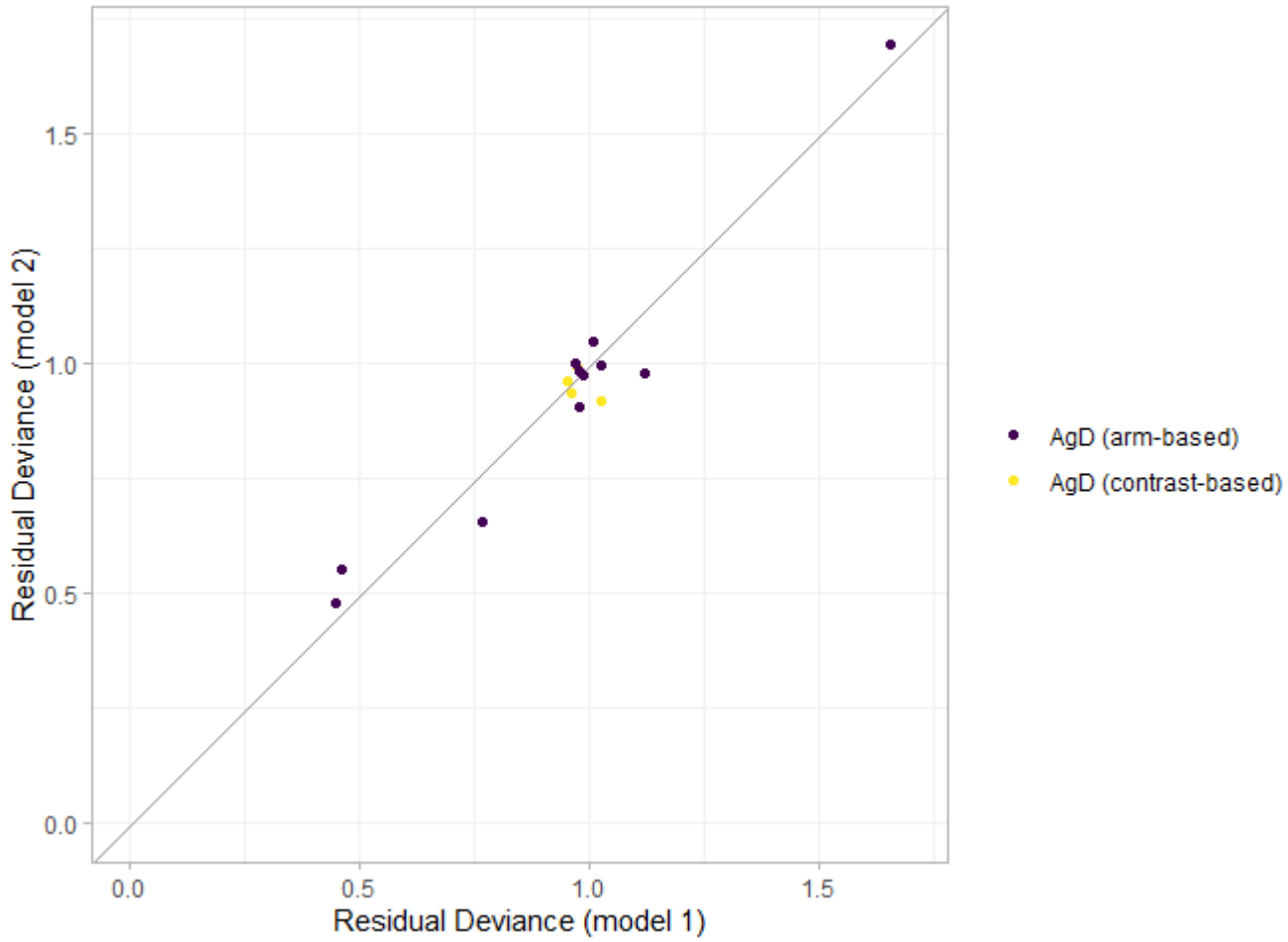


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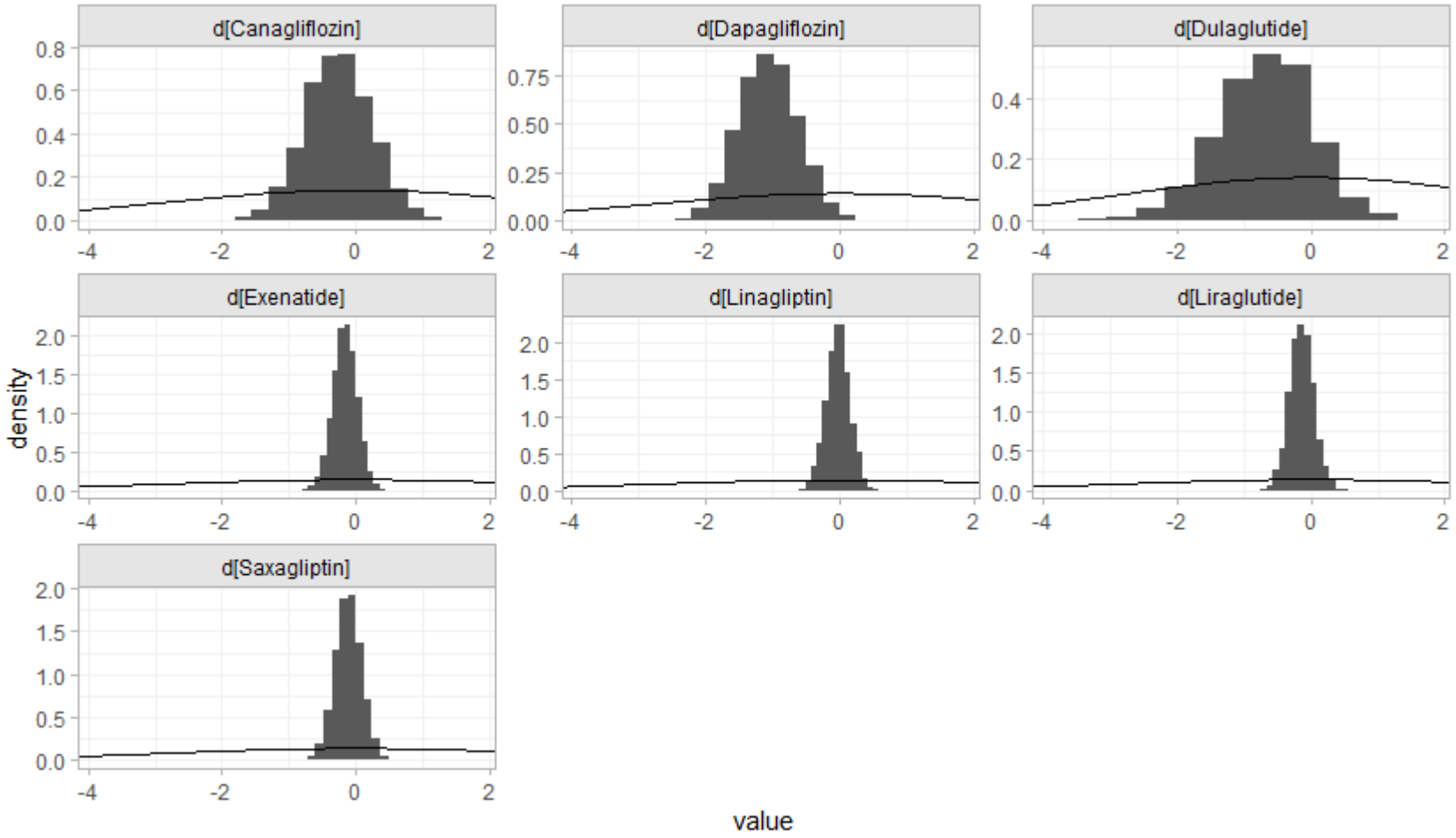
**Figure 27:Prior and posterior distributions for development of end-stage renal failure**



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# 6. Results – model 5 – high cardiovascular risk

## 6.1. Relative effectiveness matrices

**Matrices key:**

| | | |
|---|---|---|
| **FI** = Favours intervention<br><br>Above the dark line (indicated by NA values): Interventions are listed along the row at the top<br><br>Below the dark line (indicated by NA values): Interventions are listed down the first column. | **NC** = Not clear (95% credible intervals cross the line of null effect) | **FC** = Favours comparison<br><br>Above the dark line (indicated by NA values): Comparisons are listed down the first column<br><br>Below the dark line (indicated by NA values): Interventions are listed along the row at the top. |

| | |
|---|---|
| Colour highlights intervention listed across top row is favoured in the results from the analysis | Colour highlights intervention listed down first column is favoured in the results from the analysis |

**Drug name abbreviations used:**

- ALO = Alogliptin
- CANA = Canagliflozin
- DAPA = Dapagliflozin
- DAPA/EXEN = Dapagliflozin + Exenatide
- DAPA/SAXA = Dapagliflozin + Saxagliptin
- DULA = Dulaglutide
- EMPA = Empagliflozin
- EMPA/LINA = Empagliflozin + Linagliptin
- ERTU = Ertugliflozin
- ERTU/SITA = Ertugliflozin + Sitagliptin
- EXEN = Exenatide
- GLIC = Gliclazide
- GLIM = Glimepiride
- GLIP = Glipizide
- IDegLira = Insulin Degludec/Liraglutide
- INS = Insulin
- IGlarLixi = Insulin Glargine/Lixisenatide

- LINA = Linagliptin
- LIRA = Liraglutide
- LIXI = Lixisenatide
- MET = Metformin
- PIO = Pioglitazone
- PIO/ALO = Pioglitazone/Alogliptin
- PCO = Placebo
- SAXA = Saxagliptin
- SEMA-O = Semagliptin; Oral
- SEMA-S = Semagliptin; Subcutaneous
- SITA = Sitagliptin
- TIRZE = Tirzepatide
- VILDA = Vildagliptin

### 6.1.1. Cardiovascular mortality

**Table 11: Relative effectiveness (hazard ratios) showing all pairwise combinations for cardiovascular mortality for the base case analysis**

| | PCO | ALO | CANA | DAPA | DAPA/EXEN | DAPA/SAXA | DULA | EMPA | EMPA/LINA | ERTU | ERTU/SITA | EXEN | GLIC | GLIM | GLIP | IDegLira | INS | IGlarLixi | LINA | LIRA | LIXI | MET | PIO | PIO/ALO | SAXA | SEMA-O | SEMA-S | SITA | TIRZE | VILDA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PCO | NA | 5.98 (0.29, 489.01) NC | 0.88 (0.72, 1.06) NC | 0.99 (0.84, 1.18) NC | NA | NA | 0.91 (0.78, 1.06) NC | 7.79 (0.3, 793.63) NC | NA | NA | NA | 0.88 (0.76, 1.01) NC | NA | NA | NA | NA | NA | NA | 0.97 (0.82, 1.16) NC | 0.79 (0.67, 0.93) FI | 0.63 (0.09, 4.98) NC | 2.91 (0.4, 36.08) NC | 1.15 (0.06, 20.1) NC | NA | 1.03 (0.87, 1.22) NC | 0.5 (0.28, 0.91) FC | 0.97 (0.65, 1.49) NC | 0.07 (0, 1.03) NC | NA | 1 (0.06, 15.48) NC |
| ALO | 3.18 (0.46, 32.11) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 1.91 (0.47, 7.73) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| CANA | 0.88 (0.73, 1.06) NC | 0.27 (0.03, 1.86) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 8.12 (0.24, 569.46) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 6.07 (0.17, 628.84) NC | 0.09 (0, 1.96) NC | NA | NA |
| DAPA | 1 (0.84, 1.19) NC | 0.31 (0.03, 2.15) NC | 1.14 (0.88, 1.48) NC | NA | 0.97 (0.06, 13.82) NC | 0.11 (0, 2.24) NC | NA | NA | NA | NA | NA | 0.99 (0.06, 14.71) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.11 (0, 2.37) NC | NA | NA | NA | NA | NA |
| DAPA/EXEN | 0.86 (0.05, 8.64) NC | 0.25 (0.01, 5.2) NC | 0.98 (0.06, 9.88) NC | 0.85 (0.05, 8.62) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| DAPA/SAXA | 0.15 (0, 2.85) NC | 0.04 (0, 1.5) NC | 0.17 (0, 3.3) NC | 0.15 (0, 2.79) NC | 0.16 (0, 10.75) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| DULA | 0.92 (0.78, 1.06) NC | 0.29 (0.03, 2) NC | 1.04 (0.82, 1.33) NC | 0.91 (0.73, 1.15) NC | 1.07 (0.11, 18.5) NC | 6.12 (0.32, 485.25) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.24 (0, 8.68) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.48 (0.03, 4.68) NC | 7.65 (0.23, 496.17) NC | NA | NA |
| EMPA | 4.11 (0.37, 98.87) NC | 1.28 (0.04, 54.45) NC | 4.69 (0.41, 115.35) NC | 4.11 (0.37, 99.26) NC | 5.22 (0.16, 299.37) NC | 33.72 (0.53, 6784.28) NC | 4.56 (0.41, 110) NC | NA | 7.9 (0.23, 688.74) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.5 (0, 44.08) NC | NA | NA | NA | NA | NA | NA | 0.17 (0, 5.6) NC | NA | NA | NA | NA |
| EMPA/LINA | 15.48 (0.31, 1229.69) NC | 4.53 (0.05, 547.64) NC | 17.51 (0.35, 1399.04) NC | 15.56 (0.32, 1242.54) NC | 19.67 (0.21, 3017.69) NC | 129.18 (0.67, 52157.39) NC | 16.8 (0.35, 1323.74) NC | 3.25 (0.06, 362.89) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| ERTU | 2.07 (0.25, 31.97) NC | 0.62 (0.03, 17.11) NC | 2.38 (0.28, 37) NC | 2.12 (0.23, 30.66) NC | 2.71 (0.1, 98.64) NC | 16.4 (0.31, 2269.22) NC | 2.29 (0.26, 35.2) NC | 0.48 (0.01, 22.39) NC | 0.14 (0, 15.31) NC | NA | 0.19 (0, 8.08) NC | NA | NA | 0.9 (0.06, 8.66) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.28 (0, 13.12) NC | NA | NA |
| ERTU/SITA | 0.27 (0, 14.15) NC | 0.08 (0, 6.52) NC | 0.31 (0, 15.74) NC | 0.28 (0, 14.38) NC | 0.32 (0, 36.23) NC | 2 (0.01, 747.6) NC | 0.3 (0, 14.81) NC | 0.06 (0, 6.76) NC | 0.02 (0, 5.05) NC | 0.13 (0, 7.2) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| EXEN | 0.88 (0.76, 1.02) NC | 0.27 (0.03, 1.92) NC | 1 (0.79, 1.28) NC | 0.88 (0.7, 1.12) NC | 1.03 (0.1, 16.93) NC | 5.95 (0.3, 487.33) NC | 0.96 (0.78, 1.2) NC | 0.21 (0.01, 2.35) NC | 0.06 (0, 2.82) NC | 0.42 (0.03, 3.69) NC | 3.25 (0.06, 351.01) NC | NA | NA | NA | NA | NA | 0.1 (0, 1.8) NC | NA | NA | NA | NA | NA | 0.43 (0, 32.77) NC | NA | NA | NA | NA | 8.82 (0.21, 819.59) NC | NA | NA |
| GLIC | 6.54 (0.18, 738.69) NC | 2.06 (0.03, 320.38) NC | 7.61 (0.2, 800.54) NC | 6.58 (0.18, 714.03) NC | 8.56 (0.1, 1650.5) NC | 56.14 (0.38, 21847.11) NC | 7.27 (0.19, 815.16) NC | 1.55 (0.01, 324.14) NC | 0.47 (0, 177.42) NC | 3.13 (0.04, 445.23) NC | 29.35 (0.13, 19495.34) NC | 7.48 (0.2, 833.73) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.18 (0, 6.96) NC |
| GLIM | 0.98 (0.76, 1.29) NC | 0.31 (0.03, 2.01) NC | 1.12 (0.8, 1.57) NC | 0.98 (0.71, 1.37) NC | 1.15 (0.12, 19.01) NC | 6.56 (0.35, 509.14) NC | 1.08 (0.8, 1.47) NC | 0.24 (0.01, 2.65) NC | 0.06 (0, 3.39) NC | 0.47 (0.03, 4.03) NC | 3.61 (0.07, 395.7) NC | 1.12 (0.82, 1.53) NC | 0.15 (0, 5.55) NC | NA | NA | NA | NA | NA | 1 (0.8, 1.23) NC | NA | NA | NA | NA | NA | 5.78 (0.19, 616.63) NC | NA | NA | 0.16 (0, 6.26) NC | NA | 1.96 (0.2, 30.76) NC |
| GLIP | 6.16 (1.16, 47.87) FC | 1.9 (0.48, 7.48) NC | 6.95 (1.32, 54.43) FC | 6.12 (1.16, 48.37) FC | 7.42 (0.43, 229.13) NC | 43.8 (1.25, 5930.45) FC | 6.73 (1.28, 51.91) FC | 1.5 (0.04, 36.68) NC | 0.4 (0, 30.89) NC | 2.97 (0.13, 55.69) NC | 24.35 (0.32, 4049.83) NC | 6.95 (1.29, 55.11) FC | 0.95 (0.01, 64.44) NC | 6.29 (1.17, 48.99) FC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.52 (0.04, 4.8) NC | NA | NA | 0.07 (0, 1.11) NC | NA | NA |
| IDegLira | 0.48 (0.07, 2.54) NC | 0.14 (0.01, 1.8) NC | 0.54 (0.08, 2.87) NC | 0.48 (0.07, 2.53) NC | 0.56 (0.03, 14.37) NC | 3.46 (0.09, 365.99) NC | 0.53 (0.08, 2.83) NC | 0.11 (0, 2.04) NC | 0.03 (0, 2.01) NC | 0.22 (0.01, 3.25) NC | 1.89 (0.02, 233.29) NC | 0.55 (0.08, 2.89) NC | 0.07 (0, 3.8) NC | 0.48 (0.07, 2.73) NC | 0.07 (0, 0.78) FI | NA | 3.33 (0.69, 21.73) NC | NA | NA | NA | 0.24 (0, 7.45) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| INS | 1.3 (0.65, 2.55) NC | 0.4 (0.04, 2.93) NC | 1.49 (0.73, 3) NC | 1.3 (0.64, 2.67) NC | 1.51 (0.14, 27.09) NC | 8.89 (0.41, 791.09) NC | 1.43 (0.7, 2.84) NC | 0.31 (0.01, 3.74) NC | 0.08 (0, 4.15) NC | 0.62 (0.04, 6.03) NC | 4.77 (0.09, 531.14) NC | 1.48 (0.73, 2.99) NC | 0.2 (0, 7.82) NC | 1.33 (0.63, 2.75) NC | 0.21 (0.03, 1.23) NC | 2.67 (0.57, 16.89) NC | NA | 0.31 (0.02, 2.18) NC | NA | NA | 0.6 (0.04, 4.11) NC | 0.17 (0, 6.37) NC | NA | NA | NA | NA | 0.81 (0.15, 6.15) NC | 0.99 (0.56, 1.8) NC | 0.37 (0.05, 2.76) NC | NA |
| IGlarLixi | 0.37 (0.03, 2.69) NC | 0.11 (0, 1.72) NC | 0.43 (0.03, 3.08) NC | 0.38 (0.02, 2.75) NC | 0.42 (0.01, 13.33) NC | 2.59 (0.04, 309.36) NC | 0.41 (0.03, 2.94) NC | 0.08 (0, 2.3) NC | 0.02 (0, 2.08) NC | 0.16 (0, 3.61) NC | 1.31 (0.01, 251.29) NC | 0.43 (0.03, 3.1) NC | 0.05 (0, 3.6) NC | 0.38 (0.02, 2.88) NC | 0.06 (0, 0.82) FI | 0.78 (0.03, 11.43) NC | 0.29 (0.02, 1.96) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| LINA | 0.98 (0.82, 1.17) NC | 0.31 (0.03, 2.08) NC | 1.11 (0.86, 1.45) NC | 0.98 (0.76, 1.25) NC | 1.15 (0.11, 19.63) NC | 6.6 (0.35, 513.1) NC | 1.07 (0.86, 1.34) NC | 0.24 (0.01, 2.61) NC | 0.06 (0, 3.16) NC | 0.46 (0.03, 3.98) NC | 3.62 (0.07, 381.67) NC | 1.11 (0.89, 1.4) NC | 0.15 (0, 5.72) NC | 0.99 (0.81, 1.22) NC | 0.16 (0.02, 0.84) FI | 2.04 (0.38, 13.51) NC | 0.75 (0.37, 1.56) NC | 2.64 (0.35, 38.33) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| LIRA | 0.77 (0.65, 0.9) FI | 0.24 (0.02, 1.65) NC | 0.87 (0.68, 1.12) NC | 0.76 (0.6, 0.98) FI | 0.89 (0.09, 14.77) NC | 5.11 (0.26, 418.72) NC | 0.84 (0.67, 1.05) NC | 0.19 (0.01, 2.04) NC | 0.05 (0, 2.43) NC | 0.36 (0.02, 3.17) NC | 2.8 (0.05, 319.16) NC | 0.87 (0.69, 1.09) NC | 0.12 (0, 4.45) NC | 0.78 (0.57, 1.05) NC | 0.12 (0.02, 0.66) FI | 1.59 (0.29, 10.84) NC | 0.58 (0.3, 1.18) NC | 2.02 (0.29, 29.62) NC | 0.78 (0.61, 0.99) FI | NA | NA | NA | NA | NA | NA | NA | NA | NA | 2.61 (1.3, 5.46) FC | NA | NA |
| LIXI | 0.68 (0.13, 3.12) NC | 0.2 (0.01, 2.38) NC | 0.77 (0.15, 3.5) NC | 0.68 (0.13, 3.15) NC | 0.81 (0.05, 18.01) NC | 4.63 (0.17, 503.14) NC | 0.75 (0.14, 3.4) NC | 0.16 (0, 2.73) NC | 0.04 (0, 3.1) NC | 0.31 (0.01, 4.64) NC | 2.58 (0.04, 338.68) NC | 0.78 (0.15, 3.52) NC | 0.1 (0, 6.07) NC | 0.69 (0.13, 3.08) NC | 0.11 (0.01, 1.05) NC | 1.43 (0.15, 13.94) NC | 0.52 (0.09, 2.36) NC | 1.8 (0.16, 35.15) NC | 0.7 (0.13, 3.14) NC | 0.9 (0.17, 4) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| MET | 1.58 (0.26, 10.63) NC | 0.49 (0.03, 7.27) NC | 1.82 (0.29, 12.21) NC | 1.58 (0.26, 10.8) NC | 1.89 (0.1, 58.04) NC | 11.37 (0.29, 1222.39) NC | 1.71 (0.28, 11.7) NC | 0.38 (0.01, 8.34) NC | 0.1 (0, 6.89) NC | 0.73 (0.03, 13.79) NC | 6.22 (0.08, 864.03) NC | 1.8 (0.29, 12.39) NC | 0.23 (0, 15.92) NC | 1.6 (0.27, 11) NC | 0.26 (0.02, 3) NC | 3.31 (0.31, 42.78) NC | 1.21 (0.19, 9.02) NC | 4.32 (0.28, 118.15) NC | 1.6 (0.27, 10.82) NC | 2.07 (0.34, 14) NC | 2.36 (0.22, 26.1) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| PIO | 0.99 (0.09, 8.58) NC | 0.29 (0.01, 5.59) NC | 1.13 (0.11, 10.25) NC | 1 (0.09, 8.83) NC | 1.16 (0.04, 40.16) NC | 7.03 (0.14, 871.74) NC | 1.08 (0.1, 9.62) NC | 0.22 (0.01, 6.8) NC | 0.06 (0, 6.05) NC | 0.46 (0.01, 8.8) NC | 3.75 (0.03, 587.89) NC | 1.13 (0.11, 9.98) NC | 0.15 (0, 9.76) NC | 1 (0.09, 8.91) NC | 0.15 (0.01, 2.5) NC | 2.15 (0.11, 36.45) NC | 0.76 (0.06, 7.45) NC | 2.57 (0.12, 89.1) NC | 1.01 (0.1, 8.87) NC | 1.29 (0.12, 11.5) NC | 1.45 (0.1, 21.68) NC | 0.6 (0.03, 10.64) NC | NA | 0.12 (0, 3.91) NC | NA | NA | NA | NA | NA | NA |
| PIO/ALO | 0.11 (0, 5.47) NC | 0.03 (0, 2.77) NC | 0.12 (0, 6.17) NC | 0.11 (0, 5.59) NC | 0.13 (0, 15.81) NC | 0.82 (0, 317.24) NC | 0.12 (0, 6.07) NC | 0.02 (0, 2.97) NC | 0.01 (0, 1.87) NC | 0.05 (0, 4.04) NC | 0.44 (0, 160.64) NC | 0.12 (0, 6.43) NC | 0.02 (0, 3.56) NC | 0.11 (0, 5.81) NC | 0.02 (0, 1.46) NC | 0.22 (0, 18.16) NC | 0.08 (0, 5.05) NC | 0.31 (0, 37.65) NC | 0.11 (0, 5.84) NC | 0.14 (0, 7.44) NC | 0.16 (0, 12.14) NC | 0.07 (0, 5.26) NC | 0.12 (0, 6.11) NC | NA | NA | NA | NA | NA | NA | NA |
| SAXA | 1.03 (0.87, 1.22) NC | 0.32 (0.03, 2.22) NC | 1.17 (0.92, 1.51) NC | 1.03 (0.8, 1.32) NC | 1.21 (0.12, 20.23) NC | 6.95 (0.36, 592.47) NC | 1.13 (0.9, 1.42) NC | 0.25 (0.01, 2.84) NC | 0.07 (0, 3.36) NC | 0.5 (0.03, 4.23) NC | 3.81 (0.07, 405.59) NC | 1.17 (0.95, 1.46) NC | 0.16 (0, 5.64) NC | 1.05 (0.76, 1.43) NC | 0.17 (0.02, 0.9) FI | 2.15 (0.4, 14.14) NC | 0.79 (0.4, 1.63) NC | 2.73 (0.37, 39.98) NC | 1.05 (0.83, 1.34) NC | 1.35 (1.07, 1.7) FC | 1.5 (0.33, 7.79) NC | 0.65 (0.1, 3.97) NC | 1.06 (0.12, 11.19) NC | 9.51 (0.19, 827.57) NC | NA | NA | NA | NA | NA | NA |
| SEMA-O | 0.53 (0.3, 0.93) FI | 0.16 (0.02, 1.13) NC | 0.6 (0.33, 1.09) NC | 0.52 (0.29, 0.96) FI | 0.62 (0.06, 10.74) NC | 3.5 (0.17, 298.93) NC | 0.57 (0.33, 1.03) NC | 0.13 (0, 1.48) NC | 0.03 (0, 1.79) NC | 0.25 (0.02, 2.22) NC | 1.99 (0.04, 219.97) NC | 0.6 (0.33, 1.09) NC | 0.08 (0, 3.09) NC | 0.53 (0.29, 1) NC | 0.09 (0.01, 0.49) FI | 1.1 (0.19, 8.14) NC | 0.41 (0.17, 0.95) FI | 1.4 (0.18, 22.82) NC | 0.54 (0.3, 0.97) FI | 0.69 (0.37, 1.25) NC | 0.77 (0.16, 4.35) NC | 0.33 (0.05, 2.3) NC | 0.53 (0.06, 6.14) NC | 4.9 (0.09, 465.75) NC | 0.51 (0.29, 0.92) FI | NA | NA | 1.13 (0.16, 6.79) NC | NA | NA |
| SEMA-S | 0.95 (0.65, 1.4) NC | 0.29 (0.03, 2.11) NC | 1.08 (0.71, 1.66) NC | 0.95 (0.62, 1.44) NC | 1.11 (0.11, 18.96) NC | 6.45 (0.33, 551.01) NC | 1.04 (0.69, 1.59) NC | 0.23 (0.01, 2.61) NC | 0.06 (0, 3.06) NC | 0.46 (0.03, 4.19) NC | 3.46 (0.07, 381.14) NC | 1.08 (0.72, 1.64) NC | 0.14 (0, 5.61) NC | 0.96 (0.61, 1.54) NC | 0.15 (0.02, 0.83) FI | 2 (0.35, 13.12) NC | 0.74 (0.35, 1.53) NC | 2.54 (0.34, 36.73) NC | 0.97 (0.64, 1.49) NC | 1.25 (0.82, 1.92) NC | 1.39 (0.3, 7.31) NC | 0.6 (0.09, 4.05) NC | 0.96 (0.11, 10.52) NC | 8.86 (0.17, 820.87) NC | 0.92 (0.61, 1.4) NC | 1.81 (0.92, 3.51) NC | NA | 0.94 (0.14, 4.79) NC | 10.35 (0.74, 843.01) NC | NA |
| SITA | 1.22 (0.7, 2.14) NC | 0.37 (0.04, 2.75) NC | 1.4 (0.78, 2.48) NC | 1.23 (0.68, 2.22) NC | 1.44 (0.13, 23.75) NC | 8.45 (0.42, 690.9) NC | 1.34 (0.76, 2.36) NC | 0.29 (0.01, 3.62) NC | 0.08 (0, 4.04) NC | 0.59 (0.04, 5.31) NC | 4.42 (0.08, 491.76) NC | 1.39 (0.79, 2.47) NC | 0.19 (0, 7.37) NC | 1.24 (0.68, 2.28) NC | 0.2 (0.03, 1.05) NC | 2.52 (0.5, 16.39) NC | 0.94 (0.56, 1.6) NC | 3.27 (0.45, 46.45) NC | 1.25 (0.71, 2.26) NC | 1.61 (0.92, 2.81) NC | 1.79 (0.38, 9.77) NC | 0.78 (0.11, 5) NC | 1.24 (0.13, 14.24) NC | 11.42 (0.21, 1057.57) NC | 1.19 (0.67, 2.13) NC | 2.33 (1.1, 4.91) FC | 1.29 (0.69, 2.35) NC | NA | NA | NA |
| TIRZE | 1.4 (0.32, 8.72) NC | 0.44 (0.03, 6) NC | 1.59 (0.36, 10.03) NC | 1.4 (0.32, 8.74) NC | 1.71 (0.11, 45.65) NC | 10.66 (0.36, 1187.53) NC | 1.53 (0.35, 9.6) NC | 0.34 (0.01, 6.62) NC | 0.1 (0, 6.13) NC | 0.68 (0.03, 11.15) NC | 5.65 (0.09, 791.78) NC | 1.6 (0.36, 10.3) NC | 0.22 (0, 14.37) NC | 1.42 (0.31, 9.33) NC | 0.23 (0.02, 2.69) NC | 3.03 (0.34, 41.07) NC | 1.08 (0.24, 6.96) NC | 4.06 (0.33, 91.55) NC | 1.43 (0.32, 9.23) NC | 1.83 (0.42, 11.28) NC | 2.13 (0.24, 24.69) NC | 0.88 (0.08, 11.64) NC | 1.45 (0.11, 30.57) NC | 13.72 (0.2, 1815.96) NC | 1.35 (0.31, 8.55) NC | 2.66 (0.56, 17.98) NC | 1.47 (0.34, 9.49) NC | 1.16 (0.26, 7.18) NC | NA | NA |
| VILDA | 1.21 (0.21, 8.08) NC | 0.36 (0.02, 5.86) NC | 1.4 (0.24, 8.94) NC | 1.22 (0.21, 7.98) NC | 1.47 (0.08, 38.83) NC | 8.54 (0.26, 1031.86) NC | 1.33 (0.23, 8.53) NC | 0.29 (0.01, 6.11) NC | 0.08 (0, 6.23) NC | 0.57 (0.02, 9.08) NC | 4.79 (0.06, 712.29) NC | 1.38 (0.24, 8.82) NC | 0.2 (0, 6.62) NC | 1.24 (0.21, 8.22) NC | 0.19 (0.01, 2.5) NC | 2.66 (0.22, 36.01) NC | 0.93 (0.14, 6.91) NC | 3.27 (0.21, 77.48) NC | 1.24 (0.22, 8.4) NC | 1.59 (0.28, 10.29) NC | 1.79 (0.19, 20.77) NC | 0.78 (0.06, 9.91) NC | 1.24 (0.07, 22.34) NC | 11.23 (0.18, 1373.34) NC | 1.17 (0.21, 7.82) NC | 2.35 (0.35, 16.88) NC | 1.29 (0.22, 8.7) NC | 0.99 (0.15, 7.03) NC | 0.84 (0.07, 9.68) NC | NA |

**Table 12: Relative effectiveness (hazard ratios) showing pairwise comparisons for cardiovascular mortality for the base case analysis (first half of table)**

| Line | PCO | ALO | CANA | DAPA | DAPA/EXEN | DAPA/SAXA | DULA | EMPA | EMPA/LINA | ERTU | ERTU/SITA | EXEN | GLIC | GLIM |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PCO** | Line | 5.98 (0.29, 489.01) NC | 0.88 (0.72, 1.06) NC | 0.99 (0.84, 1.18) NC | NA | NA | 0.91 (0.78, 1.06) NC | 7.79 (0.3, 793.63) NC | NA | NA | NA | 0.88 (0.76, 1.01) NC | NA | NA |
| **ALO** | 3.18 (0.46, 32.11) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **CANA** | 0.88 (0.73, 1.06) NC | 0.27 (0.03, 1.86) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 8.12 (0.24, 569.46) NC |
| **DAPA** | 1 (0.84, 1.19) NC | 0.31 (0.03, 2.15) NC | 1.14 (0.88, 1.48) NC | Line | 0.97 (0.06, 13.82) NC | 0.11 (0, 2.24) NC | NA | NA | NA | NA | NA | 0.99 (0.06, 14.71) NC | NA | NA |
| **DAPA/EXEN** | 0.86 (0.05, 8.64) NC | 0.25 (0.01, 5.2) NC | 0.98 (0.06, 9.88) NC | 0.85 (0.05, 8.62) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DAPA/SAXA** | 0.15 (0, 2.85) NC | 0.04 (0, 1.5) NC | 0.17 (0, 3.3) NC | 0.15 (0, 2.79) NC | 0.16 (0, 10.75) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **DULA** | 0.92 (0.78, 1.06) NC | 0.29 (0.03, 2) NC | 1.04 (0.82, 1.33) NC | 0.91 (0.73, 1.15) NC | 1.07 (0.11, 18.5) NC | 6.12 (0.32, 485.25) NC | Line | NA | NA | NA | NA | NA | NA | NA |
| **EMPA** | 4.11 (0.37, 98.87) NC | 1.28 (0.04, 54.45) NC | 4.69 (0.41, 115.35) NC | 4.11 (0.37, 99.26) NC | 5.22 (0.16, 299.37) NC | 33.72 (0.53, 6784.28) NC | 4.56 (0.41, 110) NC | Line | 7.9 (0.23, 688.74) NC | NA | NA | NA | NA | NA |
| **EMPA/LINA** | 15.48 (0.31, 1229.69) NC | 4.53 (0.05, 547.64) NC | 17.51 (0.35, 1399.04) NC | 15.56 (0.32, 1242.54) NC | 19.67 (0.21, 3017.69) NC | 129.18 (0.67, 52157.39) NC | 16.8 (0.35, 1323.74) NC | 3.25 (0.06, 362.89) NC | Line | NA | NA | NA | NA | NA |
| **ERTU** | 2.07 (0.25, 31.97) NC | 0.62 (0.03, 17.11) NC | 2.38 (0.28, 37) NC | 2.12 (0.23, 30.66) NC | 2.71 (0.1, 98.64) NC | 16.4 (0.31, 2269.22) NC | 2.29 (0.26, 35.2) NC | 0.48 (0.01, 22.39) NC | 0.14 (0, 15.31) NC | Line | 0.19 (0, 8.08) NC | NA | NA | 0.9 (0.06, 8.66) NC |
| **ERTU/SITA** | 0.27 (0, 14.15) NC | 0.08 (0, 6.52) NC | 0.31 (0, 15.74) NC | 0.28 (0, 14.38) NC | 0.32 (0, 36.23) NC | 2 (0.01, 747.6) NC | 0.3 (0, 14.81) NC | 0.06 (0, 6.76) NC | 0.02 (0, 5.05) NC | 0.13 (0, 7.2) NC | Line | NA | NA | NA |
| **EXEN** | 0.88 (0.76, 1.02) NC | 0.27 (0.03, 1.92) NC | 1 (0.79, 1.28) NC | 0.88 (0.7, 1.12) NC | 1.03 (0.1, 16.93) NC | 5.95 (0.3, 487.33) NC | 0.96 (0.78, 1.2) NC | 0.21 (0.01, 2.35) NC | 0.06 (0, 2.82) NC | 0.42 (0.03, 3.69) NC | 3.25 (0.06, 351.01) NC | Line | NA | NA |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **GLIC** | 6.54 (0.18, 738.69) NC | 2.06 (0.03, 320.38) NC | 7.61 (0.2, 800.54) NC | 6.58 (0.18, 714.03) NC | 8.56 (0.1, 1650.5) NC | 56.14 (0.38, 21847.11) NC | 7.27 (0.19, 815.16) NC | 1.55 (0.01, 324.14) NC | 0.47 (0, 177.42) NC | 3.13 (0.04, 445.23) NC | 29.35 (0.13, 19495.34) NC | 7.48 (0.2, 833.73) NC | Line | NA |
| **GLIM** | 0.98 (0.76, 1.29) NC | 0.31 (0.03, 2.01) NC | 1.12 (0.8, 1.57) NC | 0.98 (0.71, 1.37) NC | 1.15 (0.12, 19.01) NC | 6.56 (0.35, 509.14) NC | 1.08 (0.8, 1.47) NC | 0.24 (0.01, 2.65) NC | 0.06 (0, 3.39) NC | 0.47 (0.03, 4.03) NC | 3.61 (0.07, 395.7) NC | 1.12 (0.82, 1.53) NC | 0.15 (0, 5.55) NC | Line |
| **GLIP** | 6.16 (1.16, 47.87) FC | 1.9 (0.48, 7.48) NC | 6.95 (1.32, 54.43) FC | 6.12 (1.16, 48.37) FC | 7.42 (0.43, 229.13) NC | 43.8 (1.25, 5930.45) FC | 6.73 (1.28, 51.91) FC | 1.5 (0.04, 36.68) NC | 0.4 (0, 30.89) NC | 2.97 (0.13, 55.69) NC | 24.35 (0.32, 4049.83) NC | 6.95 (1.29, 55.11) FC | 0.95 (0.01, 64.44) NC | 6.29 (1.17, 48.99) FC |
| **IDegLira** | 0.48 (0.07, 2.54) NC | 0.14 (0.01, 1.8) NC | 0.54 (0.08, 2.87) NC | 0.48 (0.07, 2.53) NC | 0.56 (0.03, 14.37) NC | 3.46 (0.09, 365.99) NC | 0.53 (0.08, 2.83) NC | 0.11 (0, 2.04) NC | 0.03 (0, 2.01) NC | 0.22 (0.01, 3.25) NC | 1.89 (0.02, 233.29) NC | 0.55 (0.08, 2.89) NC | 0.07 (0, 3.8) NC | 0.48 (0.07, 2.73) NC |
| **INS** | 1.3 (0.65, 2.55) NC | 0.4 (0.04, 2.93) NC | 1.49 (0.73, 3) NC | 1.3 (0.64, 2.67) NC | 1.51 (0.14, 27.09) NC | 8.89 (0.41, 791.09) NC | 1.43 (0.7, 2.84) NC | 0.31 (0.01, 3.74) NC | 0.08 (0, 4.15) NC | 0.62 (0.04, 6.03) NC | 4.77 (0.09, 531.14) NC | 1.48 (0.73, 2.99) NC | 0.2 (0, 7.82) NC | 1.33 (0.63, 2.75) NC |
| **IGlarLixi** | 0.37 (0.03, 2.69) NC | 0.11 (0, 1.72) NC | 0.43 (0.03, 3.08) NC | 0.38 (0.02, 2.75) NC | 0.42 (0.01, 13.33) NC | 2.59 (0.04, 309.36) NC | 0.41 (0.03, 2.94) NC | 0.08 (0, 2.3) NC | 0.02 (0, 2.08) NC | 0.16 (0, 3.61) NC | 1.31 (0.01, 251.29) NC | 0.43 (0.03, 3.1) NC | 0.05 (0, 3.6) NC | 0.38 (0.02, 2.88) NC |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **LINA** | 0.98 (0.82, 1.17) NC | 0.31 (0.03, 2.08) NC | 1.11 (0.86, 1.45) NC | 0.98 (0.76, 1.25) NC | 1.15 (0.11, 19.63) NC | 6.6 (0.35, 513.1) NC | 1.07 (0.86, 1.34) NC | 0.24 (0.01, 2.61) NC | 0.06 (0, 3.16) NC | 0.46 (0.03, 3.98) NC | 3.62 (0.07, 381.67) NC | 1.11 (0.89, 1.4) NC | 0.15 (0, 5.72) NC | 0.99 (0.81, 1.22) NC |
| **LIRA** | 0.77 (0.65, 0.9) FI | 0.24 (0.02, 1.65) NC | 0.87 (0.68, 1.12) NC | 0.76 (0.6, 0.98) FI | 0.89 (0.09, 14.77) NC | 5.11 (0.26, 418.72) NC | 0.84 (0.67, 1.05) NC | 0.19 (0.01, 2.04) NC | 0.05 (0, 2.43) NC | 0.36 (0.02, 3.17) NC | 2.8 (0.05, 319.16) NC | 0.87 (0.69, 1.09) NC | 0.12 (0, 4.45) NC | 0.78 (0.57, 1.05) NC |
| **LIXI** | 0.68 (0.13, 3.12) NC | 0.2 (0.01, 2.38) NC | 0.77 (0.15, 3.5) NC | 0.68 (0.13, 3.15) NC | 0.81 (0.05, 18.01) NC | 4.63 (0.17, 503.14) NC | 0.75 (0.14, 3.4) NC | 0.16 (0, 2.73) NC | 0.04 (0, 3.1) NC | 0.31 (0.01, 4.64) NC | 2.58 (0.04, 338.68) NC | 0.78 (0.15, 3.52) NC | 0.1 (0, 6.07) NC | 0.69 (0.13, 3.08) NC |
| **MET** | 1.58 (0.26, 10.63) NC | 0.49 (0.03, 7.27) NC | 1.82 (0.29, 12.21) NC | 1.58 (0.26, 10.8) NC | 1.89 (0.1, 58.04) NC | 11.37 (0.29, 1222.39) NC | 1.71 (0.28, 11.7) NC | 0.38 (0.01, 8.34) NC | 0.1 (0, 6.89) NC | 0.73 (0.03, 13.79) NC | 6.22 (0.08, 864.03) NC | 1.8 (0.29, 12.39) NC | 0.23 (0, 15.92) NC | 1.6 (0.27, 11) NC |
| **PIO** | 0.99 (0.09, 8.58) NC | 0.29 (0.01, 5.59) NC | 1.13 (0.11, 10.25) NC | 1 (0.09, 8.83) NC | 1.16 (0.04, 40.16) NC | 7.03 (0.14, 871.74) NC | 1.08 (0.1, 9.62) NC | 0.22 (0.01, 6.8) NC | 0.06 (0, 6.05) NC | 0.46 (0.01, 8.8) NC | 3.75 (0.03, 587.89) NC | 1.13 (0.11, 9.98) NC | 0.15 (0, 9.76) NC | 1 (0.09, 8.91) NC |
| **PIO/ALO** | 0.11 (0, 5.47) NC | 0.03 (0, 2.77) NC | 0.12 (0, 6.17) NC | 0.11 (0, 5.59) NC | 0.13 (0, 15.81) NC | 0.82 (0, 317.24) NC | 0.12 (0, 6.07) NC | 0.02 (0, 2.97) NC | 0.01 (0, 1.87) NC | 0.05 (0, 4.04) NC | 0.44 (0, 160.64) NC | 0.12 (0, 6.43) NC | 0.02 (0, 3.56) NC | 0.11 (0, 5.81) NC |
| **SAXA** | 1.03 (0.87, 1.22) NC | 0.32 (0.03, 2.22) NC | 1.17 (0.92, 1.51) NC | 1.03 (0.8, 1.32) NC | 1.21 (0.12, 20.23) NC | 6.95 (0.36, 592.47) NC | 1.13 (0.9, 1.42) NC | 0.25 (0.01, 2.84) NC | 0.07 (0, 3.36) NC | 0.5 (0.03, 4.23) NC | 3.81 (0.07, 405.59) NC | 1.17 (0.95, 1.46) NC | 0.16 (0, 5.64) NC | 1.05 (0.76, 1.43) NC |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SEMA-O** | 0.53 (0.3, 0.93) FI | 0.16 (0.02, 1.13) NC | 0.6 (0.33, 1.09) NC | 0.52 (0.29, 0.96) FI | 0.62 (0.06, 10.74) NC | 3.5 (0.17, 298.93) NC | 0.57 (0.33, 1.03) NC | 0.13 (0, 1.48) NC | 0.03 (0, 1.79) NC | 0.25 (0.02, 2.22) NC | 1.99 (0.04, 219.97) NC | 0.6 (0.33, 1.09) NC | 0.08 (0, 3.09) NC | 0.53 (0.29, 1) NC |
| **SEMA-S** | 0.95 (0.65, 1.4) NC | 0.29 (0.03, 2.11) NC | 1.08 (0.71, 1.66) NC | 0.95 (0.62, 1.44) NC | 1.11 (0.11, 18.96) NC | 6.45 (0.33, 551.01) NC | 1.04 (0.69, 1.59) NC | 0.23 (0.01, 2.61) NC | 0.06 (0, 3.06) NC | 0.46 (0.03, 4.19) NC | 3.46 (0.07, 381.14) NC | 1.08 (0.72, 1.64) NC | 0.14 (0, 5.61) NC | 0.96 (0.61, 1.54) NC |
| **SITA** | 1.22 (0.7, 2.14) NC | 0.37 (0.04, 2.75) NC | 1.4 (0.78, 2.48) NC | 1.23 (0.68, 2.22) NC | 1.44 (0.13, 23.75) NC | 8.45 (0.42, 690.9) NC | 1.34 (0.76, 2.36) NC | 0.29 (0.01, 3.62) NC | 0.08 (0, 4.04) NC | 0.59 (0.04, 5.31) NC | 4.42 (0.08, 491.76) NC | 1.39 (0.79, 2.47) NC | 0.19 (0, 7.37) NC | 1.24 (0.68, 2.28) NC |
| **TIRZE** | 1.4 (0.32, 8.72) NC | 0.44 (0.03, 6) NC | 1.59 (0.36, 10.03) NC | 1.4 (0.32, 8.74) NC | 1.71 (0.11, 45.65) NC | 10.66 (0.36, 1187.53) NC | 1.53 (0.35, 9.6) NC | 0.34 (0.01, 6.62) NC | 0.1 (0, 6.13) NC | 0.68 (0.03, 11.15) NC | 5.65 (0.09, 791.78) NC | 1.6 (0.36, 10.3) NC | 0.22 (0, 14.37) NC | 1.42 (0.31, 9.33) NC |
| **VILDA** | 1.21 (0.21, 8.08) NC | 0.36 (0.02, 5.86) NC | 1.4 (0.24, 8.94) NC | 1.22 (0.21, 7.98) NC | 1.47 (0.08, 38.83) NC | 8.54 (0.26, 1031.86) NC | 1.33 (0.23, 8.53) NC | 0.29 (0.01, 6.11) NC | 0.08 (0, 6.23) NC | 0.57 (0.02, 9.08) NC | 4.79 (0.06, 712.29) NC | 1.38 (0.24, 8.82) NC | 0.2 (0, 6.62) NC | 1.24 (0.21, 8.22) NC |

**Table 13: Relative effectiveness (hazard ratios) showing pairwise comparisons for cardiovascular mortality for the base case analysis (second half of table)**

| LINE | GLIP | IDegLira | INS | IGlarLixi | LINA | LIRA | LIXI | MET | PIO | PIO/ALO | SAXA | SEMA-O | SEMA-S | SITA | TIRZE | VILDA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PCO** | NA | NA | NA | NA | 0.97 (0.82, 1.16) NC | 0.79 (0.67, 0.93) FI | 0.63 (0.09, 4.98) NC | 2.91 (0.4, 36.08 ) NC | 1.15 (0.06, 20.1) NC | NA | 1.03 (0.87, 1.22) NC | 0.5 (0.28, 0.91) FC | 0.97 (0.65, 1.49) NC | 0.07 (0, 1.03) NC | NA | 1 (0.06, 15.48 ) NC |
| **ALO** | 1.91 (0.47 , 7.73) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **CANA** | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 6.07 (0.17, 628.84 ) NC | 0.09 (0, 1.96) NC | NA | NA |
| **DAPA** | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.11 (0, 2.37) NC | NA | NA | NA | NA | NA |
| **DAPA/EXEN** | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DAPA/SAXA** | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DULA** | NA | NA | 0.24 (0, 8.68) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.48 (0.03, 4.68) NC | 7.65 (0.23, 496.17 ) NC | NA | NA |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **EMPA** | NA | NA | NA | NA | 0.5 (0, 44.08) NC | NA | NA | NA | NA | NA | NA | 0.17 (0, 5.6) NC | NA | NA | NA | NA |
| **EMPA/LINA** | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **ERTU** | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.28 (0, 13.12) NC | NA | NA |
| **ERTU/SITA** | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **EXEN** | NA | NA | 0.1 (0, 1.8) NC | NA | NA | NA | NA | NA | 0.43 (0, 32.77) NC | NA | NA | NA | NA | 8.82 (0.21, 819.59) NC | NA | NA |
| **GLIC** | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.18 (0, 6.96) NC |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **GLIM** | NA | NA | NA | NA | 1 (0.8, 1.23) NC | NA | NA | NA | NA | NA | 5.78 (0.19, 616.63 ) NC | NA | NA | 0.16 (0, 6.26) NC | NA | 1.96 (0.2, 30.76 ) NC |
| **GLIP** | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.52 (0.04, 4.8) NC | NA | NA | 0.07 (0, 1.11) NC | NA | NA |
| **IDegLira** | 0.07 (0, 0.78) FI | Line | 3.33 (0.69, 21.73 ) NC | NA | NA | 0.24 (0, 7.45) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **INS** | 0.21 (0.03 , 1.23) NC | 2.67 (0.57, 16.89) NC | Line | 0.31 (0.02, 2.18) NC | NA | NA | 0.6 (0.04, 4.11) NC | 0.17 (0, 6.37) NC | NA | NA | NA | NA | 0.81 (0.15, 6.15) NC | 0.99 (0.56, 1.8) NC | 0.37 (0.05, 2.76) NC | NA |
| **IGlarLixi** | 0.06 (0, 0.82) FI | 0.78 (0.03, 11.43) NC | 0.29 (0.02, 1.96) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **LINA** | 0.16 (0.02 , 0.84) FI | 2.04 (0.38, 13.51) NC | 0.75 (0.37, 1.56) NC | 2.64 (0.35, 38.33) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **LIRA** | 0.12 (0.02, 0.66) FI | 1.59 (0.29, 10.84) NC | 0.58 (0.3, 1.18) NC | 2.02 (0.29, 29.62) NC | 0.78 (0.61, 0.99) FI | Line | NA | NA | NA | NA | NA | NA | NA | 2.61 (1.3, 5.46) FC | NA | NA |
| **LIXI** | 0.11 (0.01, 1.05) NC | 1.43 (0.15, 13.94) NC | 0.52 (0.09, 2.36) NC | 1.8 (0.16, 35.15) NC | 0.7 (0.13, 3.14) NC | 0.9 (0.17, 4) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **MET** | 0.26 (0.02, 3) NC | 3.31 (0.31, 42.78) NC | 1.21 (0.19, 9.02) NC | 4.32 (0.28, 118.15) NC | 1.6 (0.27, 10.82) NC | 2.07 (0.34, 14) NC | 2.36 (0.22, 26.1) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA |
| **PIO** | 0.15 (0.01, 2.5) NC | 2.15 (0.11, 36.45) NC | 0.76 (0.06, 7.45) NC | 2.57 (0.12, 89.1) NC | 1.01 (0.1, 8.87) NC | 1.29 (0.12, 11.5) NC | 1.45 (0.1, 21.68) NC | 0.6 (0.03, 10.64) NC | Line | 0.12 (0, 3.91) NC | NA | NA | NA | NA | NA | NA |
| **PIO/ALO** | 0.02 (0, 1.46) NC | 0.22 (0, 18.16) NC | 0.08 (0, 5.05) NC | 0.31 (0, 37.65) NC | 0.11 (0, 5.84) NC | 0.14 (0, 7.44) NC | 0.16 (0, 12.14) NC | 0.07 (0, 5.26) NC | 0.12 (0, 6.11) NC | Line | NA | NA | NA | NA | NA | NA |
| **SAXA** | 0.17 (0.02, 0.9) FI | 2.15 (0.4, 14.14) NC | 0.79 (0.4, 1.63) NC | 2.73 (0.37, 39.98) NC | 1.05 (0.83, 1.34) NC | 1.35 (1.07, 1.7) FC | 1.5 (0.33, 7.79) NC | 0.65 (0.1, 3.97) NC | 1.06 (0.12, 11.19) NC | 9.51 (0.19, 827.57) NC | Line | NA | NA | NA | NA | NA |
| **SEMA-O** | 0.09 (0.01, 0.49) FI | 1.1 (0.19, 8.14) NC | 0.41 (0.17, 0.95) FI | 1.4 (0.18, 22.82) NC | 0.54 (0.3, 0.97) FI | 0.69 (0.37, 1.25) NC | 0.77 (0.16, 4.35) NC | 0.33 (0.05, 2.3) NC | 0.53 (0.06, 6.14) NC | 4.9 (0.09, 465.75) NC | 0.51 (0.29, 0.92) FI | Line | NA | 1.13 (0.16, 6.79) NC | NA | NA |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SEMA-S** | 0.15 (0.02, 0.83) FI | 2 (0.35, 13.12) NC | 0.74 (0.35, 1.53) NC | 2.54 (0.34, 36.73) NC | 0.97 (0.64, 1.49) NC | 1.25 (0.82, 1.92) NC | 1.39 (0.3, 7.31) NC | 0.6 (0.09, 4.05) NC | 0.96 (0.11, 10.52) NC | 8.86 (0.17, 820.87) NC | 0.92 (0.61, 1.4) NC | 1.81 (0.92, 3.51) NC | Line | 0.94 (0.14, 4.79) NC | 10.35 (0.74, 843.01) NC | NA |
| **SITA** | 0.2 (0.03, 1.05) NC | 2.52 (0.5, 16.39) NC | 0.94 (0.56, 1.6) NC | 3.27 (0.45, 46.45) NC | 1.25 (0.71, 2.26) NC | 1.61 (0.92, 2.81) NC | 1.79 (0.38, 9.77) NC | 0.78 (0.11, 5) NC | 1.24 (0.13, 14.24) NC | 11.42 (0.21, 1057.57) NC | 1.19 (0.67, 2.13) NC | 2.33 (1.1, 4.91) FC | 1.29 (0.69, 2.35) NC | Line | NA | NA |
| **TIRZE** | 0.23 (0.02, 2.69) NC | 3.03 (0.34, 41.07) NC | 1.08 (0.24, 6.96) NC | 4.06 (0.33, 91.55) NC | 1.43 (0.32, 9.23) NC | 1.83 (0.42, 11.28) NC | 2.13 (0.24, 24.69) NC | 0.88 (0.08, 11.64) NC | 1.45 (0.11, 30.57) NC | 13.72 (0.2, 1815.96) NC | 1.35 (0.31, 8.55) NC | 2.66 (0.56, 17.98) NC | 1.47 (0.34, 9.49) NC | 1.16 (0.26, 7.18) NC | Line | NA |
| **VILDA** | 0.19 (0.01, 2.5) NC | 2.66 (0.22, 36.01) NC | 0.93 (0.14, 6.91) NC | 3.27 (0.21, 77.48) NC | 1.24 (0.22, 8.4) NC | 1.59 (0.28, 10.29) NC | 1.79 (0.19, 20.77) NC | 0.78 (0.06, 9.91) NC | 1.24 (0.07, 22.34) NC | 11.23 (0.18, 1373.34) NC | 1.17 (0.21, 7.82) NC | 2.35 (0.35, 16.88) NC | 1.29 (0.22, 8.7) NC | 0.99 (0.15, 7.03) NC | 0.84 (0.07, 9.68) NC | Line |

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### 6.1.2. 3-item MACE

**Table 14: Relative effectiveness (hazard ratios) showing all pairwise combinations for 3-item MACE in the base case analysis**

| LINE | PCO | CANA | DAPA | DULA | EXEN | GLIM | IDegLira | INS | LINA | LIRA | PIO | SAXA | SEMA-O | SEMA-S | SITA | TIRZE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PCO** | Line | 0.86 (0.76, 0.98) FI | 0.93 (0.84, 1.03) NC | 0.88 (0.79, 0.98) FI | 0.91 (0.83, 1) NC | NA | NA | NA | 1.03 (0.9, 1.18) NC | 0.87 (0.78, 0.96) FI | 1.54 (0.85, 2.92) NC | 1 (0.89, 1.12) NC | 0.79 (0.56, 1.09) NC | 0.74 (0.58, 0.94) FI | NA | 0.92 (0.28, 3.29) NC |
| **CANA** | 0.86 (0.76, 0.98) FI | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DAPA** | 0.93 (0.84, 1.03) NC | 1.08 (0.91, 1.28) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DULA** | 0.88 (0.79, 0.98) FI | 1.02 (0.86, 1.21) NC | 0.95 (0.81, 1.1) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **EXEN** | 0.91 (0.83, 1) NC | 1.06 (0.9, 1.24) NC | 0.98 (0.86, 1.12) NC | 1.03 (0.9, 1.19) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **GLIM** | 1.07 (0.87, 1.31) NC | 1.24 (0.98, 1.58) NC | 1.15 (0.91, 1.44) NC | 1.22 (0.96, 1.54) NC | 1.17 (0.94, 1.48) NC | Line | NA | NA | 0.98 (0.84, 1.14) NC | NA | 0.09 (0, 1.76) NC | NA | NA | NA | 1.17 (0.85, 1.6) NC | NA |
| **IDegLira** | 1.59 (0.46, 6.52) NC | 1.85 (0.53, 7.41) NC | 1.73 (0.49, 7) NC | 1.81 (0.51, 7.31) NC | 1.77 (0.5, 7.18) NC | 1.5 (0.42, 6.14) NC | Line | 0.71 (0.16, 2.75) NC | NA | 0.5 (0.04, 3.25) NC | NA | NA | NA | NA | NA | NA |

| LINE | PCO | CANA | DAPA | DULA | EXEN | GLIM | IDegLira | INS | LINA | LIRA | PIO | SAXA | SEMA-O | SEMA-S | SITA | TIRZE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **INS** | 1.15 (0.71, 1.91) NC | 1.35 (0.81, 2.25) NC | 1.25 (0.76, 2.06) NC | 1.31 (0.81, 2.2) NC | 1.27 (0.78, 2.13) NC | 1.09 (0.64, 1.85) NC | 0.72 (0.19, 2.42) NC | Line | NA | NA | NA | NA | NA | NA | 1.06 (0.76, 1.49) NC | NA |
| **LINA** | 1.04 (0.91, 1.19) NC | 1.21 (1.01, 1.45) FC | 1.12 (0.94, 1.32) NC | 1.18 (1, 1.4) NC | 1.14 (0.97, 1.35) NC | 0.97 (0.84, 1.14) NC | 0.65 (0.16, 2.31) NC | 0.9 (0.54, 1.47) NC | Line | NA | NA | NA | NA | NA | NA | NA |
| **LIRA** | 0.87 (0.78, 0.96) FI | 1.01 (0.85, 1.19) NC | 0.94 (0.8, 1.08) NC | 0.99 (0.85, 1.15) NC | 0.96 (0.83, 1.1) NC | 0.81 (0.65, 1.03) NC | 0.54 (0.14, 1.88) NC | 0.75 (0.46, 1.21) NC | 0.84 (0.71, 0.99) FI | Line | NA | NA | NA | NA | 1.43 (0.99, 2.08) NC | NA |
| **PIO** | 1.39 (0.81, 2.59) NC | 1.62 (0.92, 2.98) NC | 1.5 (0.85, 2.79) NC | 1.58 (0.9, 2.96) NC | 1.53 (0.87, 2.83) NC | 1.3 (0.74, 2.48) NC | 0.86 (0.19, 3.59) NC | 1.2 (0.57, 2.61) NC | 1.34 (0.76, 2.53) NC | 1.6 (0.91, 3.01) NC | Line | NA | NA | NA | NA | NA |
| **SAXA** | 1 (0.89, 1.12) NC | 1.16 (0.98, 1.39) NC | 1.07 (0.92, 1.25) NC | 1.14 (0.97, 1.33) NC | 1.1 (0.95, 1.27) NC | 0.94 (0.74, 1.18) NC | 0.63 (0.15, 2.21) NC | 0.86 (0.52, 1.42) NC | 0.96 (0.81, 1.15) NC | 1.15 (0.98, 1.34) NC | 0.72 (0.38, 1.25) NC | Line | NA | NA | NA | NA |
| **SEMA-O** | 0.79 (0.56, 1.1) NC | 0.92 (0.64, 1.31) NC | 0.85 (0.6, 1.21) NC | 0.89 (0.63, 1.28) NC | 0.86 (0.62, 1.22) NC | 0.74 (0.5, 1.09) NC | 0.49 (0.12, 1.81) NC | 0.68 (0.37, 1.21) NC | 0.75 (0.53, 1.09) NC | 0.91 (0.64, 1.3) NC | 0.56 (0.28, 1.08) NC | 0.79 (0.55, 1.13) NC | Line | NA | NA | NA |
| **SEMA-S** | 0.74 (0.57, 0.95) FI | 0.86 (0.65, 1.14) NC | 0.79 (0.6, 1.05) NC | 0.84 (0.64, 1.1) NC | 0.81 (0.62, 1.06) NC | 0.69 (0.51, 0.95) FI | 0.46 (0.12, 1.65) NC | 0.64 (0.36, 1.1) NC | 0.71 (0.53, 0.94) FI | 0.85 (0.64, 1.12) NC | 0.53 (0.28, 0.98) FI | 0.74 (0.56, 0.97) FI | 0.94 (0.61, 1.44) NC | Line | NA | NA |
| **SITA** | 1.24 (0.84, 1.79) NC | 1.44 (0.97, 2.11) NC | 1.33 (0.9, 1.95) NC | 1.41 (0.95, 2.05) NC | 1.36 (0.92, 2) NC | 1.15 (0.75, 1.76) NC | 0.76 (0.2, 2.66) NC | 1.06 (0.75, 1.5) NC | 1.19 (0.8, 1.77) NC | 1.42 (0.99, 2.03) NC | 0.88 (0.44, 1.73) NC | 1.23 (0.83, 1.82) NC | 1.57 (0.96, 2.58) NC | 1.67 (1.06, 2.67) FC | Line | NA |

| LINE | PCO | CANA | DAPA | DULA | EXEN | GLIM | IDegLira | INS | LINA | LIRA | PIO | SAXA | SEMA-O | SEMA-S | SITA | TIRZE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIRZE | 0.91 (0.27, 3.57) NC | 1.06 (0.32, 4.18) NC | 0.98 (0.29, 3.86) NC | 1.04 (0.31, 4.18) NC | 1.01 (0.3, 3.93) NC | 0.86 (0.25, 3.41) NC | 0.59 (0.09, 3.61) NC | 0.78 (0.21, 3.56) NC | 0.88 (0.26, 3.44) NC | 1.05 (0.32, 4.22) NC | 0.66 (0.17, 2.94) NC | 0.91 (0.27, 3.62) NC | 1.16 (0.34, 4.65) NC | 1.24 (0.37, 4.91) NC | 0.74 (0.2, 3.11) NC | Line |

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### 6.1.3. 4-item MACE

**Table 15: Relative effectiveness (hazard ratios) showing all pairwise combinations for 4-item MACE**

| Line | PCO | GLIM | INS | LINA | LIRA | SITA | TIRZE |
|---|---|---|---|---|---|---|---|
| **PCO** | Line | NA | NA | 1 (0.89, 1.14) NC | NA | NA | 0.75 (0.08, 11.2) NC |
| **GLIM** | 1.01 (0.84, 1.23) NC | Line | NA | 0.99 (0.86, 1.14) NC | NA | NA | NA |
| **INS** | 0.71 (0.09, 5.61) NC | 0.7 (0.09, 5.59) NC | Line | NA | 0.75 (0.53, 1.08) NC | 1.1 (0.79, 1.54) NC | 1.3 (0.46, 4.41) NC |
| **LINA** | 1 (0.89, 1.14) NC | 0.99 (0.86, 1.14) NC | 1.4 (0.18, 11.15) NC | Line | NA | NA | NA |
| **LIRA** | 0.53 (0.07, 4.27) NC | 0.53 (0.07, 4.25) NC | 0.75 (0.53, 1.08) NC | 0.53 (0.07, 4.31) NC | Line | NA | NA |
| **SITA** | 0.79 (0.1, 6.1) NC | 0.78 (0.1, 6.11) NC | 1.1 (0.81, 1.5) NC | 0.79 (0.1, 5.97) NC | 1.46 (1.03, 2.09) FC | Line | NA |
| **TIRZE** | 0.92 (0.13, 6.88) NC | 0.91 (0.13, 7.1) NC | 1.26 (0.47, 3.97) NC | 0.92 (0.13, 7.03) NC | 1.67 (0.57, 5.57) NC | 1.14 (0.4, 3.86) NC | Line |

### 6.1.4. 5-item MACE

**Table 16: Relative effectiveness showing all pairwise combinations for 5-item MACE**

| LINE | PCO | LINA | SEMA-O | SEMA-S |
|---|---|---|---|---|
| **PCO** | Line | 1.66 (0.79, 3.49), NC | 0.82 (0.61, 1.09), NC | 0.74 (0.61, 0.89), FI |
| **LINA** | 1.65 (0.79, 3.49), NC | Line | NA | NA |
| **SEMA-O** | 0.82 (0.61, 1.1), NC | 0.49 (0.22, 1.11), NC | Line | NA |
| **SEMA-S** | 0.74 (0.62, 0.89), FI | 0.45 (0.2, 0.96), FI | 0.9 (0.64, 1.27), NC | Line |

### 6.1.5. Non-fatal myocardial infarction

**Table 17: Relative effectiveness (hazard ratios) showing all pairwise combinations for non-fatal myocardial infarction**

| LINE | PCO | ALO | CANA | DAPA | DULA | EXEN | GLIC | GLIM | GLIP | IDegLira | INS | LINA | LIRA | LIXI | PIO | SAXA | SEMA-O | SEMA-S | SITA | TIRZE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PCO** | LINE | 6.63 (0.28, 506.84), NC | 0.85 (0.69, 1.05), NC | 0.89 (0.78, 1.01), NC | 0.95 (0.79, 1.15), NC | 0.95 (0.83, 1.08), NC | NA | 0.33 (0.02, 2.29), NC | NA | 4.56 (0.11, 411.97), NC | NA | 1.17 (0.93, 1.47), NC | 0.88 (0.76, 1.04), NC | 5.78 (0.16, 446.85), NC | 0.77 (0.22, 2.31), NC | 0.95 (0.81, 1.13), NC | 1.1 (0.7, 1.72), NC | 0.73 (0.51, 1.06), NC | 0.6 (0.04, 5.82), NC | NA |
| **ALO** | 2.98 (0.25, 88.99), NC | LINE | NA | NA | NA | NA | NA | NA | 1.55 (0.35, 5.86), NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **CANA** | 0.85 (0.69, 1.05), NC | 0.28 (0.01, 3.37), NC | LINE | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DAPA** | 0.89 (0.77, 1.02), NC | 0.3 (0.01, 3.59), NC | 1.05 (0.81, 1.35), NC | LINE | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **DULA** | 0.96 (0.79, 1.17), NC | 0.33 (0.01, 3.84), NC | 1.12 (0.84, 1.51), NC | 1.08 (0.86, 1.37), NC | LINE | NA | NA | NA | NA | NA | 0.17 (0, 6.47), NC | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **EXEN** | 0.95 (0.83, 1.08), NC | 0.32 (0.01, 3.59), NC | 1.11 (0.88, 1.41), NC | 1.06 (0.89, 1.29), NC | 0.99 (0.78, 1.24), NC | LINE | NA | NA | NA | NA | 10.72 (0.5, 793.69), NC | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **GLIC** | 2.04 (0.2, 34.38), NC | 0.7 (0.01, 28.33), NC | 2.39 (0.23, 42.84), NC | 2.28 (0.22, 38.23), NC | 2.13 (0.2, 36.01), NC | 2.15 (0.21, 36.12), NC | LINE | 0.09 (0, 1.83), NC | NA | NA | NA | NA | NA | NA | 6.01 (0.15, 604.64), NC | NA | NA | NA | NA | NA |
| **GLIM** | 1.16 (0.84, 1.59), NC | 0.39 (0.01, 4.59), NC | 1.36 (0.92, 2.01), NC | 1.3 (0.92, 1.84), NC | 1.21 (0.83, 1.75), NC | 1.23 (0.87, 1.73), NC | 0.57 (0.03, 5.86), NC | LINE | NA | NA | NA | 0.98 (0.78, 1.24), NC | NA | NA | 0.09 (0, 1.95), NC | 0.17 (0, 6.27), NC | NA | NA | NA | NA |
| **GLIP** | 4.36 (0.26, 126.14), NC | 1.45 (0.34, 5.41), NC | 5.11 (0.3, 154.83), NC | 4.86 (0.28, 144.49), NC | 4.55 (0.27, 132.94), NC | 4.58 (0.27, 133.83), NC | 2.05 (0.04, 116.34), NC | 3.74 (0.21, 113.83), NC | LINE | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **IDegLi** | 1.55 (0.34, 8.08), NC | 0.5 (0.01, 10.31), NC | 1.81 (0.39, 9.72), NC | 1.74 (0.37, 9.17), NC | 1.61 (0.35, 8.49), NC | 1.64 (0.35, 8.53), NC | 0.73 (0.03, 12.06), NC | 1.31 (0.28, 7.29), NC | 0.35 (0.01, 8.86), NC | LINE | 0.68 (0.19, 2.22), NC | NA | 0.79 (0.06, 6.79), NC | NA | NA | NA | NA | NA | NA | NA |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ra** | | | | | | | | | | | | | | | | | | | |
| **INS** | 0.99 (0.23, 4.57), NC | 0.33 (0.01, 6.5), NC | 1.16 (0.27, 5.37), NC | 1.11 (0.26, 5.11), NC | 1.02 (0.24, 4.79), NC | 1.04 (0.24, 4.78), NC | 0.49 (0.02, 7.59), NC | 0.85 (0.19, 4.02), NC | 0.23 (0.01, 6.13), NC | 0.66 (0.18, 2.14), NC | LINE | NA | NA | NA | NA | NA | NA | NA | 5.49 (0.16, 468.21), NC | 3.24 (0.09, 463.31), NC |
| **LINA** | 1.15 (0.92, 1.46), NC | 0.39 (0.01, 4.57), NC | 1.35 (1, 1.86), NC | 1.3 (0.99, 1.69), NC | 1.21 (0.9, 1.63), NC | 1.22 (0.94, 1.6), NC | 0.57 (0.03, 5.87), NC | 0.99 (0.8, 1.24), NC | 0.26 (0.01, 4.5), NC | 0.76 (0.14, 3.52), NC | 1.17 (0.25, 5.08), NC | LINE | NA | NA | NA | NA | NA | NA | NA | NA |
| **LIRA** | 0.88 (0.76, 1.04), NC | 0.29 (0.01, 3.48), NC | 1.04 (0.8, 1.35), NC | 0.99 (0.8, 1.23), NC | 0.92 (0.72, 1.19), NC | 0.93 (0.77, 1.14), NC | 0.43 (0.03, 4.44), NC | 0.76 (0.53, 1.1), NC | 0.2 (0.01, 3.51), NC | 0.57 (0.11, 2.68), NC | 0.89 (0.2, 3.83), NC | 0.76 (0.58, 1.01), NC | LINE | NA | NA | NA | NA | NA | 6.09 (0.18, 524.26), NC | NA |
| **LIXI** | 5.81 (0.17, 636.53), NC | 1.93 (0.02, 367.65), NC | 6.92 (0.2, 723.97), NC | 6.55 (0.19, 708.72), NC | 6.12 (0.17, 662.51), NC | 6.21 (0.18, 688.45), NC | 2.8 (0.03, 622.41), NC | 5.09 (0.14, 525.35), NC | 1.33 (0.01, 292.78), NC | 3.95 (0.07, 461.92), NC | 5.91 (0.11, 758.14), NC | 5.07 (0.14, 515.97), NC | 6.62 (0.19, 737.52), NC | LINE | NA | NA | NA | NA | NA | NA |
| **PIO** | 0.75 (0.25, 2.11), NC | 0.24 (0.01, 3.74), NC | 0.89 (0.28, 2.54), NC | 0.85 (0.28, 2.42), NC | 0.78 (0.26, 2.2), NC | 0.8 (0.26, 2.22), NC | 0.36 (0.02, 3.91), NC | 0.65 (0.21, 1.86), NC | 0.17 (0.01, 3.23), NC | 0.48 (0.07, 3.17), NC | 0.75 (0.12, 4.58), NC | 0.65 (0.21, 1.83), NC | 0.85 (0.28, 2.41), NC | 0.13 (0, 5.28), NC | LINE | NA | NA | NA | NA | NA |
| **SAXA** | 0.95 (0.81, | 0.32 (0.01, | 1.12 (0.86, | 1.07 (0.87, | 0.99 (0.78, | 1 (0.82, | 0.47 (0.03, | 0.82 (0.57, | 0.22 (0.01, | 0.62 (0.12, | 0.96 (0.2, 4.22), NC | 0.82 (0.61, | 1.08 (0.86, | 0.16 (0, 5.52), NC | 1.27 (0.44, | LINE | NA | NA | NA | NA |

| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1.12), NC | 3.73), NC | 1.45), NC | 1.33), NC | 1.27), NC | 1.25), NC | 4.94), NC | 1.19), NC | 3.74), NC | 2.85), NC | | 1.1), NC | 1.36), NC | | 3.87), NC | | | | |
| **SEMA-O** | 1.1 (0.7, 1.71), NC | 0.37 (0.01, 4.4), NC | 1.29 (0.79, 2.11), NC | 1.24 (0.77, 1.99), NC | 1.14 (0.7, 1.86), NC | 1.16 (0.73, 1.84), NC | 0.54 (0.03, 5.75), NC | 0.95 (0.54, 1.63), NC | 0.25 (0.01, 4.45), NC | 0.71 (0.13, 3.57), NC | 1.11 (0.24, 4.97), NC | 0.96 (0.57, 1.56), NC | 1.25 (0.79, 1.99), NC | 0.19 (0, 6.75), NC | 1.46 (0.48, 4.85), NC | 1.16 (0.72, 1.84), NC | LINE | NA | 1.34 (0.17, 6.74), NC | NA |
| **SEMA-S** | 0.73 (0.51, 1.04), NC | 0.25 (0.01, 3.01), NC | 0.86 (0.56, 1.31), NC | 0.82 (0.56, 1.2), NC | 0.76 (0.5, 1.14), NC | 0.77 (0.52, 1.14), NC | 0.36 (0.02, 3.71), NC | 0.63 (0.39, 1.02), NC | 0.17 (0.01, 3), NC | 0.47 (0.09, 2.29), NC | 0.73 (0.15, 3.24), NC | 0.63 (0.41, 0.96), FI | 0.83 (0.55, 1.22), NC | 0.12 (0, 4.29), NC | 0.97 (0.32, 3.17), NC | 0.77 (0.51, 1.14), NC | 0.66 (0.37, 1.17), NC | LINE | NA | 7.51 (0.39, 604.36), NC |
| **SITA** | 1.58 (0.43, 5.75), NC | 0.52 (0.02, 8.36), NC | 1.85 (0.49, 6.94), NC | 1.8 (0.48, 6.51), NC | 1.66 (0.44, 6.02), NC | 1.67 (0.44, 6.21), NC | 0.74 (0.03, 10.23), NC | 1.36 (0.36, 5.23), NC | 0.36 (0.01, 7.93), NC | 1.02 (0.13, 7.68), NC | 1.55 (0.23, 10.86), NC | 1.37 (0.36, 5.08), NC | 1.78 (0.47, 6.61), NC | 0.26 (0, 13.31), NC | 2.08 (0.39, 11.63), NC | 1.67 (0.45, 6.13), NC | 1.43 (0.39, 5.23), NC | 2.19 (0.57, 8.15), NC | LINE | NA |
| **TIRZE** | 8.32 (0.48, 617.12), NC | 2.89 (0.03, 379.39), NC | 9.85 (0.56, 733.12), NC | 9.33 (0.54, 730.65), NC | 8.61 (0.49, 617.76), NC | 8.85 (0.51, 648.69), NC | 3.96 (0.07, 506.24), NC | 7.16 (0.4, 558.77), NC | 1.93 (0.02, 331.91), NC | 5.3 (0.23, 485.48), NC | 8.23 (0.38, 588.79), NC | 7.08 (0.41, 538.46), NC | 9.43 (0.53, 703.92), NC | 1.45 (0.01, 406.22), NC | 11.06 (0.53, 964.27), NC | 8.8 (0.49, 653.91), NC | 7.54 (0.42, 601.13), NC | 11.22 (0.65, 908.82), NC | 5.24 (0.21, 484.31), NC | LINE |

### 6.1.6. Non-fatal stroke

**Table 18: Relative effectiveness (hazard ratios) showing all pairwise combinations for non-fatal stroke**

| Line | PCO | CANA | DAPA | DULA | EMPA | EXEN | GLIC | GLIM | IDeg Lira | INS | IGlar Lixi | LINA | LIRA | LIXI | PIO | PIO + EXEN | SAXA | SEMA-O | SEMA-S | SITA | TIRZE | VILDA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PCO** | Line | 0.9 (0.71, 1.14) NC | 1.01 (0.85, 1.2) NC | 0.78 (0.62, 0.96) FI | 0.12 (0, 4.09) NC | 0.86 (0.7, 1.06) NC | | 5.51 (0.16, 521.61) NC | | NA | NA | 0.89 (0.64, 1.24) NC | 0.88 (0.71, 1.1) NC | 14.48 (0.91, 1092.11) NC | 1.34 (0.18, 10.24) NC | NA | 1.11 (0.88, 1.41) NC | 0.71 (0.39, 1.33) NC | 0.63 (0.39, 1.01) NC | 0.17 (0, 6.22) NC | NA | 0.22 (0.02, 1.6) NC |
| **CANA** | 0.9 (0.71, 1.15) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DAPA** | 1.01 (0.85, 1.21) NC | 1.12 (0.84, 1.5) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DULA** | 0.78 (0.63, 0.97) FI | 0.87 (0.62, 1.2) | 0.77 (0.59, 1.02) | Line | NA | NA | NA | NA | NA | 0.09 (0, 1.95) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | NC | NC | | | | | | | | | | | | | | | | | | |
| **EMPA** | 0.72 (0.04, 13.16) NC | 0.8 (0.04, 14.51) NC | 0.71 (0.04, 13.24) NC | 0.93 (0.05, 17.02) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | 0.17 (0, 5.88) NC | NA | NA | NA | NA | NA | NA | NA |
| **EXEN** | 0.86 (0.7, 1.06) NC | 0.96 (0.7, 1.31) NC | 0.85 (0.65, 1.13) NC | 1.11 (0.82, 1.48) NC | 1.21 (0.07, 22.51) NC | Line | NA | NA | NA | 0.17 (0, 6.97) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **GLIC** | 0.09 (0, 3.92) NC | 0.1 (0, 4.25) NC | 0.09 (0, 4.01) NC | 0.12 (0, 5.17) NC | 0.12 (0, 13.65) NC | 0.1 (0, 4.72) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 6.35 (0.16, 617.6) NC |
| **GLIM** | 1.11 (0.73, 1.7) | 1.23 (0.76, 2.02) | 1.09 (0.69, 1.74) | 1.42 (0.88, 2.3) NC | 1.53 (0.08, 29.55) NC | 1.27 (0.81, 2.07) NC | 12.22 (0.28, 1171.74) NC | Line | NA | NA | NA | 0.82 (0.63, 1.06) NC | NA | NA | 1.05 (0.06, 16.42) NC | NA | NA | NA | NA | NA | NA | NA |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NC | NC | NC | | | | | | | | | | | | | | | | | | |
| **IDegLira** | 0.45 (0.1, 1.84) NC | 0.5 (0.11, 2.1) NC | 0.44 (0.1, 1.88) NC | 0.58 (0.13, 2.44) NC | 0.63 (0.02, 14.69) NC | 0.51 (0.12, 2.18) NC | 5.01 (0.1, 509.09) NC | 0.4 (0.09, 1.85) NC | Line | 0.24 (0.02, 1.37) NC | NA | NA | 4.47 (0.87, 28.03) NC | NA | NA | NA | NA | NA | NA | NA | NA |
| **INS** | 0.26 (0.06, 0.96) FI | 0.29 (0.07, 1.11) NC | 0.26 (0.06, 0.96) FI | 0.34 (0.07, 1.24) NC | 0.36 (0.01, 8.23) NC | 0.3 (0.07, 1.15) NC | 2.95 (0.06, 323.53) NC | 0.24 (0.05, 0.95) FI | 0.59 (0.13, 2.51) NC | Line | 0.15 (0, 4.68) NC | NA | 0.17 (0, 6.59) NC | 2.14 (0.1, 37.75) NC | NA | 0.09 (0, 1.94) NC | NA | NA | NA | NA | 1.74 (0.46, 10.67) NC | NA |
| **IGlarLixi** | 0.16 (0, 5.58) NC | 0.17 (0, 6.12) NC | 0.15 (0, 5.52) NC | 0.2 (0, 6.87) NC | 0.2 (0, 20.58) NC | 0.18 (0, 6.41) NC | 1.62 (0.01, 467.03) NC | 0.14 (0, 4.93) NC | 0.35 (0, 16.51) NC | 0.59 (0.01, 23.66) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **LINA** | 0.89 (0.65, 1.25) NC | 1 (0.66, 1.54) NC | 0.88 (0.61, 1.3) NC | 1.15 (0.78, 1.72) NC | 1.25 (0.07, 23.78) NC | 1.04 (0.71, 1.54) NC | 9.88 (0.22, 908.73) NC | 0.81 (0.62, 1.07) NC | 2.02 (0.46, 9.11) NC | 3.39 (0.89, 15.49) NC | 5.62 (0.16, 457.91) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **LIRA** | 0.88 (0.71, 1.09) NC | 0.98 (0.71, 1.34) NC | 0.87 (0.65, 1.15) NC | 1.12 (0.84, 1.53) NC | 1.22 (0.07, 22.44) NC | 1.02 (0.75, 1.38) NC | 9.61 (0.23, 830.91) NC | 0.8 (0.5, 1.27) NC | 1.95 (0.48, 8.7) NC | 3.31 (0.91, 14.1) NC | 5.6 (0.16, 482.35) NC | 0.98 (0.67, 1.44) NC | Line | NA | NA | NA | NA | NA | NA | 5.89 (0.14, 649.72) NC | NA | NA |
| **LIXI** | 4.31 (0.56, 63.9) NC | 4.76 (0.63, 72.2) NC | 4.33 (0.55, 62.48) NC | 5.55 (0.72, 85.31) NC | 6.27 (0.2, 319.81) NC | 5.01 (0.64, 75.23) NC | 55.78 (0.64, 7607.39) NC | 3.91 (0.49, 58.76) NC | 10.13 (0.87, 190.65) NC | 16.35 (1.89, 308.59) FC | 28.51 (1.07, 3562.18) FC | 4.77 (0.61, 70.22) NC | 5 (0.65, 72.24) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA |
| **PIO** | 0.87 (0.2, 3.53) NC | 0.97 (0.21, 3.97) NC | 0.86 (0.19, 3.55) NC | 1.11 (0.25, 4.65) NC | 1.18 (0.06, 21.83) NC | 1.01 (0.22, 4.13) NC | 9.85 (0.18, 857.8) NC | 0.79 (0.17, 3.34) NC | 1.94 (0.24, 14.58) NC | 3.29 (0.43, 23.22) NC | 5.72 (0.12, 573.73) NC | 0.98 (0.22, 4.02) NC | 1 (0.22, 4.07) NC | 0.19 (0.01, 2.34) NC | Line | NA | NA | NA | NA | NA | NA | 0.48 (0.04, 4.56) NC |
| **PIO + EXEN** | 0.04 (0, 0.77) FI | 0.04 (0, 0.87) FI | 0.04 (0, 0.77) FI | 0.05 (0, 0.99) FI | 0.05 (0, 3.4) NC | 0.04 (0, 0.87) FI | 0.42 (0, 74.89) NC | 0.03 (0, 0.74) FI | 0.09 (0, 2.04) NC | 0.15 (0, 2.66) NC | 0.24 (0, 45.26) NC | 0.04 (0, 0.87) FI | 0.04 (0, 0.87) FI | 0.01 (0, 0.29) FI | 0.04 (0, 1.27) NC | Line | NA | NA | NA | NA | NA | NA |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | 9) FI | | | | | | | | |
| **SAXA** | 1.11 (0.89, 1.39) NC | 1.23 (0.89, 1.71) NC | 1.1 (0.82, 1.47) NC | 1.42 (1.06, 1.93) FC | 1.56 (0.08, 29.16) NC | 1.29 (0.96, 1.72) NC | 12.21 (0.28, 1126.97) NC | 1 (0.62, 1.62) NC | 2.51 (0.59, 11.21) NC | 4.19 (1.13, 18.88) FC | 7.27 (0.2, 546.55) NC | 1.24 (0.83, 1.83) NC | 1.27 (0.94, 1.71) NC | 0.26 (0.02, 2) NC | 1.28 (0.3, 5.7) NC | 28.99 (1.44, 1549.3) FC | Line | NA | NA | NA | NA | NA |
| **SEMA-O** | 0.77 (0.41, 1.44) NC | 0.86 (0.44, 1.68) NC | 0.76 (0.4, 1.46) NC | 0.98 (0.51, 1.92) NC | 1.09 (0.05, 21.98) NC | 0.89 (0.46, 1.74) NC | 8.77 (0.18, 784.47) NC | 0.69 (0.32, 1.48) NC | 1.73 (0.35, 8.39) NC | 2.89 (0.69, 13.91) NC | 4.92 (0.13, 401.73) NC | 0.86 (0.43, 1.75) NC | 0.88 (0.46, 1.71) NC | 0.17 (0.01, 1.48) NC | 0.9 (0.2, 4.16) NC | 19.79 (0.95, 1120.9) NC | 0.69 (0.36, 1.37) NC | Line | NA | 0.31 (0.03, 1.53) NC | NA | NA |
| **SEMA-S** | 0.62 (0.39, 0.98) FI | 0.69 (0.41, 1.15) NC | 0.62 (0.38, 1.01) NC | 0.8 (0.48, 1.3) NC | 0.86 (0.05, 16.78) NC | 0.73 (0.44, 1.19) NC | 6.94 (0.15, 614.97) NC | 0.57 (0.3, 1.07) NC | 1.4 (0.32, 6.7) NC | 2.34 (0.61, 11) NC | 4.02 (0.12, 320.85) NC | 0.69 (0.39, 1.22) NC | 0.71 (0.43, 1.16) NC | 0.15 (0.01, 1.15) NC | 0.72 (0.16, 3.41) NC | 16.58 (0.74, 880.32) NC | 0.56 (0.34, 0.92) FI | 0.81 (0.37, 1.79) NC | Line | NA | NA | NA |
| **SITA** | 0.35 (0.06, 1.55) | 0.39 (0.07, 1.8) | 0.35 (0.06, 1.58) | 0.45 (0.08, 2.06) NC | 0.48 (0.02, 12.25) NC | 0.41 (0.07, 1.82) NC | 3.79 (0.07, 382.71) NC | 0.32 (0.05, 1.45) NC | 0.76 (0.08, 6.75) NC | 1.32 (0.14, 10.34) NC | 2.2 (0.04, 191.86) NC | 0.39 (0.07, 1.8) NC | 0.4 (0.07, 1.81) NC | 0.08 (0, 0.95) FI | 0.41 (0.04, 3.25) NC | 9.17 (0.29, 622.25) NC | 0.31 (0.05, 1.4 | 0.46 (0.08, 1.83) NC | 0.56 (0.09, 2.6 | Line | NA | NA |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | NC | NC | NC | | | | | | | | | | | | | | 5) NC | | 9) NC | | | |
| **TIRZE** | 0.51 (0.08, 4.61) NC | 0.57 (0.09, 5.35) NC | 0.51 (0.08, 4.73) NC | 0.67 (0.1, 5.99) NC | 0.75 (0.02, 23.17) NC | 0.59 (0.09, 5.45) NC | 6.1 (0.09, 849.42) NC | 0.46 (0.07, 4.42) NC | 1.19 (0.16, 11.86) NC | 1.96 (0.5, 12.55) NC | 3.79 (0.07, 399.56) NC | 0.58 (0.09, 5.64) NC | 0.59 (0.09, 5.32) NC | 0.12 (0.01, 2.33) NC | 0.6 (0.06, 7.81) NC | 14.06 (0.54, 1042.52) NC | 0.47 (0.07, 4.31) NC | 0.67 (0.09, 6.25) NC | 0.81 (0.12, 7.62) NC | 1.56 (0.12, 24.48) NC | Line | NA |
| **VILDA** | 0.33 (0.05, 1.62) NC | 0.37 (0.06, 1.83) NC | 0.33 (0.05, 1.65) NC | 0.42 (0.06, 2.14) NC | 0.44 (0.02, 11.42) NC | 0.38 (0.06, 1.85) NC | 3.39 (0.09, 326.77) NC | 0.3 (0.04, 1.57) NC | 0.74 (0.07, 6.36) NC | 1.25 (0.13, 10.32) NC | 2.09 (0.04, 220) NC | 0.37 (0.06, 1.91) NC | 0.38 (0.06, 1.87) NC | 0.07 (0, 0.99) FI | 0.39 (0.05, 2.33) NC | 9.06 (0.25, 634.28) NC | 0.3 (0.05, 1.46) NC | 0.43 (0.06, 2.36) NC | 0.54 (0.08, 2.8) NC | 0.96 (0.09, 10.29) NC | 0.62 (0.04, 7.45) NC | Line |

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### 6.1.7. Unstable angina

**Table 19: Relative effectiveness (hazard ratios) showing all pairwise combinations for unstable angina in the base case analysis**

| Line | PCO | DAPA | DULA | EMPA | EXEN | GLIM | IDeg Lira | INS | IGlar Lixi | LINA | LIRA | LIXI | MET | PIO | SAXA | SEMA-O | SEMA-S | SITA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PCO** | Line | 1.02 (0.85, 1.22) NC | 1.12 (0.83, 1.52) NC | 0.12 (0, 4.56) NC | 1.14 (0.91, 1.44) NC | NA | NA | NA | NA | 0.88 (0.58, 1.36) NC | 0.97 (0.75, 1.26) NC | NA | NA | NA | 1.18 (0.9, 1.58) NC | 1.71 (0.71, 4.23) NC | 0.83 (0.47, 1.46) NC | 0.95 (0.06, 14.78 ) NC |
| **DAPA** | 1.02 (0.85, 1.22) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | 1.16 (0.16, 8.31) NC | NA | NA | NA | NA | NA | NA | NA |
| **DULA** | 1.12 (0.83, 1.5) NC | 1.1 (0.78, 1.56) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **EMPA** | 0.11 (0, 4.85) NC | 0.11 (0, 4.6) NC | 0.1 (0, 4.41) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **EXEN** | 1.14 (0.92, 1.42) NC | 1.12 (0.84, 1.48) NC | 1.02 (0.7, 1.49) NC | 9.68 (0.23, 964.58) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | 9.39 (0.21, 765.71) NC | NA | NA | NA | 0.4 (0, 31.39 ) NC |
| **GLIM** | 0.82 (0.47, 1.45) NC | 0.81 (0.45, 1.45) NC | 0.74 (0.39, 1.37) NC | 7.05 (0.17, 701.42) NC | 0.72 (0.4, 1.32) NC | Line | NA | NA | NA | 1.07 (0.74, 1.54) NC | NA | NA | NA | NA | NA | NA | NA | NA |
| **IDeg Lira** | 5.49 (0.81, 61.1) NC | 5.45 (0.75, 62.52 ) NC | 4.96 (0.72, 56.53 ) NC | 51.97 (0.72, 9219.28) NC | 4.83 (0.7, 52.44 ) NC | 6.67 (0.9, 81.28 ) NC | Line | 0.23 (0.02, 1.38) NC | NA | NA | 0.25 (0, 10.51 ) NC | NA | NA | NA | NA | NA | NA | NA |

| Line | PCO | DAPA | DULA | EMPA | EXEN | GLIM | IDeg Lira | INS | IGlar Lixi | LINA | LIRA | LIXI | MET | PIO | SAXA | SEMA-O | SEMA-S | SITA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **INS** | 1.18 (0.51, 2.74) NC | 1.16 (0.49, 2.77) NC | 1.07 (0.42, 2.57) NC | 10.12 (0.22, 1219.63) NC | 1.04 (0.43, 2.44) NC | 1.45 (0.52, 3.8) NC | 0.22 (0.02, 1.28) NC | Line | 1.2 (0.07, 20.13) NC | NA | 0.67 (0.24, 1.71) NC | 0.21 (0, 7.75) NC | NA | NA | NA | NA | 1 (0.06, 19.52) NC | 1.35 (0.61, 3.1) NC |
| **IGlar Lixi** | 1.32 (0.07, 24.85) NC | 1.29 (0.06, 24.51) NC | 1.19 (0.06, 22) NC | 12.26 (0.1, 2514.06) NC | 1.17 (0.06, 21.54) NC | 1.58 (0.08, 31.47) NC | 0.23 (0.01, 7.28) NC | 1.13 (0.06, 19.52) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **LINA** | 0.88 (0.58, 1.34) NC | 0.87 (0.56, 1.35) NC | 0.79 (0.48, 1.31) NC | 7.66 (0.18, 723.8) NC | 0.77 (0.49, 1.25) NC | 1.07 (0.75, 1.53) NC | 0.16 (0.01, 1.14) NC | 0.75 (0.3, 1.89) NC | 0.68 (0.03, 13.83) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA |
| **LIRA** | 0.96 (0.75, 1.23) NC | 0.95 (0.69, 1.28) NC | 0.86 (0.58, 1.27) NC | 8.3 (0.2, 821.88) NC | 0.84 (0.61, 1.17) NC | 1.17 (0.64, 2.1) NC | 0.18 (0.02, 1.2) NC | 0.81 (0.36, 1.89) NC | 0.73 (0.04, 15.12) NC | 1.1 (0.68, 1.75) NC | Line | NA | NA | NA | NA | NA | NA | NA |
| **LIXI** | 0.24 (0, 8.04) NC | 0.23 (0, 8.51) NC | 0.21 (0, 8.05) NC | 2.01 (0, 562.4) NC | 0.21 (0, 7.38) NC | 0.28 (0, 10.69) NC | 0.04 (0, 2.57) NC | 0.19 (0, 6.76) NC | 0.18 (0, 10.12) NC | 0.27 (0, 9.9) NC | 0.25 (0, 8.95) NC | Line | NA | NA | NA | NA | NA | NA |
| **MET** | 0.45 (0, 44.74) NC | 0.44 (0, 43.16) NC | 0.41 (0, 41.28) NC | 4 (0.01, 2075.86) NC | 0.41 (0, 38.29) NC | 0.56 (0, 51.95) NC | 0.08 (0, 11.97) NC | 0.39 (0, 36.26) NC | 0.33 (0, 70.15) NC | 0.52 (0, 49.81) NC | 0.48 (0, 45.59) NC | 1.93 (0, 1424.23) NC | Line | 6.47 (0.16, 499.2) NC | NA | NA | NA | NA |
| **PIO** | 14.96 (0.55, 964.6) NC | 14.76 (0.55, 940.62) NC | 13.6 (0.48, 808.89) NC | 148.58 (0.9, 5253 | 13.24 (0.5, 832.1) NC | 18.56 (0.62, 1246.41) NC | 2.63 (0.05, 275.15) NC | 12.62 (0.48, 835.74) NC | 12.38 (0.13, 1535.51) NC | 17.02 (0.61, 1093.63) NC | 15.7 (0.57, 967.05) NC | 69.25 (0.52, 26580.04) NC | 33.04 (0.4, 14457.49) NC | Line | NA | NA | NA | NA |

| Line | PCO | DAPA | DULA | EMPA | EXEN | GLIM | IDegLira | INS | IGlarLixi | LINA | LIRA | LIXI | MET | PIO | SAXA | SEMA-O | SEMA-S | SITA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 9.27) NC | | | | | | | | | | | | | | |
| **SAXA** | 1.18 (0.88, 1.6) NC | 1.16 (0.83, 1.64) NC | 1.06 (0.7, 1.64) NC | 10.09 (0.25, 1027) NC | 1.04 (0.72, 1.51) NC | 1.45 (0.77, 2.69) NC | 0.22 (0.02, 1.54) NC | 1.01 (0.41, 2.4) NC | 0.9 (0.05, 18.22 ) NC | 1.35 (0.81, 2.24) NC | 1.23 (0.84, 1.79) NC | 5.17 (0.14, 507.93) NC | 2.6 (0.03, 420.48) NC | 0.08 (0, 2.21) NC | Line | NA | NA | NA |
| **SEMA-O** | 1.92 (0.84, 4.38) NC | 1.89 (0.82, 4.34) NC | 1.71 (0.72, 4.19) NC | 17.05 (0.35, 1783.28) NC | 1.68 (0.72, 3.96) NC | 2.34 (0.87, 6.24) NC | 0.35 (0.03, 2.78) NC | 1.64 (0.55, 5.08) NC | 1.46 (0.07, 33.94 ) NC | 2.17 (0.86, 5.5) NC | 2 (0.86, 4.68) NC | 8.22 (0.21, 837.22) NC | 4.13 (0.05, 814.4 ) NC | 0.13 (0, 3.94) NC | 1.62 (0.69, 3.86) NC | Line | NA | 0.46 (0.04, 2.54) NC |
| **SEMA-S** | 0.83 (0.48, 1.44) NC | 0.82 (0.45, 1.46) NC | 0.75 (0.4, 1.41) NC | 7.22 (0.17, 756.85) NC | 0.73 (0.4, 1.31) NC | 1.01 (0.45, 2.26) NC | 0.15 (0.01, 1.1) NC | 0.69 (0.27, 1.97) NC | 0.62 (0.03, 13.94 ) NC | 0.95 (0.46, 1.91) NC | 0.87 (0.47, 1.58) NC | 3.56 (0.09, 358.72) NC | 1.81 (0.02, 305.81) NC | 0.06 (0, 1.58) NC | 0.7 (0.39, 1.3) NC | 0.43 (0.16, 1.17) NC | Line | NA |
| **SITA** | 1.54 (0.73, 3.42) NC | 1.51 (0.7, 3.44) NC | 1.39 (0.63, 3.19) NC | 13.45 (0.3, 1460.14) NC | 1.36 (0.63, 3.08) NC | 1.87 (0.76, 4.89) NC | 0.28 (0.03, 1.94) NC | 1.3 (0.62, 2.85) NC | 1.13 (0.06, 26.36 ) NC | 1.76 (0.75, 4.2) NC | 1.6 (0.77, 3.5) NC | 6.7 (0.17, 728.15) NC | 3.3 (0.04, 623.82) NC | 0.1 (0, 2.78) NC | 1.29 (0.6, 2.99) NC | 0.81 (0.29, 2.09) NC | 1.86 (0.73, 4.66) NC | Line |

**Table 20: Relative effectiveness (hazard ratios) showing all pairwise combinations for unstable angina in the sensitivity analysis**

| Line | PCO | DAPA | DULA | EMPA | EXEN | GLIM | IDegLira | INS | IGlarLixi | LINA | LIRA | LIXI | MET | PIO | SAXA | SEMA-O | SEMA-S | SITA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PCO** | Line | 1.02 (0.85, | 1.12 (0.83, | 0.12 (0, | 1.14 (0.92, | NA | NA | NA | NA | 0.88 (0.58, | 0.97 (0.76, | NA | NA | NA | 1.19 (0.88, | 1.7 (0.65, | 0.82 (0.47, | 0.96 (0.05, |

| Line | PCO | DAPA | DULA | EMPA | EXEN | GLIM | IDegLira | INS | IGlarLixi | LINA | LIRA | LIXI | MET | PIO | SAXA | SEMA-O | SEMA-S | SITA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1.22) NC | 1.52) NC | 4.1) NC | 1.42) NC | | | | | 1.33) NC | 1.25) NC | | | | 1.6) NC | 4.36) NC | 1.45) NC | 16.62) NC |
| **DAPA** | 1.02 (0.85, 1.22) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | 1.12 (0.15, 9.19) NC | NA | NA | NA | NA | NA | NA | NA |
| **DULA** | 1.12 (0.83, 1.53) NC | 1.11 (0.77, 1.56) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **EMPA** | 0.12 (0, 3.83) NC | 0.12 (0, 4.01) NC | 0.11 (0, 3.39) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **EXEN** | 1.14 (0.92, 1.42) NC | 1.12 (0.85, 1.49) NC | 1.02 (0.71, 1.46) NC | 8.99 (0.3, 684.53) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | 8.79 (0.2, 763.04) NC | NA | NA | NA | 0.37 (0, 30.98) NC |
| **GLIM** | 0.99 (0.62, 1.54) NC | 0.97 (0.58, 1.58) NC | 0.88 (0.51, 1.52) NC | 7.8 (0.25, 638.14) NC | 0.87 (0.52, 1.42) NC | Line | NA | 0.74 (0.31, 1.77) NC | NA | 1.07 (0.75, 1.52) NC | 0.59 (0.22, 1.4) NC | NA | NA | NA | NA | NA | NA | 1.26 (0.61, 2.67) NC |
| **IDegLira** | 4.68 (0.76, 52.92) NC | 4.57 (0.73, 51.96) NC | 4.19 (0.68, 47.64) NC | 39.61 (0.78, 4653.06) NC | 4.1 (0.65, 48.61) NC | 4.73 (0.77, 57.1) NC | Line | 0.23 (0.02, 1.35) NC | NA | NA | 0.26 (0, 11.84) NC | NA | NA | NA | NA | NA | NA | NA |

| Line | PCO | DAPA | DULA | EMPA | EXEN | GLIM | IDegLira | INS | IGlarLixi | LINA | LIRA | LIXI | MET | PIO | SAXA | SEMA-O | SEMA-S | SITA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **INS** | 0.98 (0.45, 2.07) NC | 0.96 (0.43, 2.08) NC | 0.88 (0.38, 1.91) NC | 7.75 (0.24, 605.71) NC | 0.86 (0.39, 1.87) NC | 1 (0.46, 2.1) NC | 0.21 (0.02, 1.16) NC | Line | 1.17 (0.07, 26.64) NC | NA | NA | 0.22 (0, 7.54) NC | NA | NA | NA | NA | 0.98 (0.06, 20.33) NC | 0.09 (0, 1.55) NC |
| **IGlarLixi** | 1.14 (0.05, 21.08) NC | 1.12 (0.05, 20.14) NC | 1.02 (0.05, 17.98) NC | 9.68 (0.1, 1390.67) NC | 1 (0.05, 18) NC | 1.13 (0.06, 21.93) NC | 0.23 (0.01, 6.54) NC | 1.16 (0.06, 20.54) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **LINA** | 0.98 (0.67, 1.42) NC | 0.96 (0.63, 1.45) NC | 0.87 (0.54, 1.4) NC | 7.72 (0.25, 610.53) NC | 0.86 (0.55, 1.32) NC | 0.99 (0.71, 1.41) NC | 0.21 (0.02, 1.3) NC | 0.99 (0.47, 2.2) NC | 0.87 (0.04, 18.06) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA |
| **LIRA** | 0.94 (0.74, 1.2) NC | 0.92 (0.67, 1.24) NC | 0.84 (0.57, 1.25) NC | 7.42 (0.24, 598.14) NC | 0.82 (0.59, 1.14) NC | 0.96 (0.59, 1.53) NC | 0.2 (0.02, 1.23) NC | 0.95 (0.46, 2.06) NC | 0.83 (0.04, 16.6) NC | 0.96 (0.62, 1.46) NC | Line | NA | NA | NA | NA | NA | NA | NA |
| **LIXI** | 0.22 (0, 6.88) NC | 0.21 (0, 6.72) NC | 0.19 (0, 6.08) NC | 1.52 (0, 452.65) NC | 0.19 (0, 6.01) NC | 0.22 (0, 7.28) NC | 0.04 (0, 2.23) NC | 0.22 (0, 7.11) NC | 0.18 (0, 12.85) NC | 0.22 (0, 7.38) NC | 0.23 (0, 7.32) NC | Line | NA | NA | NA | NA | NA | NA |
| **MET** | 0.43 (0, 40.02) NC | 0.42 (0, 39.4) NC | 0.38 (0, 34.37) NC | 3.56 (0.01, 1977.26) NC | 0.37 (0, 34.63) NC | 0.43 (0, 38.74) NC | 0.08 (0, 11.52) NC | 0.44 (0, 38.11) NC | 0.38 (0, 68.28) NC | 0.43 (0, 41.37) NC | 0.45 (0, 42.08) NC | 2.09 (0, 1336.07) NC | Line | 6.04 (0.17, 549.19) NC | NA | NA | NA | NA |

| Line | PCO | DAPA | DULA | EMPA | EXEN | GLIM | IDegLira | INS | IGlarLixi | LINA | LIRA | LIXI | MET | PIO | SAXA | SEMA-O | SEMA-S | SITA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PIO** | 15.29 (0.47, 813.53) NC | 15.1 (0.47, 777.38) NC | 13.67 (0.43, 720.06) NC | 134.48 (0.86, 42100.5) NC | 13.42 (0.4, 708.84) NC | 15.57 (0.46, 887) NC | 2.88 (0.05, 268.96) NC | 15.69 (0.45, 938.36) NC | 14.24 (0.13, 1710.31) NC | 15.89 (0.47, 881.35) NC | 16.51 (0.52, 887.32) NC | 79.55 (0.54, 43088.17) NC | 32.27 (0.38, 17554.41) NC | Line | NA | NA | NA | NA |
| **SAXA** | 1.2 (0.89, 1.6) NC | 1.18 (0.83, 1.65) NC | 1.07 (0.69, 1.63) NC | 9.49 (0.31, 698.15) NC | 1.05 (0.72, 1.51) NC | 1.22 (0.71, 2.07) NC | 0.25 (0.02, 1.62) NC | 1.22 (0.55, 2.8) NC | 1.04 (0.06, 22.2) NC | 1.22 (0.75, 1.96) NC | 1.28 (0.88, 1.87) NC | 5.58 (0.17, 656.98) NC | 2.81 (0.03, 417.19) NC | 0.08 (0, 2.59) NC | Line | NA | NA | NA |
| **SEMA-O** | 1.84 (0.83, 4.29) NC | 1.81 (0.79, 4.31) NC | 1.64 (0.71, 4.06) NC | 14.68 (0.42, 1208.74) NC | 1.62 (0.7, 3.85) NC | 1.89 (0.76, 4.89) NC | 0.4 (0.03, 2.85) NC | 1.89 (0.66, 5.68) NC | 1.61 (0.08, 34.11) NC | 1.9 (0.77, 4.81) NC | 1.98 (0.84, 4.59) NC | 8.92 (0.22, 974.27) NC | 4.27 (0.04, 747.07) NC | 0.12 (0, 4.24) NC | 1.55 (0.65, 3.74) NC | Line | NA | 0.44 (0.03, 2.42) NC |
| **SEMA-S** | 0.82 (0.47, 1.42) NC | 0.81 (0.45, 1.42) NC | 0.73 (0.39, 1.33) NC | 6.47 (0.22, 504.68) NC | 0.72 (0.4, 1.27) NC | 0.83 (0.41, 1.72) NC | 0.18 (0.01, 1.11) NC | 0.84 (0.34, 2.06) NC | 0.72 (0.04, 15.34) NC | 0.84 (0.43, 1.63) NC | 0.88 (0.48, 1.59) NC | 3.81 (0.11, 429.94) NC | 1.93 (0.02, 317.45) NC | 0.05 (0, 1.78) NC | 0.69 (0.37, 1.27) NC | 0.44 (0.17, 1.15) NC | Line | NA |
| **SITA** | 1.28 (0.63, 2.47) NC | 1.26 (0.61, 2.47) NC | 1.13 (0.53, 2.34) NC | 10.24 (0.31, 773.89) NC | 1.12 (0.54, 2.24) NC | 1.29 (0.64, 2.6) NC | 0.27 (0.02, 1.77) NC | 1.29 (0.61, 2.84) NC | 1.11 (0.06, 22.66) NC | 1.31 (0.64, 2.56) NC | 1.35 (0.67, 2.65) NC | 5.96 (0.18, 752.37) NC | 2.96 (0.03, 470.03) NC | 0.08 (0, 2.75) NC | 1.07 (0.5, 2.19) NC | 0.69 (0.25, 1.8) NC | 1.56 (0.64, 3.73) NC | Line |

### 6.1.8. Hospitalisation for heart failure

**Table 21: Relative effectiveness (hazard ratios) showing all pairwise combinations for hospitalisation for heart failure in the base case analysis**

| LINE | PCO | ALO | CANA | DAPA | DAPA/SAXA | DULA | EMPA | EXEN | GLIM | IDegLira | INS | IGlarLixi | LINA | LIRA | LIXI | MET | PIO | SAXA | SEMA-O | SEMA-S | SITA | TIRZE |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **PCO** | Line | 6.52 (0.3, 530.92) NC | 0.67 (0.52, 0.87) FI | 0.73 (0.6, 0.88) FI | NA | 0.93 (0.77, 1.13) NC | NA | 0.94 (0.79, 1.13) NC | NA | NA | NA | NA | 0.9 (0.74, 1.09) NC | 0.87 (0.73, 1.04) NC | NA | 0.72 (0.16, 3.18) NC | 2.55 (0.27, 36.85) NC | 1.27 (1.07, 1.5) FC | 0.92 (0.53, 1.63) NC | 1.09 (0.75, 1.58) NC | NA | NA |
| **ALO** | 6.53 (0.31, 721.77) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **CANA** | 0.67 (0.52, 0.87) FI | 0.1 (0, 2.32) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DAPA** | 0.73 (0.61, 0.88) FI | 0.11 (0, 2.42) NC | 1.09 (0.78, 1.5) NC | Line | 0.41 (0, 39.85) NC | NA | NA | NA | 8.94 (0.18, 871.41) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **DAPA/SAXA** | 0.2 (0, 7.42) NC | 0.03 (0, 3.98) NC | 0.3 (0, 11.33) NC | 0.28 (0, 10.36) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **DULA** | 0.93 (0.77, 1.12) NC | 0.14 (0, 2.98) NC | 1.38 (1.01, 1.92) FC | 1.28 (0.98, 1.64) NC | 4.65 (0.12, 398.43) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **EMPA** | 0.45 (0.03, 5.1) NC | 0.06 (0, 3.55) NC | 0.68 (0.04, 7.61) NC | 0.61 (0.04, 7.1) NC | 2.2 (0.02, 340.61) NC | 0.49 (0.03, 5.56) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | 1.99 (0.22, 26.03) NC | NA | NA | NA |
| **EXEN** | 0.94 (0.79, 1.14) NC | 0.14 (0, 3.13) NC | 1.41 (1.02, 1.94) FC | 1.3 (1, 1.69) FC | 4.66 (0.13, 389.82) NC | 1.01 (0.79, 1.31) NC | 2.1 (0.18, 35.49) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **GLIM** | 0.75 (0.54, 1.04) NC | 0.11 (0, 2.46) NC | 1.12 (0.74, 1.68) NC | 1.04 (0.7, 1.49) NC | 3.64 (0.1, 303.54) NC | 0.81 (0.55, 1.16) NC | 1.64 (0.14, 28.55) NC | 0.8 (0.55, 1.16) NC | Line | NA | NA | NA | 1.22 (0.92, 1.59) NC | NA | NA | NA | 2.48 (0.56, 15.21) NC | NA | NA | NA | NA | NA |

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **IDegLira** | 0.76 (0.05, 8.02) NC | 0.1 (0, 5.8) NC | 1.15 (0.07, 12.42) NC | 1.05 (0.06, 11.21) NC | 3.65 (0.04, 648.99) NC | 0.81 (0.05, 8.94) NC | 1.67 (0.04, 67.18) NC | 0.8 (0.05, 8.41) NC | 1 (0.06, 11.42) NC | Line | 2.08 (0.2, 30.06) NC | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **INS** | 1.7 (0.77, 3.65) NC | 0.26 (0, 6.43) NC | 2.55 (1.09, 5.74) FC | 2.33 (1.06, 5.17) FC | 8.33 (0.21, 722.44) NC | 1.83 (0.82, 4.05) NC | 3.74 (0.3, 65.85) NC | 1.81 (0.8, 3.96) NC | 2.27 (0.98, 5.18) NC | 2.22 (0.23, 35.91) NC | Line | 0.11 (0, 2.13) NC | NA | NA | 0.16 (0, 4.15) NC | NA | NA | NA | NA | NA | 1.15 (0.69, 1.89) NC | 3.21 (0.09, 399.75) NC |
| **IGlarLixi** | 0.14 (0, 3.33) NC | 0.02 (0, 1.62) NC | 0.21 (0, 4.73) NC | 0.19 (0, 4.59) NC | 0.67 (0, 180.74) NC | 0.15 (0, 3.64) NC | 0.3 (0, 18.94) NC | 0.15 (0, 3.47) NC | 0.19 (0, 4.51) NC | 0.2 (0, 12.23) NC | 0.08 (0, 1.9) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **LINA** | 0.9 (0.75, 1.08) NC | 0.14 (0, 2.93) NC | 1.34 (0.98, 1.87) NC | 1.24 (0.94, 1.62) NC | 4.49 (0.12, 371.28) NC | 0.97 (0.75, 1.26) NC | 2.02 (0.17, 33.47) NC | 0.96 (0.73, 1.25) NC | 1.2 (0.92, 1.56) NC | 1.2 (0.11, 20.01) NC | 0.53 (0.24, 1.19) NC | 6.52 (0.28, 478.13) NC | Line | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| **LIRA** | 0.87 (0.73, 1.04) NC | 0.13 (0, 2.87) NC | 1.3 (0.95, 1.78) NC | 1.2 (0.92, 1.55) NC | 4.29 (0.11, 364.06) NC | 0.94 (0.73, 1.21) NC | 1.91 (0.17, 32.62) NC | 0.92 (0.71, 1.19) NC | 1.16 (0.81, 1.69) NC | 1.15 (0.11, 19.04) NC | 0.51 (0.24, 1.12) NC | 6.32 (0.26, 460.77) NC | 0.97 (0.74, 1.26) NC | NA | NA | NA | NA | NA | NA | NA | 2.11 (1.14, 3.95) FC | NA |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **LIXI** | 0.21 (0, 5.81) NC | 0.03 (0, 3.19) NC | 0.31 (0, 9.08) NC | 0.29 (0, 7.81) NC | 1 (0, 286.58) NC | 0.23 (0, 6.35) NC | 0.46 (0, 34.66) NC | 0.22 (0, 6.31) NC | 0.28 (0, 7.98) NC | 0.28 (0, 19.55) NC | 0.12 (0, 3.38) NC | 1.49 (0.01, 275.98) NC | 0.23 (0, 6.78) NC | 0.24 (0, 6.68) NC | NA | NA | NA | NA | NA | NA | NA | NA |
| **MET** | 0.75 (0.15, 3.27) NC | 0.11 (0, 3.56) NC | 1.1 (0.22, 4.79) NC | 1.01 (0.21, 4.55) NC | 3.47 (0.07, 379.66) NC | 0.8 (0.17, 3.57) NC | 1.69 (0.1, 35.92) NC | 0.78 (0.16, 3.5) NC | 0.99 (0.2, 4.45) NC | 0.98 (0.06, 23.72) NC | 0.44 (0.07, 2.31) NC | 5.43 (0.15, 570.89) NC | 0.83 (0.17, 3.67) NC | 0.85 (0.17, 3.68) NC | 3.46 (0.09, 548.76) NC | NA | NA | NA | NA | NA | NA | NA |
| **PIO** | 2.1 (0.57, 9.49) NC | 0.33 (0, 10.04) NC | 3.15 (0.85, 14.26) NC | 2.9 (0.78, 13.2) NC | 10.28 (0.22, 1079.08) NC | 2.27 (0.62, 10.33) NC | 4.87 (0.3, 108) NC | 2.23 (0.63, 10.18) NC | 2.81 (0.8, 12.69) NC | 2.94 (0.18, 75.2) NC | 1.26 (0.27, 6.97) NC | 15.43 (0.51, 1439.15) NC | 2.33 (0.64, 10.43) NC | 2.42 (0.65, 11.03) NC | 10.55 (0.28, 1431.48) NC | 2.96 (0.38, 24.5) NC | NA | NA | NA | NA | NA | NA |
| **SAXA** | 1.27 (1.07, 1.52) FC | 0.19 (0, 4.19) NC | 1.89 (1.4, 2.63) FC | 1.75 (1.34, 2.26) FC | 6.26 (0.16, 532.38) NC | 1.37 (1.06, 1.76) FC | 2.82 (0.25, 47.43) NC | 1.35 (1.04, 1.73) FC | 1.69 (1.17, 2.45) FC | 1.68 (0.16, 26.33) NC | 0.74 (0.34, 1.69) NC | 9.02 (0.38, 669.52) NC | 1.41 (1.09, 1.82) FC | 1.46 (1.14, 1.89) FC | 6.18 (0.22, 651.83) NC | 1.72 (0.39, 8.32) NC | 0.6 (0.13, 2.2) NC | NA | NA | NA | NA | NA |
| **SEMA-O** | 0.91 (0.54, 1.54) NC | 0.14 (0, 3.06) NC | 1.35 (0.75, 2.43) NC | 1.24 (0.73, 2.18) NC | 4.41 (0.13, 376.06) NC | 0.97 (0.57, 1.71) NC | 2 (0.18, 30.31) NC | 0.96 (0.55, 1.66) NC | 1.2 (0.65, 2.22) NC | 1.22 (0.11, 21.61) NC | 0.53 (0.22, 1.28) NC | 6.54 (0.26, 513.75) NC | 1 (0.58, 1.74) NC | 1.04 (0.59, 1.78) NC | 4.35 (0.14, 516.35) NC | 1.22 (0.25, 6.35) NC | 0.42 (0.09, 1.67) NC | 0.71 (0.41, 1.24) NC | NA | NA | 2.36 (0.63, 8.73) NC | NA |

| | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SEMA-S** | 1.08 (0.75, 1.54) NC | 0.17 (0, 3.68) NC | 1.61 (1.05, 2.51) FC | 1.49 (0.99, 2.23) NC | 5.32 (0.14, 477.5) NC | 1.16 (0.79, 1.75) NC | 2.41 (0.21, 41.38) NC | 1.15 (0.76, 1.73) NC | 1.44 (0.89, 2.39) NC | 1.44 (0.12, 24.88) NC | 0.63 (0.27, 1.5) NC | 7.82 (0.32, 600.48) NC | 1.2 (0.79, 1.81) NC | 1.24 (0.83, 1.86) NC | 5.17 (0.18, 620.78) NC | 1.47 (0.31, 7.31) NC | 0.51 (0.11, 2.01) NC | 0.85 (0.57, 1.27) NC | 1.2 (0.62, 2.24) NC | NA | NA | NA |
| **SITA** | 1.92 (1.08, 3.53) FC | 0.3 (0, 6.63) NC | 2.88 (1.5, 5.63) FC | 2.66 (1.45, 5) FC | 9.43 (0.25, 799.08) NC | 2.07 (1.12, 3.88) FC | 4.2 (0.36, 74.89) NC | 2.06 (1.11, 3.84) FC | 2.57 (1.32, 5.12) FC | 2.51 (0.25, 41.14) NC | 1.13 (0.67, 1.94) NC | 13.56 (0.59, 1122.79) NC | 2.15 (1.15, 4.05) FC | 2.23 (1.27, 3.98) FC | 9.19 (0.33, 1088.65) NC | 2.62 (0.51, 14.32) NC | 0.9 (0.19, 3.79) NC | 1.52 (0.84, 2.81) NC | 2.12 (1.04, 4.56) FC | 1.79 (0.9, 3.53) NC | NA | NA |
| **TIRZE** | 4.5 (0.11, 403.27) NC | 0.62 (0, 156.51) NC | 6.78 (0.16, 618.09) NC | 6.23 (0.15, 532.92) NC | 25.61 (0.13, 11628.8) NC | 4.85 (0.12, 424.41) NC | 11 (0.15, 1894.93) NC | 4.79 (0.11, 426.33) NC | 6.14 (0.15, 530.44) NC | 6.79 (0.08, 986.67) NC | 2.59 (0.06, 250.1) NC | 36.66 (0.23, 19015.46) NC | 4.98 (0.12, 428.79) NC | 5.15 (0.12, 449.89) NC | 25.63 (0.13, 13302.03) NC | 6.19 (0.12, 686.69) NC | 2.13 (0.04, 249.36) NC | 3.56 (0.08, 309.78) NC | 5.05 (0.12, 445.51) NC | 4.19 (0.1, 361.55) NC | 2.28 (0.06, 213.64) NC | NA |

### 6.1.9. Development of end-stage renal failure

**Table 22: Relative effectiveness (hazard ratios) showing all pairwise combinations for development of end-stage renal failure**

| LINE | PCO | CANA | DAPA | DULA | EXEN | LINA | LIRA | SAXA |
|---|---|---|---|---|---|---|---|---|
| **PCO** | Line | 0.78 (0.3, 1.94), NC | 0.35 (0.15, 0.78), FI | 0.51 (0.1, 1.85), NC | 0.85 (0.59, 1.21), NC | 0.98 (0.69, 1.39), NC | 0.88 (0.62, 1.26), NC | 0.9 (0.62, 1.31), NC |
| **CANA** | 0.77 (0.31, 1.96), NC | Line | NA | NA | NA | NA | NA | NA |
| **DAPA** | 0.35 (0.15, 0.83), FI | 0.45 (0.12, 1.64), NC | Line | NA | NA | NA | NA | NA |
| **DULA** | 0.5 (0.11, 1.87), NC | 0.65 (0.11, 3.2), NC | 1.43 (0.27, 7.15), NC | Line | NA | NA | NA | NA |
| **EXEN** | 0.86 (0.59, 1.2), NC | 1.11 (0.41, 2.94), NC | 2.44 (0.97, 6.17), NC | 1.69 (0.44, 8.13), NC | Line | NA | NA | NA |
| **LINA** | 0.98 (0.68, 1.39), NC | 1.27 (0.46, 3.39), NC | 2.79 (1.09, 7.14), FC | 1.97 (0.5, 9.02), NC | 1.15 (0.7, 1.95), NC | Line | NA | NA |
| **LIRA** | 0.89 (0.62, 1.24), NC | 1.16 (0.42, 3.02), NC | 2.53 (1.03, 6.36), FC | 1.75 (0.45, 8.07), NC | 1.03 (0.64, 1.7), NC | 0.9 (0.55, 1.47), NC | Line | NA |
| **SAXA** | 0.9 (0.62, 1.32), NC | 1.17 (0.42, 3.32), NC | 2.55 (1.01, 6.7), FC | 1.8 (0.47, 8.44), NC | 1.06 (0.64, 1.78), NC | 0.91 (0.54, 1.55), NC | 1.02 (0.61, 1.72), NC | Line |

# 6.2. Absolute effect tables

## 6.2.1. Cardiovascular mortality

**Table 23: Table showing the values calculated for the absolute effects from the baseline risk of cardiovascular mortality (base case analysis) for people at higher risk of cardiovascular disease at 46 months (baseline risk = 6.0%) (NNTB = Number needed to treat for an additional beneficial outcome, NNTH = number needed to treat for an additional harmful outcome)**

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Alogliptin | 3.06 (0.49, 31.41) | 119 more per 1,000, 32 fewer to 803 more | 8 treated for an additional harmful outcome in 1 person, 31 NNTB to 1 NNTH |
| Canagliflozin | 0.88 (0.72, 1.06) | 7 fewer per 1,000, 16 fewer to 3 more | 143 treated for an additional beneficial outcome in 1 person, 61 NNTB to 287 NNTH |
| Dapagliflozin | 1 (0.84, 1.19) | 0 fewer per 1,000, 9 fewer to 11 more | 1000 treated for an additional harmful outcome in 1 person, 107 NNTB to 91 NNTH |
| Dapagliflozin + Exenatide | 0.81 (0.05, 8.47) | 11 fewer per 1,000, 57 fewer to 348 more | 90 treated for an additional beneficial outcome in 1 person, 18 NNTB to 3 NNTH |
| Dapagliflozin + Saxagliptin | 0.15 (0, 2.87) | 51 fewer per 1,000, 60 fewer to 103 more | 20 treated for an additional beneficial outcome in 1 person, 17 NNTB to 10 NNTH |
| Dulaglutide | 0.91 (0.79, 1.07) | 5 fewer per 1,000, 12 fewer to 4 more | 191 treated for an additional beneficial outcome in 1 person, 81 NNTB to 246 NNTH |
| Empagliflozin | 3.91 (0.34, 100.03) | 155 more per 1,000, 39 fewer to 938 more | 6 treated for an additional harmful outcome in 1 person, 26 NNTB to 1 NNTH |
| Empagliflozin + Linagliptin | 14.2 (0.3, 1065.21) | 525 more per 1,000, 42 fewer to 940 more | 2 treated for an additional harmful outcome in 1 person, 24 NNTB to 1 NNTH |
| Ertugliflozin | 1.98 (0.25, 34.8) | 55 more per 1,000, 45 fewer to 824 more | 18 treated for an additional harmful outcome in 1 person, 22 NNTB to 1 NNTH |
| Ertugliflozin + Sitagliptin | 0.28 (0, 12.01) | 43 fewer per 1,000, 60 fewer to 464 more | 23 treated for an additional beneficial outcome in 1 person, 17 NNTB to 2 NNTH |
| Exenatide | 0.88 (0.77, 1.01) | 7 fewer per 1,000, 13 fewer to 1 more | 143 treated for an additional beneficial outcome in 1 person, 74 NNTB to 1000 NNTH |
| Gliclazide | 7.27 (0.16, 620.45) | 273 more per 1,000, 49 fewer to 940 more | 4 treated for an additional harmful outcome in 1 person, 20 NNTB to 1 NNTH |

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Glimepiride | 0.99 (0.77, 1.28) | 1 fewer per 1,000, 13 fewer to 16 more | 1000 treated for an additional beneficial outcome in 1 person, 74 NNTB to 62 NNTH |
| Glipizide | 5.75 (1.13, 49.13) | 257 more per 1,000, 9 more to 888 more | 4 treated for an additional harmful outcome in 1 person, 108 NNTH to 1 NNTH |
| IDegLira | 0.49 (0.07, 2.44) | 30 fewer per 1,000, 56 fewer to 80 more | 33 treated for an additional beneficial outcome in 1 person, 18 NNTB to 12 NNTH |
| IGlaLixi | 0.39 (0.03, 2.76) | 36 fewer per 1,000, 58 fewer to 97 more | 28 treated for an additional beneficial outcome in 1 person, 17 NNTB to 10 NNTH |
| Insulin | 1.36 (0.84, 2.24) | 17 more per 1,000, 21 fewer to 86 more | 58 treated for an additional harmful outcome in 1 person, 49 NNTB to 12 NNTH |
| Linagliptin | 0.98 (0.83, 1.16) | 1 fewer per 1,000, 10 fewer to 9 more | 859 treated for an additional beneficial outcome in 1 person, 101 NNTB to 108 NNTH |
| Liraglutide | 0.76 (0.64, 0.9) | 14 fewer per 1,000, 21 fewer to 6 fewer | 71 treated for an additional beneficial outcome in 1 person, 47 NNTB to 171 NNTB |
| Lixisenatide | 0.7 (0.14, 3.12) | 18 fewer per 1,000, 51 fewer to 116 more | 57 treated for an additional beneficial outcome in 1 person, 19 NNTB to 9 NNTH |
| Metformin type unspecified | 1.63 (0.28, 12.06) | 33 more per 1,000, 44 fewer to 422 more | 30 treated for an additional harmful outcome in 1 person, 23 NNTB to 2 NNTH |
| Pioglitazone | 1 (0.1, 8.61) | 0 fewer per 1,000, 54 fewer to 353 more | 1000 treated for an additional harmful outcome in 1 person, 19 NNTB to 3 NNTH |
| Pioglitazone + Alogliptin | 0.11 (0, 6.78) | 53 fewer per 1,000, 60 fewer to 227 more | 19 treated for an additional beneficial outcome in 1 person, 17 NNTB to 4 NNTH |
| Saxagliptin | 1.03 (0.87, 1.22) | 2 more per 1,000, 8 fewer to 13 more | 574 treated for an additional harmful outcome in 1 person, 132 NNTB to 79 NNTH |
| Semaglutide; Oral | 0.52 (0.3, 0.91) | 28 fewer per 1,000, 42 fewer to 5 fewer | 35 treated for an additional beneficial outcome in 1 person, 24 NNTB to 191 NNTB |
| Semaglutide; Subcutaneous | 0.95 (0.64, 1.4) | 3 fewer per 1,000, 21 fewer to 23 more | 343 treated for an additional beneficial outcome in 1 person, 47 NNTB to 44 NNTH |
| Sitagliptin | 1.16 (0.71, 1.89) | 13 more per 1,000, 17 fewer to 64 more | 79 treated for an additional harmful outcome in 1 person, 59 NNTB to 16 NNTH |
| Tirzepatide | 1.43 (0.34, 9.33) | 23 more per 1,000, 40 fewer to 357 more | 44 treated for an additional harmful outcome in 1 person, 25 NNTB to 3 NNTH |

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Vildagliptin | 1.25 (0.2, 8.73) | 12 more per 1,000, 47 fewer to 333 more | 82 treated for an additional harmful outcome in 1 person, 21 NNTB to 3 NNTH |

### 6.2.2. 3-item MACE

**Table 24: Table showing the values calculated for the absolute effects from the baseline risk of 3-item MACE (base case analysis) at 38 months (baseline risk = 12.2%)**

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Canagliflozin | 0.86 (0.76, 0.98) | 16 fewer per 1,000, 28 fewer to 2 fewer | 62 treated for an additional beneficial outcome in 1 person, 36 NNTB to 437 NNTB |
| Dapagliflozin | 0.93 (0.84, 1.03) | 8 fewer per 1,000, 18 fewer to 3 more | 124 treated for an additional beneficial outcome in 1 person, 54 NNTB to 292 NNTH |
| Dulaglutide | 0.88 (0.79, 0.98) | 14 fewer per 1,000, 24 fewer to 2 fewer | 72 treated for an additional beneficial outcome in 1 person, 41 NNTB to 437 NNTB |
| Exenatide | 0.91 (0.83, 1) | 10 fewer per 1,000, 20 fewer to 0 fewer | 97 treated for an additional beneficial outcome in 1 person, 51 NNTB to 1000 NNTB |
| Glimepiride | 1.07 (0.88, 1.29) | 8 more per 1,000, 14 fewer to 33 more | 126 treated for an additional harmful outcome in 1 person, 72 NNTB to 31 NNTH |
| IDegLira | 1.65 (0.46, 6.54) | 71 more per 1,000, 64 fewer to 451 more | 14 treated for an additional harmful outcome in 1 person, 16 NNTB to 2 NNTH |
| Insulin | 1.17 (0.76, 1.77) | 19 more per 1,000, 28 fewer to 84 more | 52 treated for an additional harmful outcome in 1 person, 36 NNTB to 12 NNTH |
| Linagliptin | 1.04 (0.91, 1.19) | 5 more per 1,000, 10 fewer to 21 more | 219 treated for an additional harmful outcome in 1 person, 97 NNTB to 47 NNTH |
| Liraglutide | 0.87 (0.78, 0.97) | 15 fewer per 1,000, 25 fewer to 3 fewer | 67 treated for an additional beneficial outcome in 1 person, 39 NNTB to 291 NNTB |
| Pioglitazone | 1.39 (0.8, 2.5) | 43 more per 1,000, 23 fewer to 156 more | 23 treated for an additional harmful outcome in 1 person, 43 NNTB to 6 NNTH |
| Saxagliptin | 1 (0.89, 1.12) | 0 fewer per 1,000, 13 fewer to 14 more | 1000 treated for an additional beneficial outcome in 1 person, 1000 NNTB to 1000 NNTH |

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Semaglutide; Oral | 0.79 (0.57, 1.1) | 24 fewer per 1,000, 51 fewer to 11 more | 41 treated for an additional beneficial outcome in 1 person, 20 NNTB to 88 NNTH |
| Semaglutide; Subcutaneous | 0.74 (0.58, 0.96) | 30 fewer per 1,000, 49 fewer to 5 fewer | 33 treated for an additional beneficial outcome in 1 person, 20 NNTB to 218 NNTB |
| Sitagliptin | 0.74 (0.59, 0.94) | 27 more per 1,000, 18 fewer to 86 more | 37 treated for an additional harmful outcome in 1 person, 54 NNTB to 12 NNTH |
| Tirzepatide | 1.25 (0.95, 1.65) | 10 fewer per 1,000, 87 fewer to 250 more | 97 treated for an additional beneficial outcome in 1 person, 11 NNTB to 4 NNTH |

### 6.2.3. 4-item MACE

**Table 25: Table showing the values calculated for the absolute effects from the baseline risk of 4-item MACE at 26 months (baseline risk = 13.2%)**

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Glimepiride | 1.01 (0.84, 1.22) | 1 more per 1,000, 20 fewer to 27 more | 814 treated for an additional harmful outcome in 1 person, 50 NNTB to 38 NNTH |
| Insulin | 1.05 (0.73, 1.53) | 36 fewer per 1,000, 119 fewer to 416 more | 27 treated for an additional beneficial outcome in 1 person, 8 NNTB to 2 NNTH |
| Linagliptin | 1 (0.88, 1.14) | 0 fewer per 1,000, 15 fewer to 17 more | 1000 treated for an additional beneficial outcome in 1 person, 67 NNTB to 59 NNTH |
| Liraglutide | 0.79 (0.54, 1.19) | 60 fewer per 1,000, 122 fewer to 322 more | 17 treated for an additional beneficial outcome in 1 person, 8 NNTB to 3 NNTH |
| Sitagliptin | 1.16 (0.8, 1.31) | 26 fewer per 1,000, 118 fewer to 446 more | 38 treated for an additional beneficial outcome in 1 person, 8 NNTB to 2 NNTH |
| Tirzepatide | 1.26 (0.46, 1.81) | 10 fewer per 1,000, 114 fewer to 490 more | 101 treated for an additional beneficial outcome in 1 person, 9 NNTB to 2 NNTH |

### 6.2.4. 5-item MACE

**Table 26: Table showing the values calculated for the absolute effects from the baseline risk of 5-item MACE at 25 months (baseline risk = 15.4%)**

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Linagliptin | 1.64 (0.81, 3.45) | 86 more per 1,000, 27 fewer to 284 more | 12 treated for an additional harmful outcome in 1 person, 37 NNTB to 4 NNTH |
| Semaglutide; Oral | 0.82 (0.62, 1.11) | 26 fewer per 1,000, 56 fewer to 15 more | 39 treated for an additional beneficial outcome in 1 person, 18 NNTB to 65 NNTH |
| Semaglutide; Subcutaneous | 0.74 (0.62, 0.89) | 38 fewer per 1,000, 56 fewer to 16 fewer | 27 treated for an additional beneficial outcome in 1 person, 18 NNTB to 64 NNTB |

### 6.2.5. Non-fatal myocardial infarction

**Table 27: Table showing the values calculated for the absolute effects from the baseline risk of non-fatal myocardial infarction at 46 months (baseline risk = 6.8%)**

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Alogliptin | 3.34 (0.28, 99.48) | 133 more per 1,000, 51 fewer to 930 more | 8 treated for an additional harmful outcome in 1 person, 20 NNTB to 1 NNTH |
| Canagliflozin | 0.85 (0.7, 1.04) | 10 fewer per 1,000, 20 fewer to 3 more | 101 treated for an additional beneficial outcome in 1 person, 50 NNTB to 381 NNTH |
| Dapagliflozin | 0.89 (0.78, 1.02) | 7 fewer per 1,000, 15 fewer to 1 more | 138 treated for an additional beneficial outcome in 1 person, 69 NNTB to 762 NNTH |
| Dulaglutide | 0.96 (0.78, 1.16) | 3 fewer per 1,000, 15 fewer to 10 more | 380 treated for an additional beneficial outcome in 1 person, 69 NNTB to 96 NNTH |
| Exenatide | 0.95 (0.83, 1.08) | 3 fewer per 1,000, 11 fewer to 5 more | 304 treated for an additional beneficial outcome in 1 person, 89 NNTB to 191 NNTH |
| Gliclazide | 2.08 (0.18, 28.66) | 70 more per 1,000, 53 fewer to 817 more | 14 treated for an additional harmful outcome in 1 person, 19 NNTB to 1 NNTH |
| Glimepiride | 1.16 (0.84, 1.59) | 10 more per 1,000, 11 fewer to 38 more | 96 treated for an additional harmful outcome in 1 person, 95 NNTB to 26 NNTH |
| Glipizide | 4.76 (0.32, 153.11) | 217 more per 1,000, 46 fewer to 932 more | 5 treated for an additional harmful outcome in 1 person, 22 NNTB to 1 NNTH |
| IDegLira | 1.48 (0.31, 8.25) | 32 more per 1,000, 44 fewer to 343 more | 32 treated for an additional harmful outcome in 1 person, 23 NNTB to 3 NNTH |

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Insulin | 0.97 (0.21, 4.93) | 3 fewer per 1,000, 53 fewer to 195 more | 304 treated for an additional beneficial outcome in 1 person, 19 NNTB to 5 NNTH |
| Linagliptin | 1.15 (0.91, 1.44) | 10 more per 1,000, 6 fewer to 28 more | 102 treated for an additional harmful outcome in 1 person, 169 NNTB to 35 NNTH |
| Liraglutide | 0.88 (0.75, 1.04) | 8 fewer per 1,000, 17 fewer to 3 more | 126 treated for an additional beneficial outcome in 1 person, 60 NNTB to 381 NNTH |
| Lixisenatide | 6.15 (0.15, 689.99) | 261 more per 1,000, 57 fewer to 932 more | 4 treated for an additional harmful outcome in 1 person, 17 NNTB to 1 NNTH |
| Pioglitazone | 0.76 (0.26, 2.1) | 16 fewer per 1,000, 50 fewer to 69 more | 63 treated for an additional beneficial outcome in 1 person, 20 NNTB to 14 NNTH |
| Saxagliptin | 0.95 (0.81, 1.12) | 3 fewer per 1,000, 13 fewer to 8 more | 304 treated for an additional beneficial outcome in 1 person, 80 NNTB to 128 NNTH |
| Semaglutide; Oral | 1.09 (0.7, 1.67) | 6 more per 1,000, 20 fewer to 43 more | 170 treated for an additional harmful outcome in 1 person, 50 NNTB to 23 NNTH |
| Semaglutide; Subcutaneous | 0.73 (0.5, 1.05) | 18 fewer per 1,000, 33 fewer to 3 more | 56 treated for an additional beneficial outcome in 1 person, 30 NNTB to 305 NNTH |
| Sitagliptin | 1.31 (0.3, 5.01) | 18 more per 1,000, 46 fewer to 245 more | 57 treated for an additional harmful outcome in 1 person, 22 NNTB to 4 NNTH |
| Tirzepatide | 8.23 (0.44, 718.07) | 362 more per 1,000, 33 fewer to 932 more | 3 treated for an additional harmful outcome in 1 person, 31 NNTB to 1 NNTH |

### 6.2.6. Non-fatal stroke

**Table 28: Table showing the values calculated for the absolute effects from the baseline risk of non-fatal stroke at 46 months (baseline risk = 3.8%)**

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Canagliflozin | 0.9 (0.71, 1.14) | 4 fewer per 1,000, 11 fewer to 6 more | 268 treated for an additional beneficial outcome in 1 person, 92 NNTB to 179 NNTH |
| Dapagliflozin | 1.01 (0.85, 1.21) | 0 fewer per 1,000, 6 fewer to 8 more | 1000 treated for an additional harmful outcome in 1 person, 178 NNTB to 128 NNTH |

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Dulaglutide | 0.78 (0.63, 0.97) | 8 fewer per 1,000, 14 fewer to 1 fewer | 121 treated for an additional beneficial outcome in 1 person, 72 NNTB to 894 NNTB |
| Empagliflozin | 0.72 (0.04, 13.16) | 10 fewer per 1,000, 36 fewer to 361 more | 95 treated for an additional beneficial outcome in 1 person, 27 NNTB to 3 NNTH |
| Exenatide | 0.86 (0.70, 1.06) | 5 fewer per 1,000, 11 fewer to 2 more | 191 treated for an additional beneficial outcome in 1 person, 89 NNTB to 448 NNTH |
| Gliclazide | 0.09 (0, 3.92) | 35 fewer per 1,000, 38 fewer to 103 more | 29 treated for an additional beneficial outcome in 1 person, 26 NNTB to 10 NNTH |
| Glimepiride | 1.11 (0.73, 1.70) | 4 more per 1,000, 10 fewer to 26 more | 244 treated for an additional harmful outcome in 1 person, 99 NNTB to 39 NNTH |
| IDegLira | 0.45 (0.1, 1.84) | 21 fewer per 1,000, 34 fewer to 31 more | 48 treated for an additional beneficial outcome in 1 person, 29 NNTB to 32 NNTH |
| IGlarLixi | 0.16 (0, 5.58) | 32 fewer per 1,000, 38 fewer to 156 more | 31 treated for an additional beneficial outcome in 1 person, 26 NNTB to 6 NNTH |
| Insulin | 0.26 (0.06, 0.96) | 28 fewer per 1,000, 36 fewer to 1 fewer | 36 treated for an additional beneficial outcome in 1 person, 28 NNTB to 670 NNTH |
| Linagliptin | 0.89 (0.65, 1.23) | 4 fewer per 1,000, 13 fewer to 9 more | 243 treated for an additional beneficial outcome in 1 person, 76 NNTB to 108 NNTH |
| Liraglutide | 0.88 (0.71, 1.09) | 4 fewer per 1,000, 11 fewer to 3 more | 223 treated for an additional beneficial outcome in 1 person, 92 NNTB to 299 NNTH |
| Lixisenatide | 4.31 (0.56, 63.90) | 116 more per 1,000, 17 fewer to 878 more | 9 treated for an additional harmful outcome in 1 person, 60 NNTB to 1 NNTH |
| Pioglitazone | 0.87 (0.2, 3.53) | 5 fewer per 1,000, 30 fewer to 90 more | 206 treated for an additional beneficial outcome in 1 person, 33 NNTB to 11 NNTH |
| Pioglitazone + Exenatide | 0.04 (0, 0.77) | 36 fewer per 1,000, 38 fewer to 9 fewer | 27 treated for an additional beneficial outcome in 1 person, 26 NNTB to 116 NNTB |
| Saxagliptin | 1.11 (0.89, 1.39) | 4 more per 1,000, 4 fewer to 14 more | 244 treated for an additional harmful outcome in 1 person, 243 NNTB to 69 NNTH |
| Semaglutide; Oral | 0.77 (0.41, 1.44) | 9 fewer per 1,000, 22 fewer to 16 more | 116 treated for an additional beneficial outcome in 1 person, 45 NNTB to 62 NNTH |
| Semaglutide; Subcutaneous | 0.62 (0.39, 0.98) | 14 fewer per 1,000, 23 fewer to 1 fewer | 70 treated for an additional beneficial outcome in 1 person, 43 NNTB to 1000 NNTH |

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Sitagliptin | 0.35 (0.06, 1.55) | 25 fewer per 1,000, 36 fewer to 20 more | 41 treated for an additional beneficial outcome in 1 person, 28 NNTB to 49 NNTH |
| Tirzepatide | 0.51 (0.08, 4.61) | 18 fewer per 1,000, 35 fewer to 126 more | 54 treated for an additional beneficial outcome in 1 person, 29 NNTB to 8 NNTH |
| Vildagliptin | 0.33 (0.05, 1.62) | 25 fewer per 1,000, 36 fewer to 23 more | 40 treated for an additional beneficial outcome in 1 person, 28 NNTB to 44 NNTH |

### 6.2.7. Unstable angina

**Table 29: Table showing the values calculated for the absolute effects from the baseline risk of unstable angina at 46 months (baseline risk = 2.7%)**

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Dapagliflozin | 1.02 (0.86, 1.22) | 1 more per 1,000, 4 fewer to 6 more | 1000 treated for an additional harmful outcome in 1 person, 268 NNTB to 171 NNTH |
| Dulaglutide | 1.12 (0.82, 1.5) | 3 more per 1,000, 5 fewer to 13 more | 313 treated for an additional harmful outcome in 1 person, 208 NNTB to 76 NNTH |
| Empagliflozin | 0.12 (0, 4.16) | 24 fewer per 1,000, 27 fewer to 97 more | 42 treated for an additional beneficial outcome in 1 person, 37 NNTB to 10 NNTH |
| Exenatide | 1.14 (0.91, 1.41) | 4 more per 1,000, 2 fewer to 11 more | 269 treated for an additional harmful outcome in 1 person, 417 NNTB to 92 NNTH |
| Glimepiride | 0.97 (0.62, 1.54) | 5 fewer per 1,000, 14 fewer to 12 more | 208 treated for an additional beneficial outcome in 1 person, 70 NNTB to 84 NNTH |
| IDegLira | 4.81 (0.7, 58.8) | 113 more per 1,000, 5 fewer to 785 more | 9 treated for an additional harmful outcome in 1 person, 197 NNTB to 1 NNTH |
| IGlarLixi | 1.26 (0.07, 27.04) | 7 more per 1,000, 25 fewer to 496 more | 145 treated for an additional harmful outcome in 1 person, 40 NNTB to 2 NNTH |
| Insulin | 0.99 (0.45, 2.07) | 5 more per 1,000, 13 fewer to 45 more | 209 treated for an additional harmful outcome in 1 person, 76 NNTB to 22 NNTH |
| Linagliptin | 0.97 (0.67, 1.4) | 3 fewer per 1,000, 11 fewer to 9 more | 312 treated for an additional beneficial outcome in 1 person, 89 NNTB to 111 NNTH |

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Liraglutide | 0.94 (0.73, 1.19) | 1 fewer per 1,000, 7 fewer to 6 more | 938 treated for an additional beneficial outcome in 1 person, 150 NNTB to 164 NNTH |
| Lixisenatide | 0.21 (0, 8.7) | 20 fewer per 1,000, 27 fewer to 171 more | 49 treated for an additional beneficial outcome in 1 person, 37 NNTB to 6 NNTH |
| Metformin type unspecified | 0.39 (0, 40.73) | 15 fewer per 1,000, 27 fewer to 679 more | 68 treated for an additional beneficial outcome in 1 person, 37 NNTB to 1 NNTH |
| Pioglitazone | 13.82 (0.47, 1063.29) | 309 more per 1,000, 12 fewer to 973 more | 3 treated for an additional harmful outcome in 1 person, 83 NNTB to 1 NNTH |
| Saxagliptin | 1.19 (0.88, 1.59) | 5 more per 1,000, 3 fewer to 16 more | 198 treated for an additional harmful outcome in 1 person, 312 NNTB to 64 NNTH |
| Semaglutide; Oral | 1.86 (0.82, 4.18) | 24 more per 1,000, 4 fewer to 86 more | 41 treated for an additional harmful outcome in 1 person, 234 NNTB to 12 NNTH |
| Semaglutide; Subcutaneous | 0.83 (0.48, 1.39) | 5 fewer per 1,000, 14 fewer to 12 more | 220 treated for an additional beneficial outcome in 1 person, 72 NNTB to 86 NNTH |
| Sitagliptin | 1.29 (0.64, 2.52) | 14 more per 1,000, 7 fewer to 62 more | 70 treated for an additional harmful outcome in 1 person, 139 NNTB to 16 NNTH |

### 6.2.8. Hospitalisation for heart failure

**Table 30: Table showing the values calculated for the absolute effects from the baseline risk of hospitalisation for heart failure (base case analysis) at 46 months (baseline risk = 5.3%)**

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Alogliptin | 6.53 (0.31, 721.77) | 246 more per 1,000, 36 fewer to 947 more | 4 treated for an additional harmful outcome in 1 person, 28 NNTB to 1 NNTH |
| Canagliflozin | 0.67 (0.52, 0.87) | 17 fewer per 1,000, 25 fewer to 7 fewer | 58 treated for an additional beneficial outcome in 1 person, 40 NNTB to 149 NNTB |
| Dapagliflozin | 0.73 (0.61, 0.88) | 14 fewer per 1,000, 20 fewer to 6 fewer | 71 treated for an additional beneficial outcome in 1 person, 49 NNTB to 161 NNTB |
| Dapagliflozin + Saxagliptin | 0.2 (0, 7.42) | 42 fewer per 1,000, 53 fewer to 279 more | 24 treated for an additional beneficial outcome in 1 person, 19 NNTB to 4 NNTH |

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Dulaglutide | 0.93 (0.77, 1.12) | 4 fewer per 1,000, 12 fewer to 6 more | 276 treated for an additional beneficial outcome in 1 person, 84 NNTB to 162 NNTH |
| Empagliflozin | 0.45 (0.03, 5.1) | 29 fewer per 1,000, 51 fewer to 189 more | 35 treated for an additional beneficial outcome in 1 person, 19 NNTB to 5 NNTH |
| Exenatide | 0.94 (0.79, 1.14) | 3 fewer per 1,000, 11 fewer to 7 more | 323 treated for an additional beneficial outcome in 1 person, 92 NNTB to 139 NNTH |
| Glimepiride | 0.75 (0.54, 1.04) | 13 fewer per 1,000, 24 fewer to 2 more | 77 treated for an additional beneficial outcome in 1 person, 42 NNTB to 485 NNTH |
| IDegLira | 0.76 (0.05, 8.02) | 12 fewer per 1,000, 50 fewer to 301 more | 80 treated for an additional beneficial outcome in 1 person, 20 NNTB to 3 NNTH |
| IGlarLixi | 0.14 (0, 3.33) | 45 fewer per 1,000, 53 fewer to 113 more | 22 treated for an additional beneficial outcome in 1 person, 19 NNTB to 9 NNTH |
| Insulin | 1.7 (0.77, 3.65) | 35 more per 1,000, 12 fewer to 127 more | 28 treated for an additional harmful outcome in 1 person, 84 NNTB to 8 NNTH |
| Linagliptin | 0.9 (0.75, 1.08) | 5 fewer per 1,000, 13 fewer to 4 more | 193 treated for an additional beneficial outcome in 1 person, 77 NNTB to 243 NNTH |
| Liraglutide | 0.87 (0.73, 1.04) | 7 fewer per 1,000, 14 fewer to 2 more | 149 treated for an additional beneficial outcome in 1 person, 71 NNTB to 485 NNTH |
| Lixisenatide | 0.21 (0, 5.81) | 42 fewer per 1,000, 53 fewer to 218 more | 24 treated for an additional beneficial outcome in 1 person, 19 NNTB to 5 NNTH |
| Metformin (type unspecified) | 0.75 (0.15, 3.27) | 13 fewer per 1,000, 45 fewer to 110 more | 77 treated for an additional beneficial outcome in 1 person, 22 NNTB to 9 NNTH |
| Pioglitazone | 2.1 (0.57, 9.49) | 55 more per 1,000, 22 fewer to 351 more | 18 treated for an additional harmful outcome in 1 person, 45 NNTB to 3 NNTH |
| Saxagliptin | 1.27 (1.07, 1.52) | 14 more per 1,000, 4 more to 26 more | 72 treated for an additional harmful outcome in 1 person, 278 NNTH to 38 NNTH |
| Semaglutide; Oral | 0.91 (0.54, 1.54) | 5 fewer per 1,000, 24 fewer to 27 more | 215 treated for an additional beneficial outcome in 1 person, 42 NNTB to 36 NNTH |
| Semaglutide; Subcutaneous | 1.08 (0.75, 1.54) | 4 more per 1,000, 13 fewer to 27 more | 243 treated for an additional harmful outcome in 1 person, 77 NNTB to 36 NNTH |
| Sitagliptin | 1.92 (1.08, 3.53) | 46 more per 1,000, 4 more to 122 more | 22 treated for an additional harmful outcome in 1 person, 243 NNTH to 8 NNTH |

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Tirzepatide | 4.5 (0.11, 403.27) | 164 more per 1,000, 47 fewer to 947 more | 6 treated for an additional harmful outcome in 1 person, 21 NNTB to 1 NNTH |

### 6.2.9. Development of end-stage renal failure

**Table 31: Table showing the values calculated for the absolute effects from the baseline risk of development of end-stage renal failure at 38 months (baseline risk = 0.9%)**

| Intervention compared to placebo | Hazard ratio | Absolute effect per 1000 people | Number needed to treat per 1000 people |
|---|---|---|---|
| Canagliflozin | 0.77 (0.31, 1.96) | 2 fewer per 1,000, 6 fewer to 9 more | 485 treated for an additional beneficial outcome in 1 person, 161 NNTB to 117 NNTH |
| Dapagliflozin | 0.35 (0.15, 0.83) | 6 fewer per 1,000, 8 fewer to 2 fewer | 171 treated for an additional beneficial outcome in 1 person, 131 NNTB to 656 NNTB |
| Dulaglutide | 0.5 (0.11, 1.87) | 4 fewer per 1,000, 8 fewer to 8 more | 223 treated for an additional beneficial outcome in 1 person, 125 NNTB to 129 NNTH |
| Exenatide | 0.86 (0.59, 1.2) | 1 fewer per 1,000, 4 fewer to 2 more | 797 treated for an additional beneficial outcome in 1 person, 272 NNTB to 559 NNTH |
| Linagliptin | 0.98 (0.68, 1.39) | 0 fewer per 1,000, 3 fewer to 3 more | 1000 treated for an additional beneficial outcome in 1 person, 348 NNTB to 287 NNTH |
| Liraglutide | 0.89 (0.62, 1.24) | 1 fewer per 1,000, 3 fewer to 2 more | 1000 treated for an additional beneficial outcome in 1 person, 293 NNTB to 466 NNTH |
| Saxagliptin | 0.9 (0.62, 1.32) | 1 fewer per 1,000, 3 fewer to 3 more | 1000 treated for an additional beneficial outcome in 1 person, 293 NNTB to 349 NNTH |

## 6.3. Rank tables

### 6.3.1. Cardiovascular mortality

**Table 32: Median rankings for each treatment with 95% credible intervals for cardiovascular mortality using the base case analysis.**

| Treatment | Median ranking (95% credibility interval) |
|---|---|
| Placebo | 16 (12 to 21) |

| Treatment | Median ranking (95% credibility interval) |
|---|---|
| Alogliptin | 26 (6 to 30) |
| Canagliflozin | 12 (7 to 20) |
| Dapagliflozin | 16 (9 to 23) |
| Dapagliflozin + Exenatide | 11 (1 to 28) |
| Dapagliflozin + Saxagliptin | 3 (1 to 25) |
| Dulaglutide | 13 (8 to 20) |
| Empagliflozin | 27 (5 to 30) |
| Empagliflozin + Linagliptin | 29 (4 to 30) |
| Ertugliflozin | 24 (3 to 30) |
| Ertugliflozin + Sitagliptin | 4 (1 to 29) |
| Exenatide | 12 (7 to 18) |
| Gliclazide | 28 (3 to 30) |
| Glimepiride | 16 (8 to 23) |
| Glipizide | 28 (20 to 30) |
| IDegLira | 6 (2 to 25) |
| Insulin | 21(8 to 26) |
| Insulin glargine/Lixisenatide | 5 (1 to 25) |
| Linagliptin | 16 (9 to 22) |
| Liraglutide | 9 (5 to 14) |
| Lixisenatide | 8 (2 to 26) |
| Metformin type unspecified | 23 (3 to 29) |
| Pioglitazone | 16 (2 to 28) |
| Pioglitazone + Alogliptin | 2 (1 to 27) |
| Saxagliptin | 17 (10 to 23) |
| Semaglutide; Oral | 6 (3 to 13.03) |
| Semaglutide; Subcutaneous | 14 (6 to 23) |
| Sitagliptin | 20 (9 to 25) |
| Tirzepatide | 22 (4 to 28) |
| Vildagliptin | 20 (3 to 28) |

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### 6.3.2. 3-item MACE

**Table 33: Median rankings for each treatment with 95% credible intervals for 3-item MACE using the base case analysis.**

| Treatment | Median rankings (95% credibility intervals) |
|---|---|
| Placebo | 10 (8 to 13) |
| Canagliflozin | 4 (2 to 10) |
| Dapagliflozin | 7 (3 to 12) |
| Dulaglutide | 5 (2 to 10) |
| Exenatide | 6 (3 to 11) |
| Glimepiride | 12 (5 to 15) |
| IDegLira | 15 (1 to 16) |
| Insulin | 13 (2 to 16) |
| Linagliptin | 11 (6 to 14) |
| Liraglutide | 5 (2 to 9) |
| Pioglitazone | 15 (3 to 16) |
| Saxagliptin | 10 (5 to 14) |
| Semaglutide; Oral | 3 (1 to 12) |
| Semaglutide; Subcutaneous | 2 (1 to 8) |
| Sitagliptin | 14 (5 to 16) |
| Tirzepatide | 7 (1 to 16) |

### 6.3.3. 4-item MACE

**Table 34: Median rankings for each treatment with 95% credible intervals for 4-item MACE using the base-case analysis.**

| Treatment | Median ranking (95% credible interval) |
|---|---|
| Placebo | 5 (1 to 7) |
| Glimepiride | 5 (1 to 7) |
| Insulin | 3 (2 to 7) |
| Linagliptin | 5 (1 to 7) |
| Liraglutide | 1 (1 to 5) |
| Sitagliptin | 4 (2 to 7) |
| Tirzepatide | 4 (1 to 7) |

### 6.3.4. 5-item MACE

**Table 35: Median rankings for each treatment with 95% credible intervals for 5-item MACE.**

| Treatment | Median ranking (95% credible interval) |
|---|---|
| Placebo | 3 (2 to 4) |

| Treatment | Median ranking (95% credible interval) |
|---|---|
| Linagliptin | 4 (2 to 4) |
| Semaglutide; Oral | 2 (1 to 3) |
| Semaglutide; Subcutaneous | 1 (1 to 2) |

### 6.3.5. Non-fatal myocardial infarction

**Table 36: Median rankings for each treatment with 95% credible intervals for non-fatal myocardial infarction.**

| Treatment | Median rankings (95% credibility interval) |
|---|---|
| Placebo | 10 (7 to 14) |
| Alogliptin | 17 (1 to 20) |
| Canagliflozin | 5 (2 to 12) |
| Dapagliflozin | 6 (2 to 12) |
| Dulaglutide | 9 (3 to 14) |
| Exenatide | 8 (3 to 13) |
| Gliclazide | 16 (1 to 20) |
| Glimepiride | 13 (5 to 17) |
| Glipizide | 18 (1 to 20) |
| IDegLira | 15 (1 to 19) |
| Insulin | 10 (1 to 18) |
| Linagliptin | 13 (7 to 17) |
| Liraglutide | 6 (2 to 12) |
| Lixisenatide | 18 (1 to 20) |
| Pioglitazone | 3 (1 to 17) |
| Saxagliptin | 8 (3 to 14) |
| Semaglutide; Oral | 12 (2 to 17) |
| Semaglutide; Subcutaneous | 3 (1 to 11) |
| Sitagliptin | 15 (1 to 19) |
| Tirzepatide | 19 (1 to 20) |

### 6.3.6. Non-fatal stroke

**Table 37: Median rankings for each treatment with 95% credible intervals for non-fatal stroke.**

| Treatment | Median rank (95% credible intervals) |
|---|---|
| Placebo | 17 (13 to 20) |
| Canagliflozin | 14 (8 to 20) |
| Dapagliflozin | 17 (11 to 21) |
| Dulaglutide | 11 (7 to 16) |

| Treatment | Median rank (95% credible intervals) |
|---|---|
| Empagliflozin | 10 (2 to 22) |
| Exenatide | 13 (8 to 18) |
| Gliclazide | 2 (1 to 21) |
| Glimepiride | 18 (10 to 21) |
| IDegLira | 7 (2 to 21) |
| Insulin | 5 (2 to 16) |
| Insulin glargine/Lixisenatide | 3 (1 to 21) |
| Linagliptin | 14 (8 to 20) |
| Liraglutide | 13 (8 to 19) |
| Lixisenatide | 22 (8 to 22) |
| Pioglitazone | 13 (4 to 22) |
| Pioglitazone + Exenatide | 2 (1 to 16) |
| Saxagliptin | 18 (13 to 21) |
| Semaglutide; Oral | 11 (6 to 21) |
| Semaglutide; Subcutaneous | 9 (5 to 16) |
| Sitagliptin | 6 (2 to 20) |
| Tirzepatide | 8 (2 to 22) |
| Vildagliptin | 6 (2 to 20) |

### 6.3.7. Unstable angina

**Table 38: Median rankings for each treatment with 95% credible intervals for unstable angina using the base case analysis.**

| Treatment | Median ranking (95% credible interval) |
|---|---|
| Placebo | 8 (5 to 12) |
| Dapagliflozin | 9 (4 to 13) |
| Dulaglutide | 11 (4 to 15) |
| Empagliflozin | 2 (1 to 17) |
| Exenatide | 11 (6 to 15) |
| Glimepiride | 5 (2 to 14) |
| IDegLira | 17 (5 to 18) |
| Insulin | 11 (3 to 16) |
| Insulin glargine/Lixisenatide | 13 (1 to 18) |
| Linagliptin | 6 (3 to 13) |
| Liraglutide | 7 (3 to 13) |
| Lixisenatide | 2 (1 to 17) |
| Metformin type unspecified | 3 (1 to 18) |
| Pioglitazone | 18 (4 to 18) |
| Saxagliptin | 12 (5 to 15) |
| Semaglutide; Oral | 15 (6 to 17) |
| Semaglutide; Subcutaneous | 5 (2 to 14) |

| Treatment | Median ranking (95% credible interval) |
|---|---|
| Sitagliptin | 14 (4 to 17) |

### 6.3.8. Hospitalisation for heart failure

**Table 39: Median rankings for each treatment with 95% credible intervals for hospitalisation for heart failure using the base case analysis.**

| Treatment | Median rankings (95% credible intervals) |
|---|---|
| Placebo | 13 (10 to 16) |
| Alogliptin | 21 (3 to 22) |
| Canagliflozin | 6 (3 to 10) |
| Dapagliflozin | 7 (4 to 11) |
| Dapagliflozin + Saxagliptin | 3 (1 to 21) |
| Dulaglutide | 11 (7 to 16) |
| Empagliflozin | 4 (1 to 21) |
| Exenatide | 12 (7 to 16) |
| Glimepiride | 7 (3 to 14) |
| IDegLira | 7 (1 to 22) |
| Insulin | 18 (9 to 21) |
| Insulin glargine/Lixisenatide | 2 (1 to 20) |
| Linagliptin | 11 (7 to 16) |
| Liraglutide | 10 (6 to 15) |
| Lixisenatide | 3 (1 to 21) |
| Metformin type unspecified | 7 (2 to 21) |
| Pioglitazone | 19 (5 to 22) |
| Saxagliptin | 16 (13 to 19) |
| Semaglutide; Oral | 11 (4 to 18) |
| Semaglutide; Subcutaneous | 15 (7 to 19) |
| Sitagliptin | 19 (15 to 21) |
| Tirzepatide | 21 (2 to 22) |

### 6.3.9. Development of end-stage renal failure

**Table 40: Median rankings for each treatment with 95% credible intervals for development of end-stage renal failure.**

| Treatment | Median ranking (95% credible interval) |
|---|---|
| Placebo | 6 (4 to 8) |
| Canagliflozin | 3 (1 to 8) |

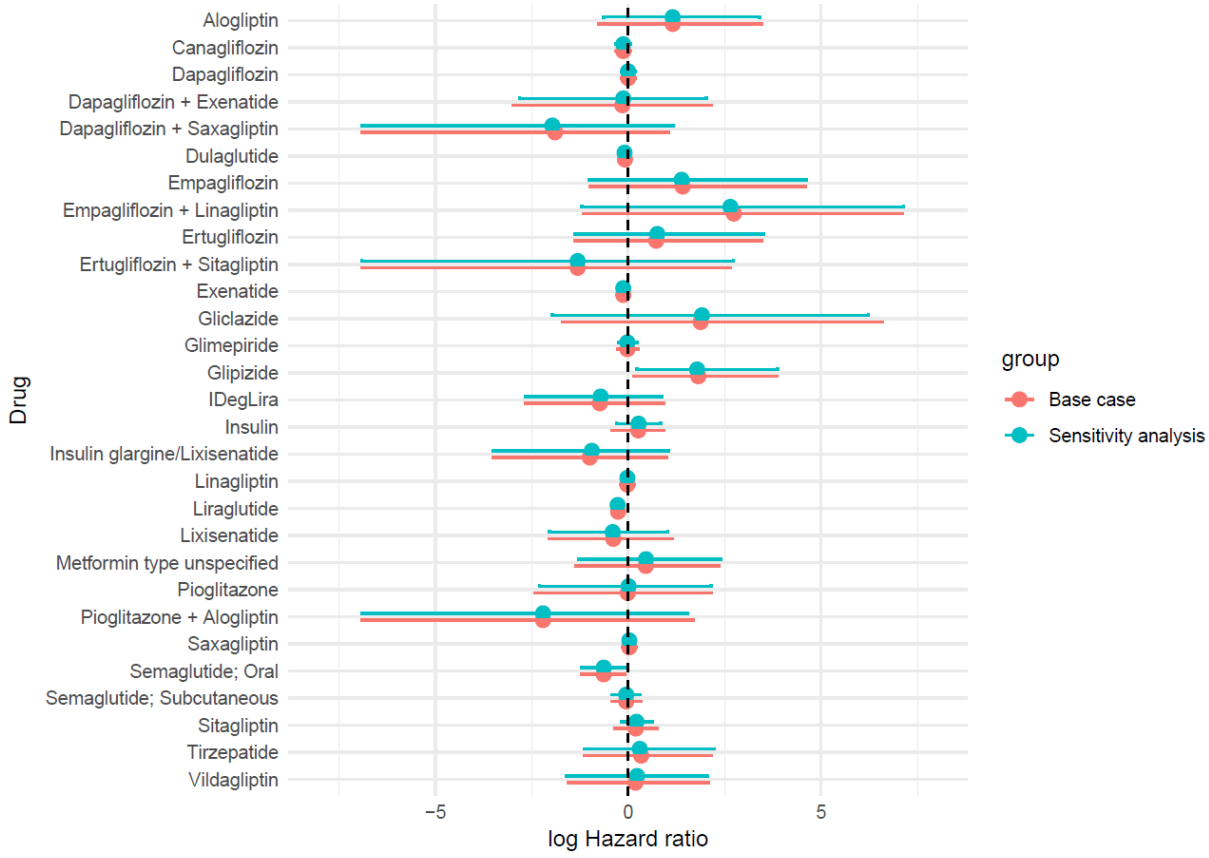
| Treatment | Median ranking (95% credible interval) |
|---|---|
| Dapagliflozin | 1 (1 to 4) |
| Dulaglutide | 2 (1 to 8) |
| Exenatide | 4 (2 to 8) |
| Linagliptin | 6 (3 to 8) |
| Liraglutide | 5 (2 to 8) |
| Saxagliptin | 5 (2 to 8) |

1
2

# 6.4. Relative effectiveness plots

## 6.4.1. Cardiovascular mortality

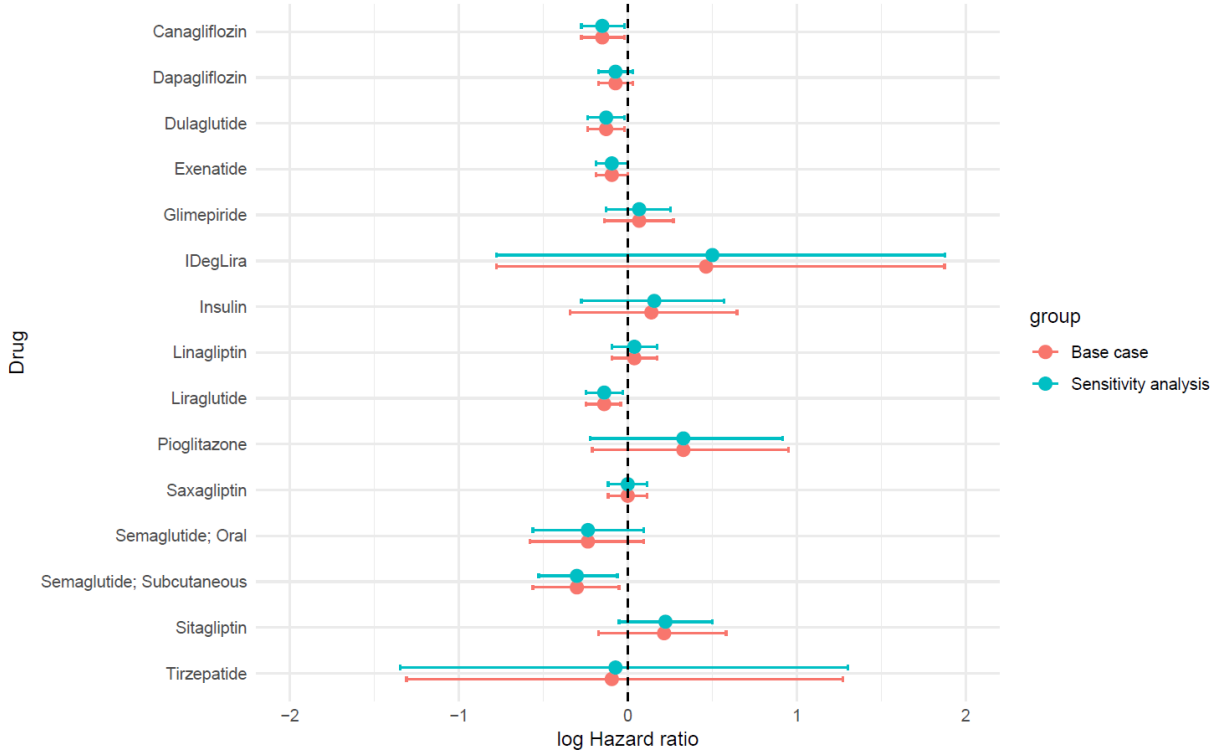
**Figure 28: Log hazard ratios of all treatments compared with placebo for cardiovascular mortality showing the base case analysis results compared to sensitivity analysis results. Circles indicate the log HR, and lines indicate 95% credible intervals.**




**Favours treatment** **Favours placebo**

### 6.4.2. 3-item MACE

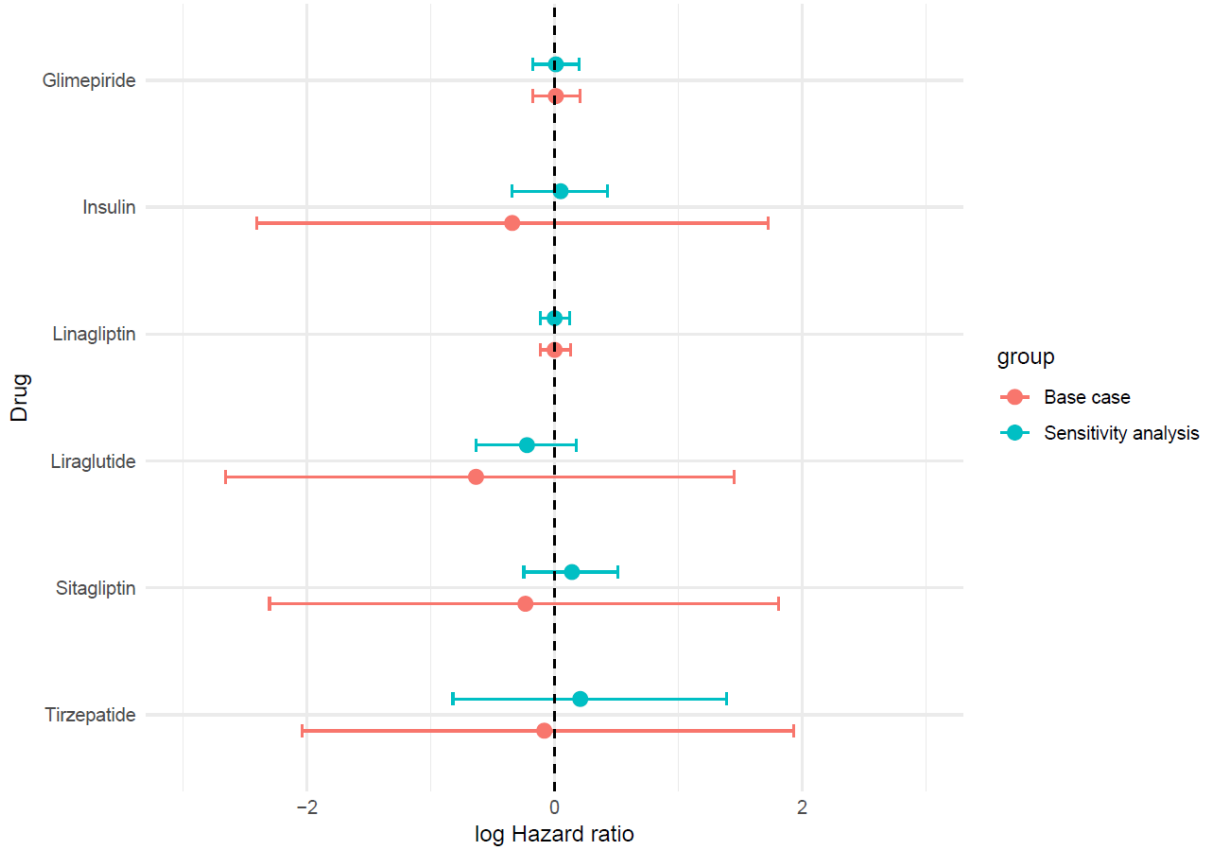
**Figure 29: Log hazard ratios of all treatments compared with placebo for 3-item MACE showing the base case analysis results compared to the sensitivity analysis results. Circles indicate the log HR, and lines indicate 95% credible intervals.**




**Favours treatment** **Favours placebo**

### 6.4.3. 4-item MACE

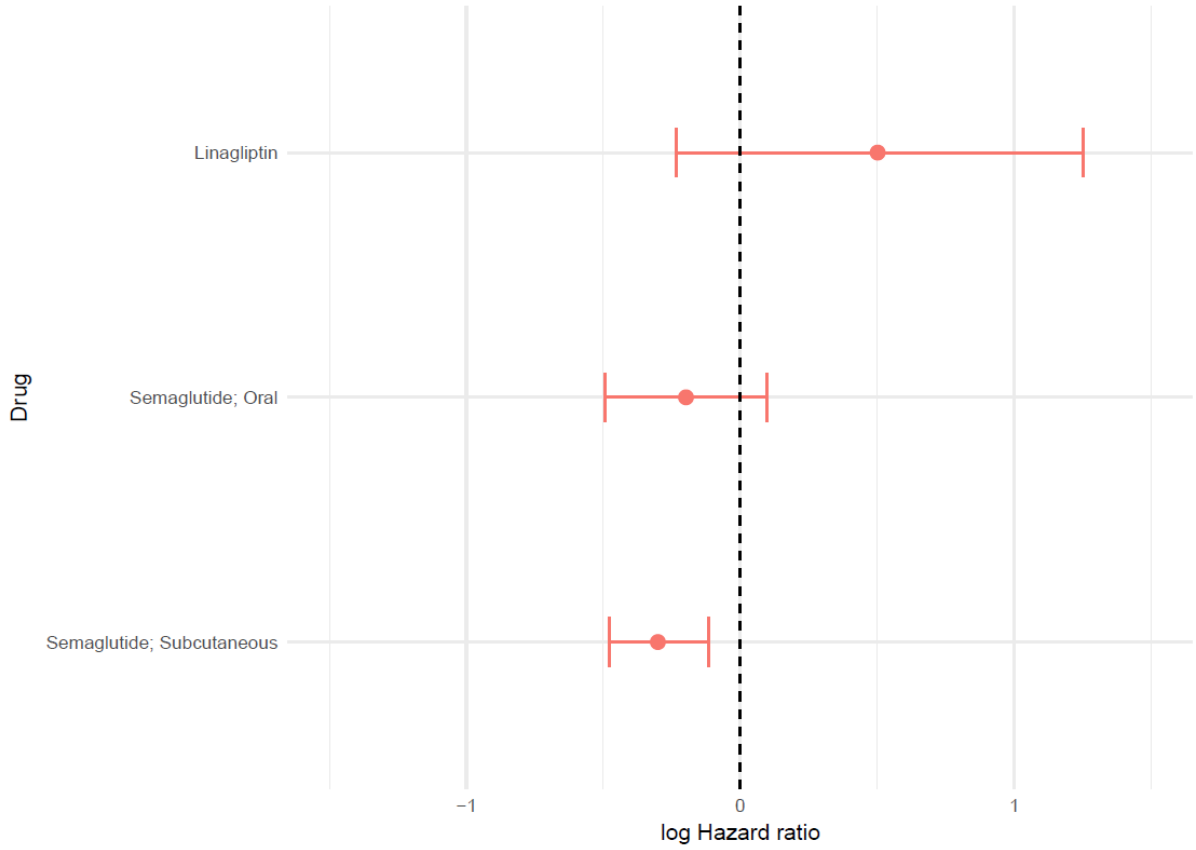
**Figure 30: Log hazard ratios of all treatments compared with placebo for 4-item MACE showing the base case analysis results compared to the sensitivity analysis results. Circles indicate the log HR, and lines indicate 95% credible intervals.**




**Favours treatment** **Favours placebo**

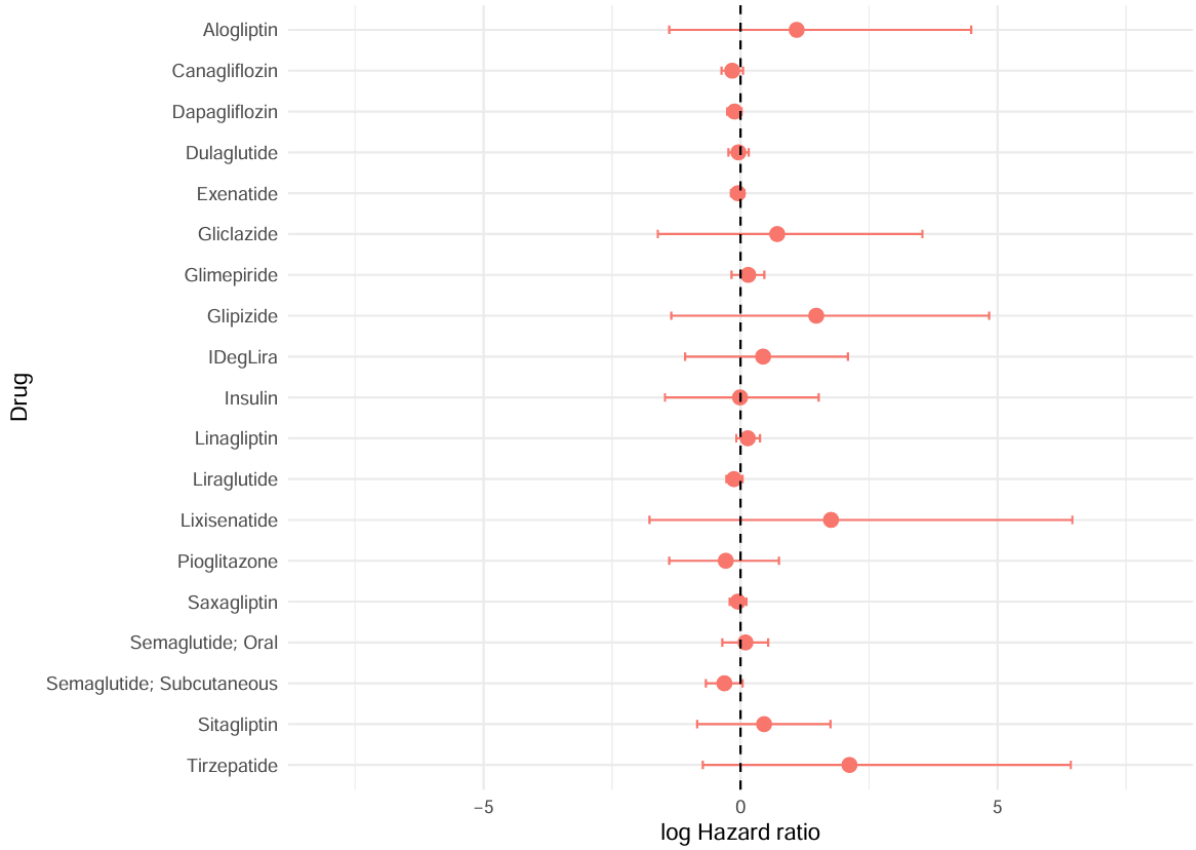
### 6.4.4. 5-item MACE

**Figure 31: Log hazard ratios of all treatments compared with placebo for 5-item MACE. Circles indicate the log HR, and lines indicate 95% credible intervals.**



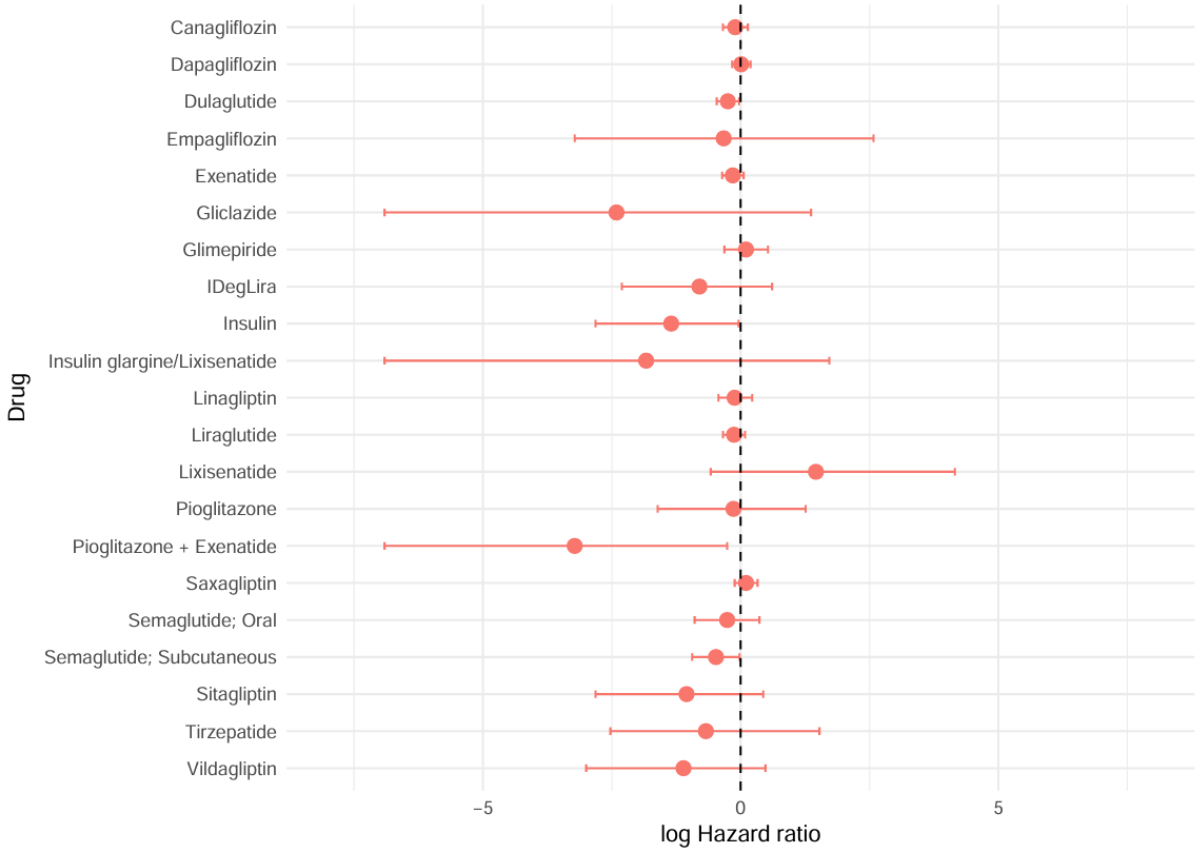
### 6.4.5. Non-fatal myocardial infarction

**Figure 32: Log hazard ratios of all treatments compared with placebo for non-fatal myocardial infarction. Circles indicate the log HR, and lines indicate 95% credible intervals.**



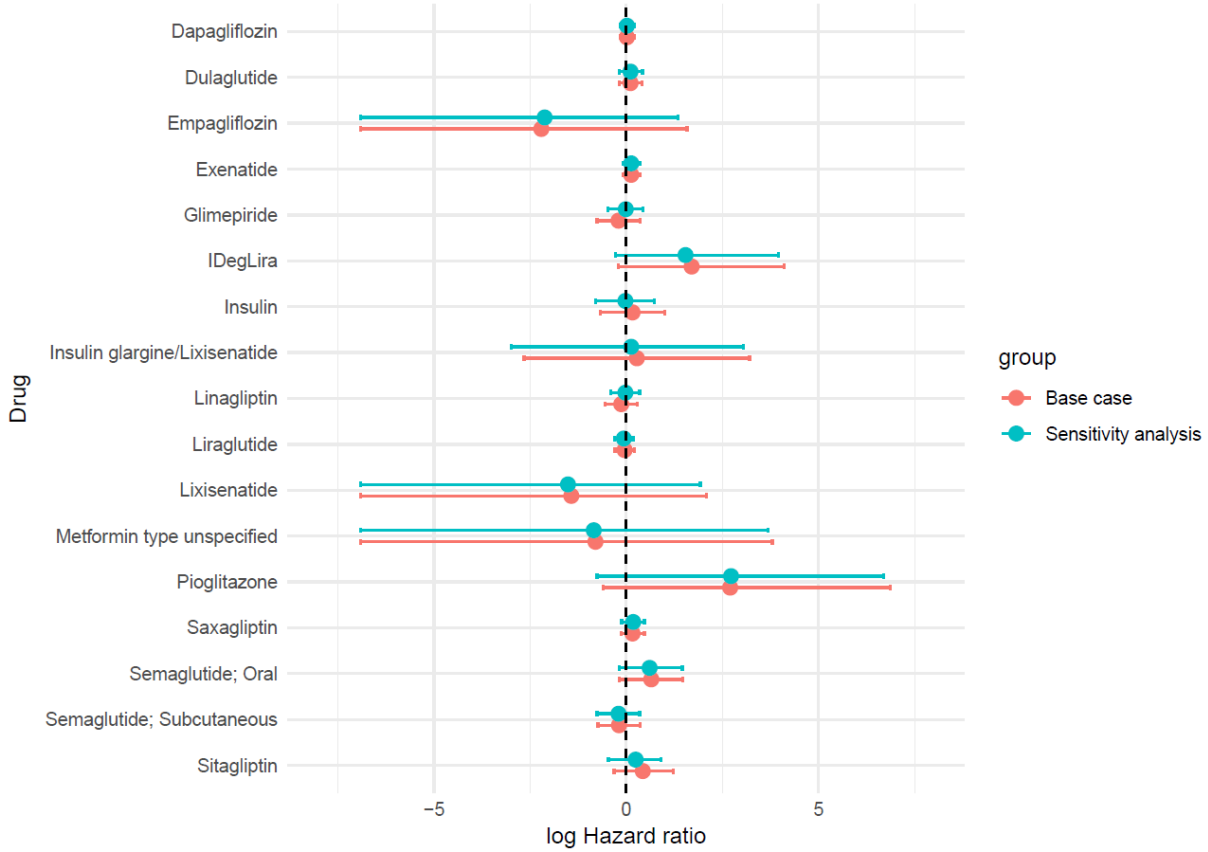
### 6.4.6. Non-fatal stroke

**Figure 33: Log hazard ratios of all treatments compared with placebo for non-fatal stroke. Circles indicate the log HR, and lines indicate 95% credible intervals.**



### 6.4.7. Unstable angina

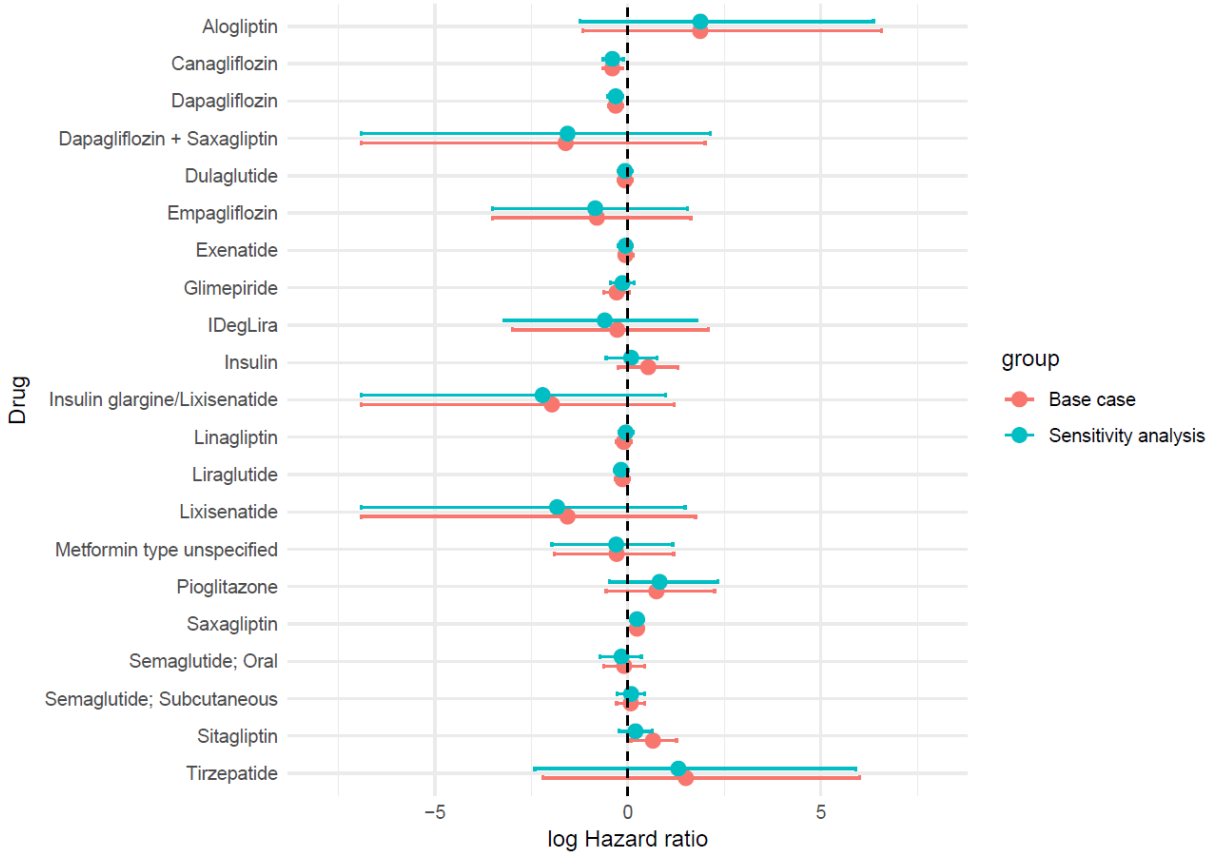
**Figure 34: Log hazard ratios of all treatments compared with placebo for unstable angina showing the base case analysis results compared to the sensitivity analysis results. Circles indicate the log HR, and lines indicate 95% credible intervals.**




**Favours treatment** **Favours placebo**

### 6.4.8. Hospitalisation for heart failure

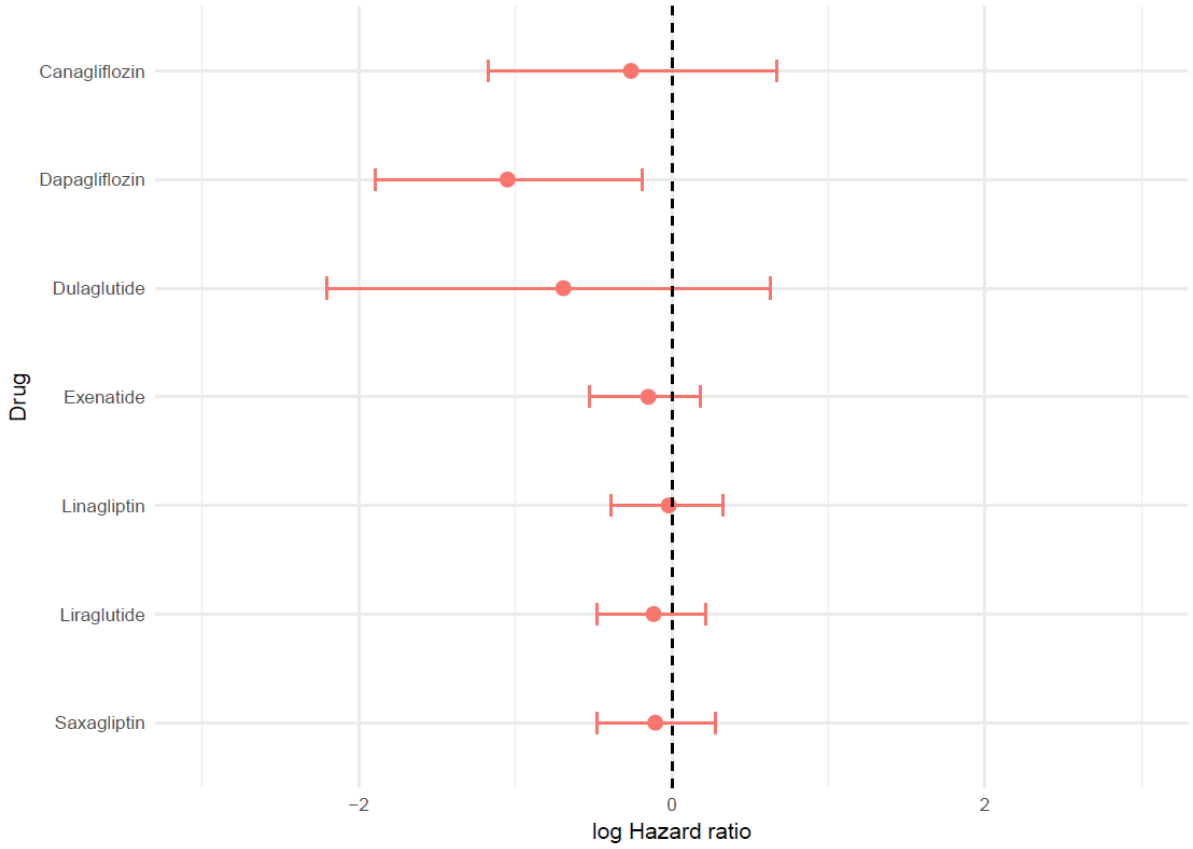
**Figure 35: Log hazard ratios of all treatments compared with placebo for hospitalisation for heart failure showing the base case analysis results compared to the sensitivity analysis results. Circles indicate the log HR, and lines indicate 95% credible intervals.**




**Favours treatment** **Favours placebo**

### 6.4.9. Development of end-stage renal failure

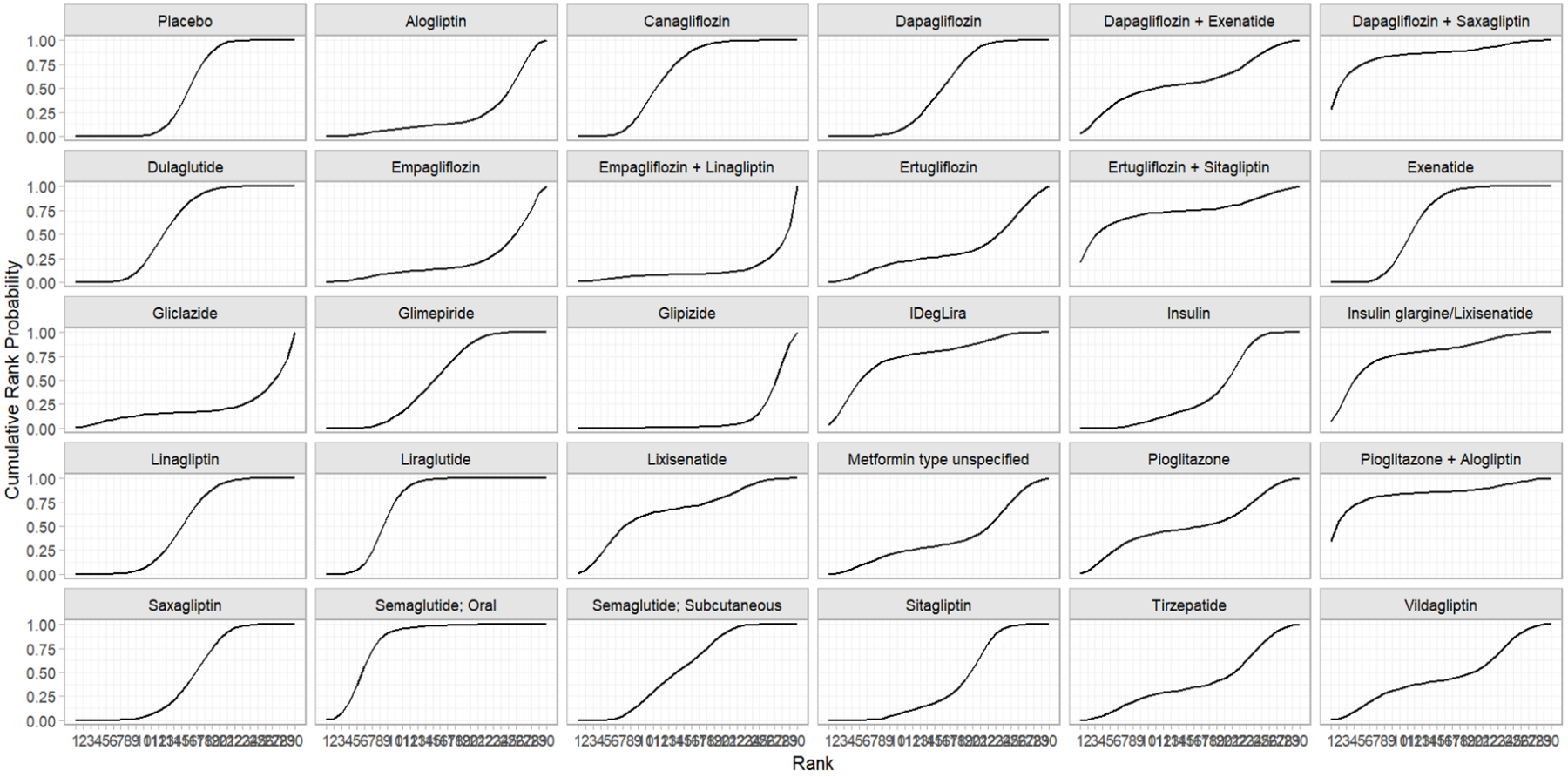
**Figure 36: Log hazard ratios of all treatments compared with placebo for development of end-stage renal failure. Circles indicate the log HR, and lines indicate 95% credible intervals.**



## 6.5. Cumulative ranking probability plots

### 6.5.1. Cardiovascular mortality

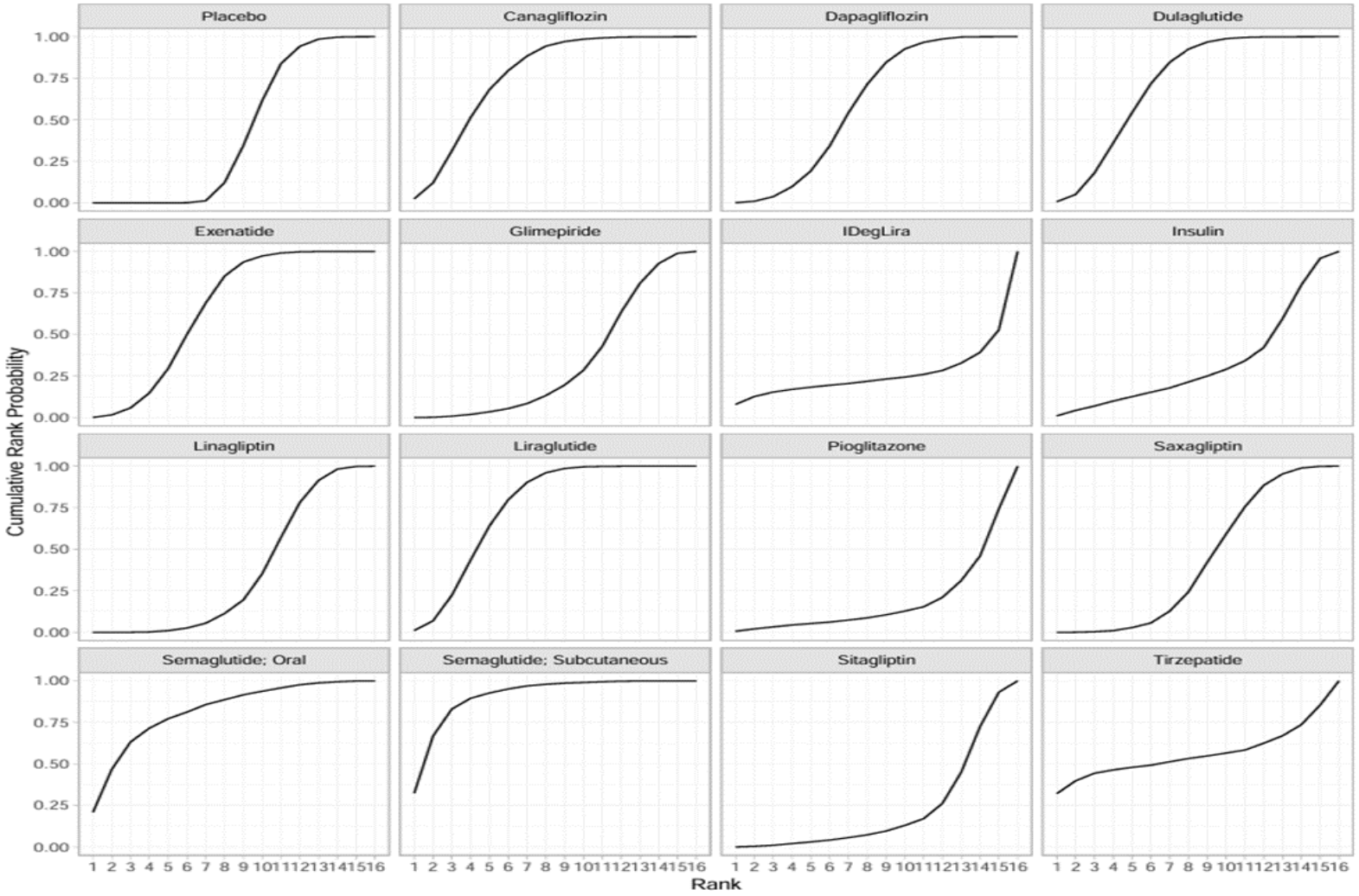
**Figure 37: Cumulative ranking probability plots for cardiovascular mortality using the base case analysis. Treatments with the largest area under the curve rank the best across the range of rankings.**


Placebo
Alogliptin
Canagliflozin
Dapagliflozin
Dapagliflozin + Exenatide
Dapagliflozin + Saxagliptin
Dulaglutide
Empagliflozin
Empagliflozin + Linagliptin
Ertugliflozin
Ertugliflozin + Sitagliptin
Exenatide
Gliclazide
Glimepiride
Glipizide
IDegLira
Insulin
Insulin glargine/Lixisenatide
Linagliptin
Liraglutide
Lixisenatide
Metformin type unspecified
Pioglitazone
Pioglitazone + Alogliptin
Saxagliptin
Semaglutide; Oral
Semaglutide; Subcutaneous
Sitagliptin
Tirzepatide
Vildagliptin
Cumulative Rank Probability
0.00
0.25
0.50
0.75
1.00
Rank

1

### 6.5.2. 3-item MACE

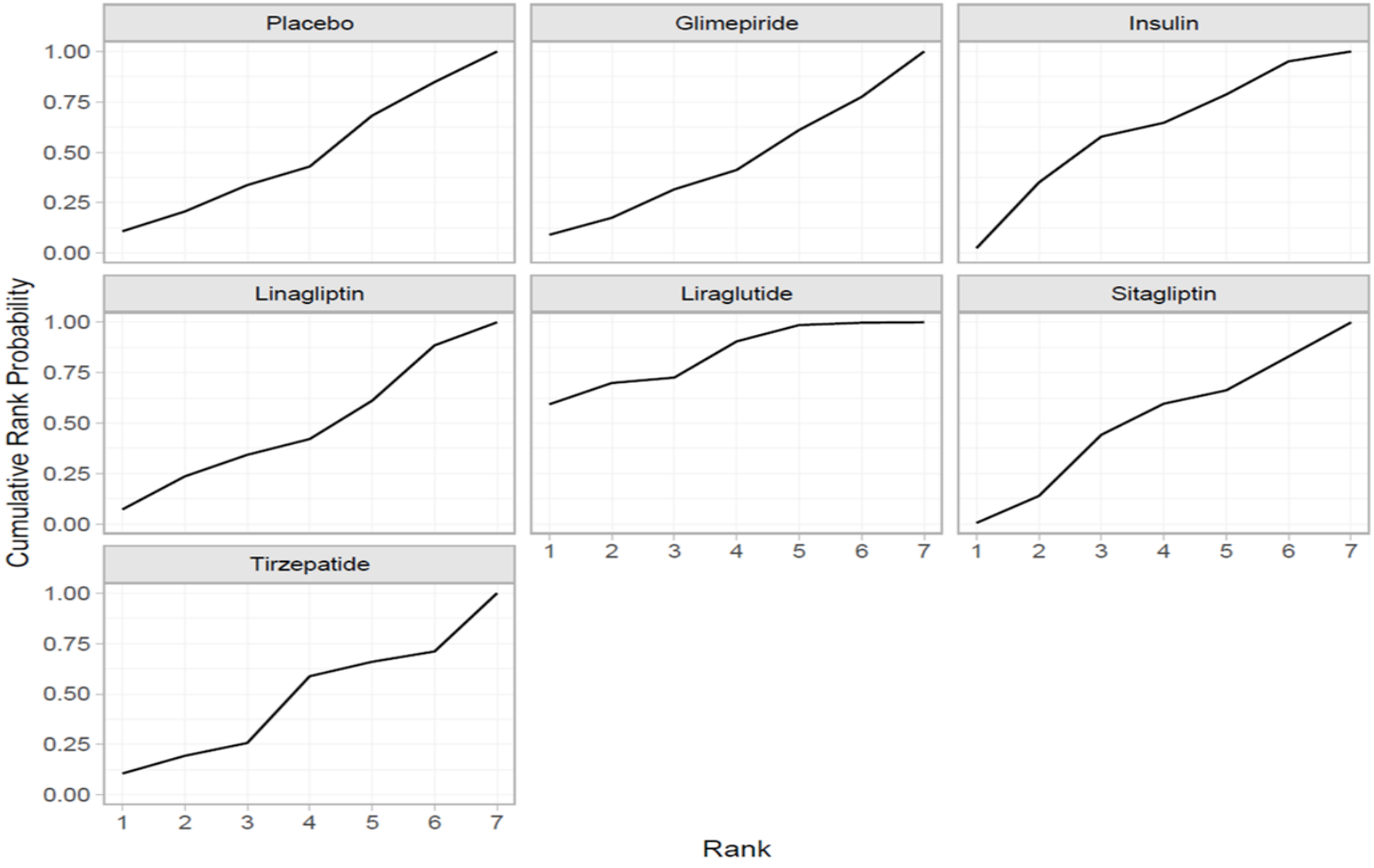
**Figure 38: Cumulative ranking probability plots for 3-item MACE using the base case analysis. Treatments with the largest area under the curve rank the best across the range of rankings.**


Placebo
Canagliflozin
Dapagliflozin
Dulaglutide
Exenatide
Glimepiride
IDegLira
Insulin
Linagliptin
Liraglutide
Pioglitazone
Saxagliptin
Semaglutide; Oral
Semaglutide; Subcutaneous
Sitagliptin
Tirzepatide
Cumulative Rank Probability
0.00
0.25
0.50
0.75
1.00
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Rank

1

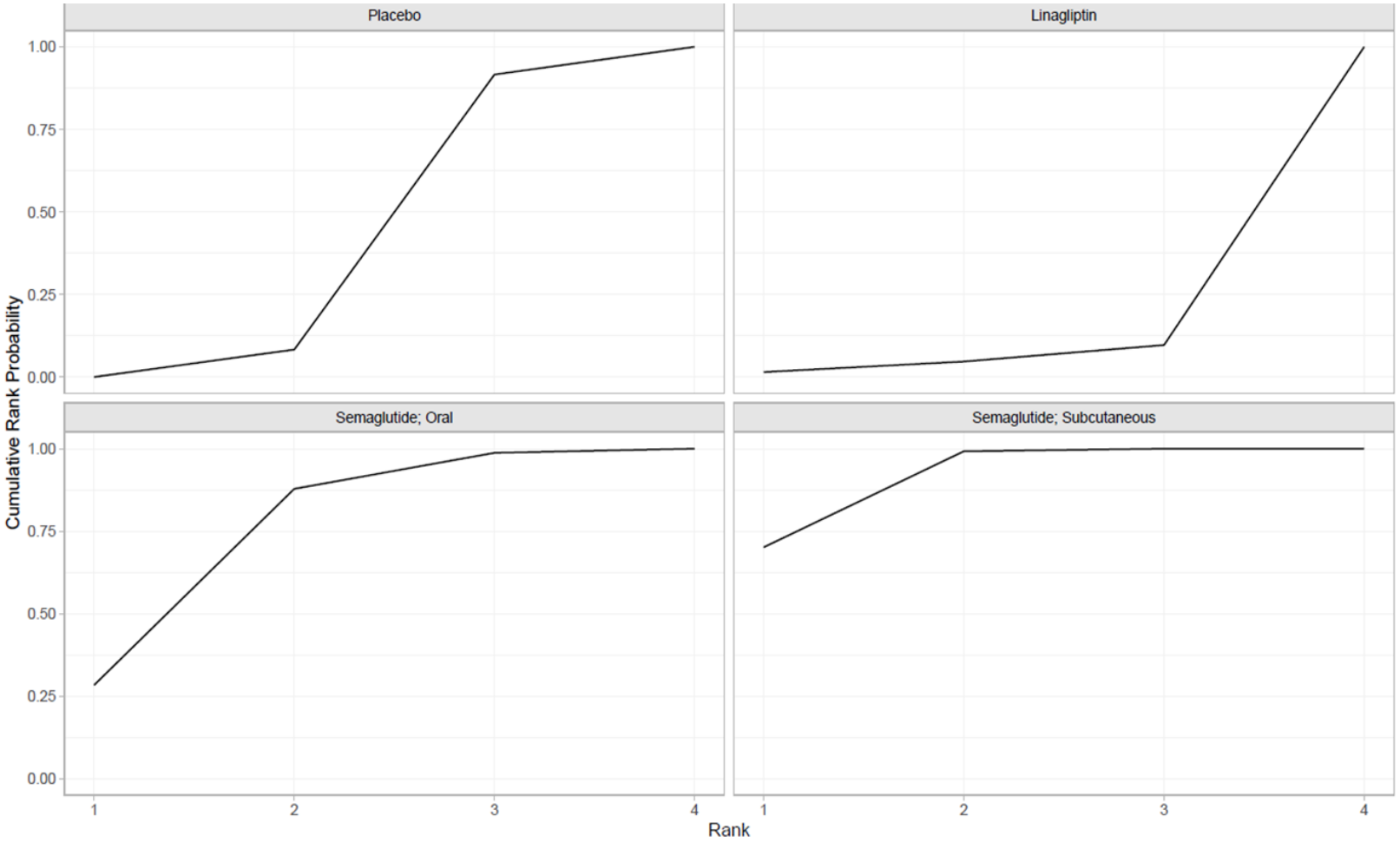
### 6.5.3. 4-item MACE

**Figure 39: Cumulative ranking probability plots for 4-item MACE using the base case analysis. Treatments with the largest area under the curve rank the best across the range of rankings.**


Placebo
Glimepiride
Insulin
Linagliptin
Liraglutide
Sitagliptin
Tirzepatide
Cumulative Rank Probability
0.00
0.25
0.50
0.75
1.00
1
2
3
4
5
6
7
Rank

### 6.5.4. 5-item MACE

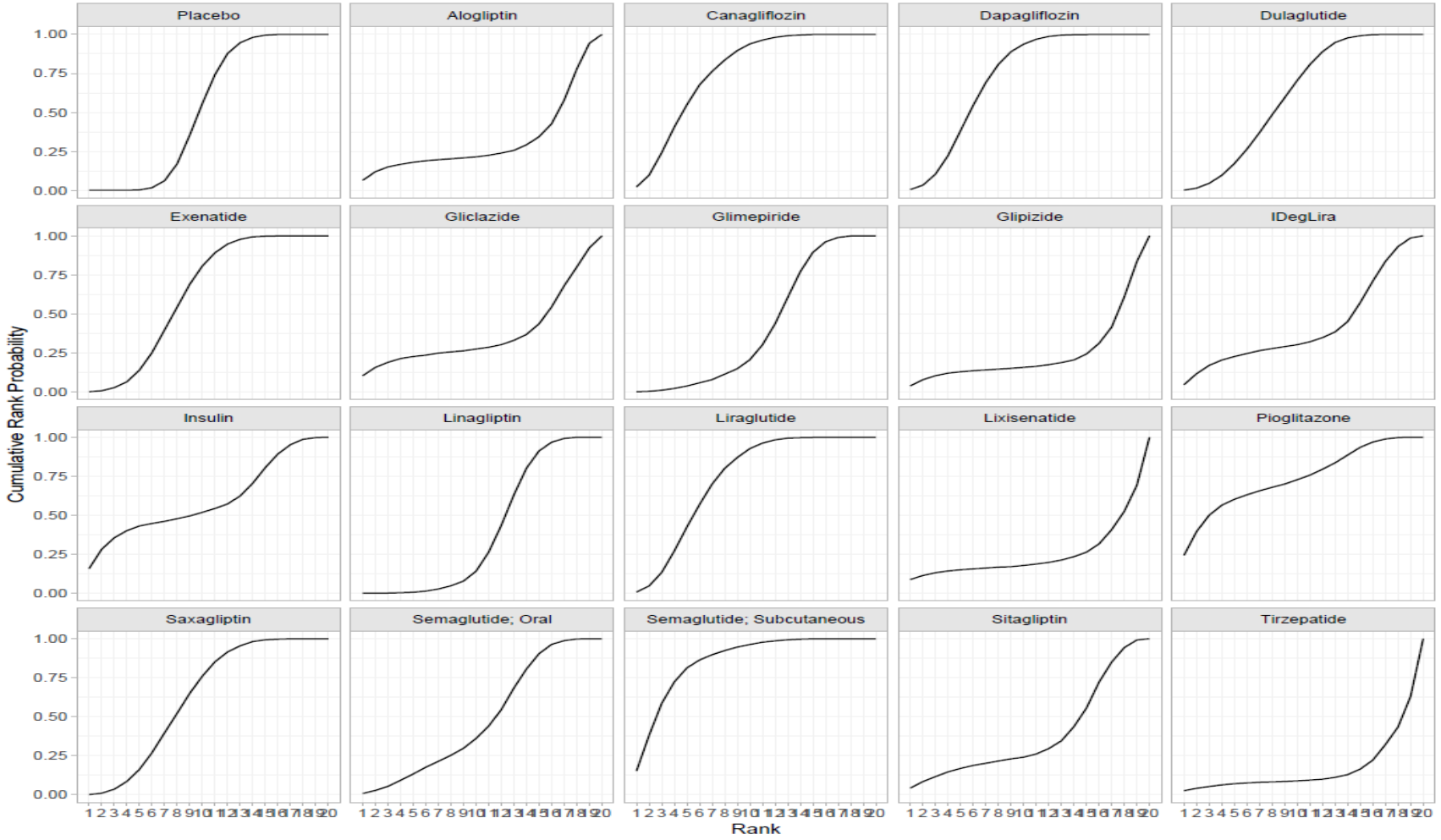
**Figure 40: Cumulative ranking probability plots for 5-item MACE. Treatments with the largest area under the curve rank the best across the range of rankings.**


Placebo
Linagliptin
Semaglutide; Oral
Semaglutide; Subcutaneous
Cumulative Rank Probability
1.00
0.75
0.50
0.25
0.00
1
2
3
4
Rank

1

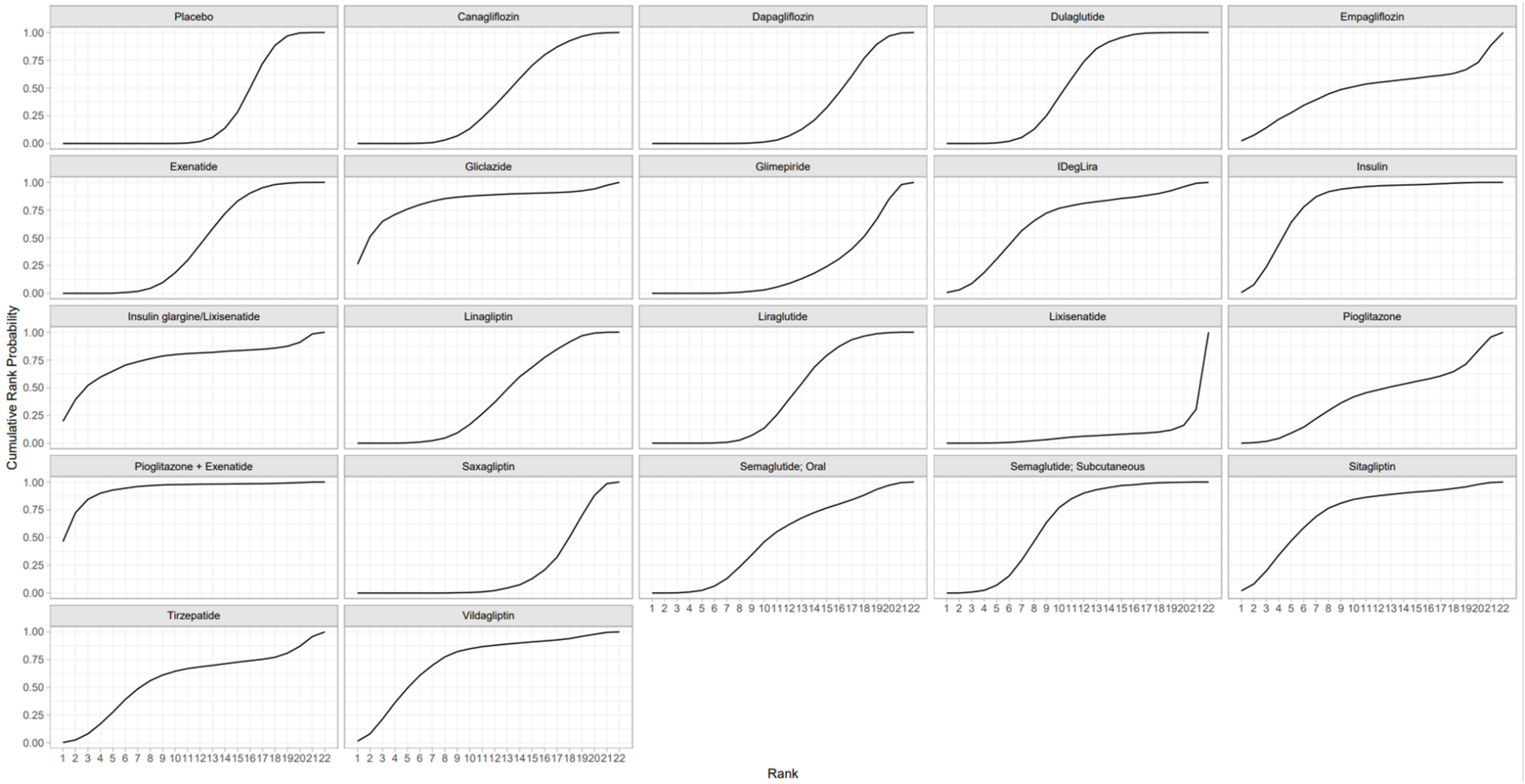
1 **6.5.5. Non-fatal myocardial infarction**

**Figure 41: Cumulative ranking probability plots for non-fatal myocardial infarction Treatments with the largest area under the curve rank the best across the range of rankings.**



### 6.5.6. Non-fatal stroke

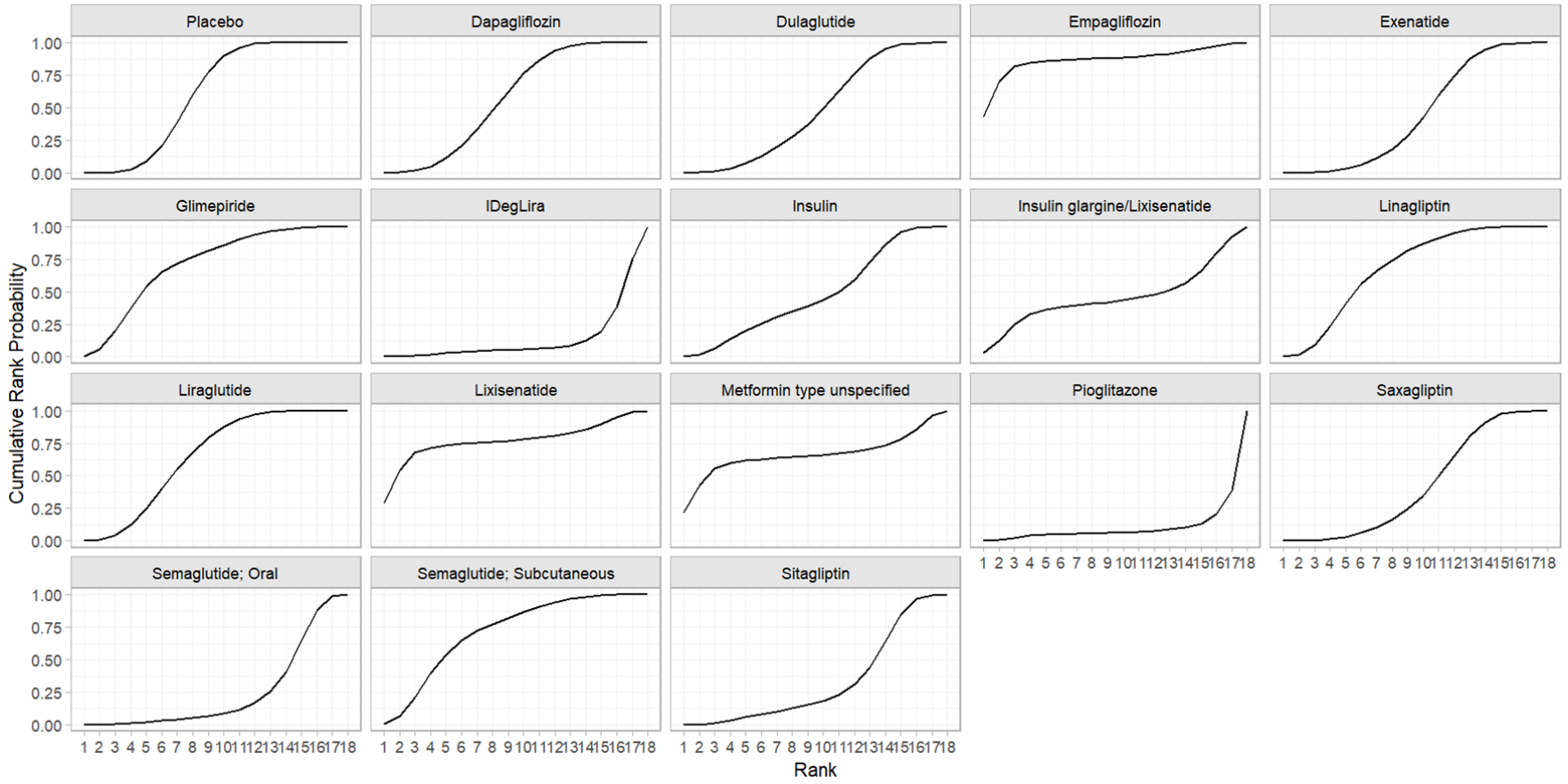
**Figure 42: Cumulative ranking probability plots for non-fatal stroke. Treatments with the largest area under the curve rank the best across the range of rankings.**


Placebo
Canagliflozin
Dapagliflozin
Dulaglutide
Empagliflozin
Exenatide
Gliclazide
Glimepiride
IDegLira
Insulin
Insulin glargine/Lixisenatide
Linagliptin
Liraglutide
Lixisenatide
Pioglitazone
Pioglitazone + Exenatide
Saxagliptin
Semaglutide; Oral
Semaglutide; Subcutaneous
Sitagliptin
Tirzepatide
Vildagliptin
Cumulative Rank Probability
0.00
0.25
0.50
0.75
1.00
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Rank

1

### 6.5.7. Unstable angina

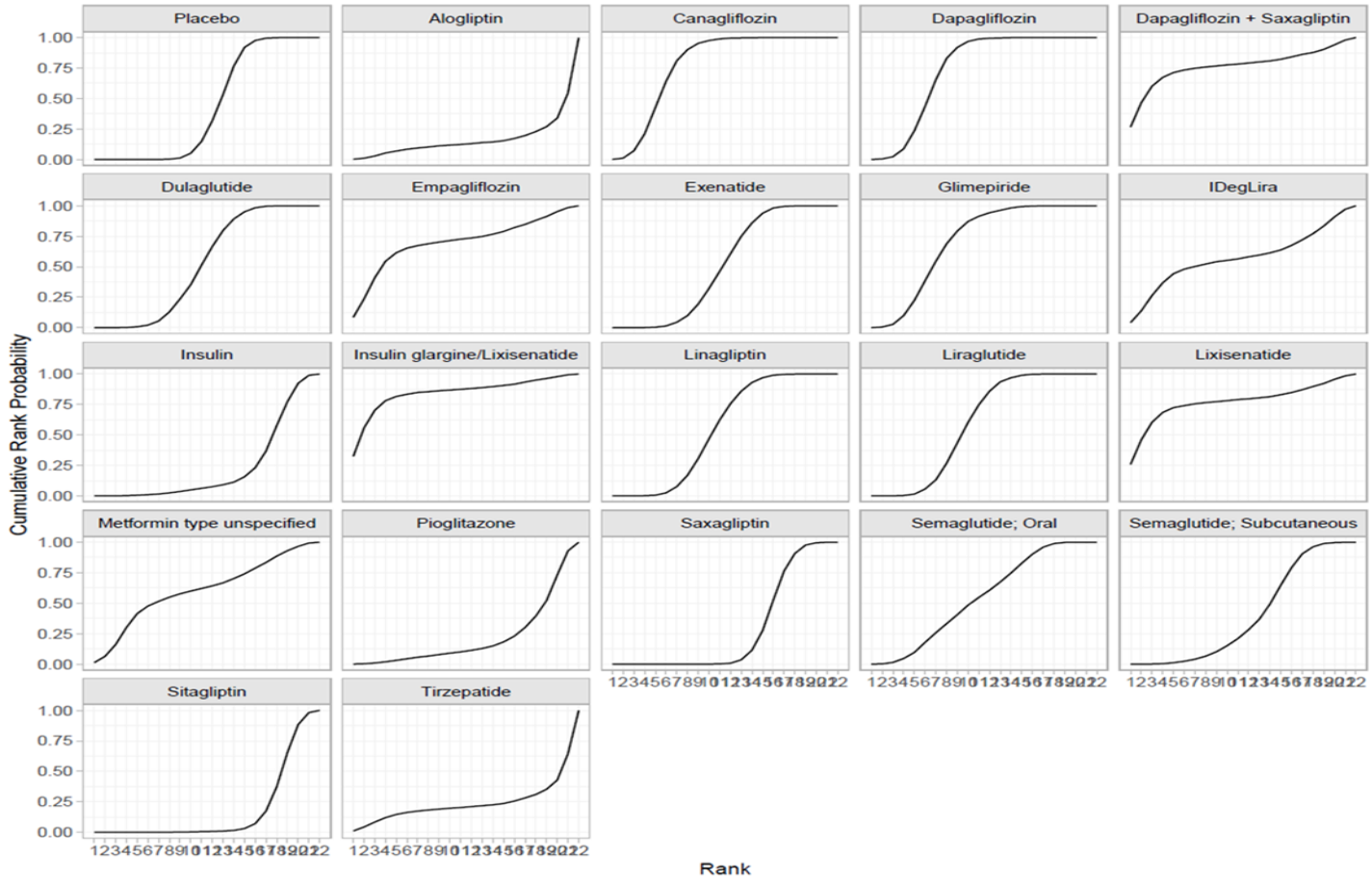
**Figure 43: Cumulative ranking probability plots for unstable angina using the base case analysis. The probability of each treatment being the most effective.**



1
2

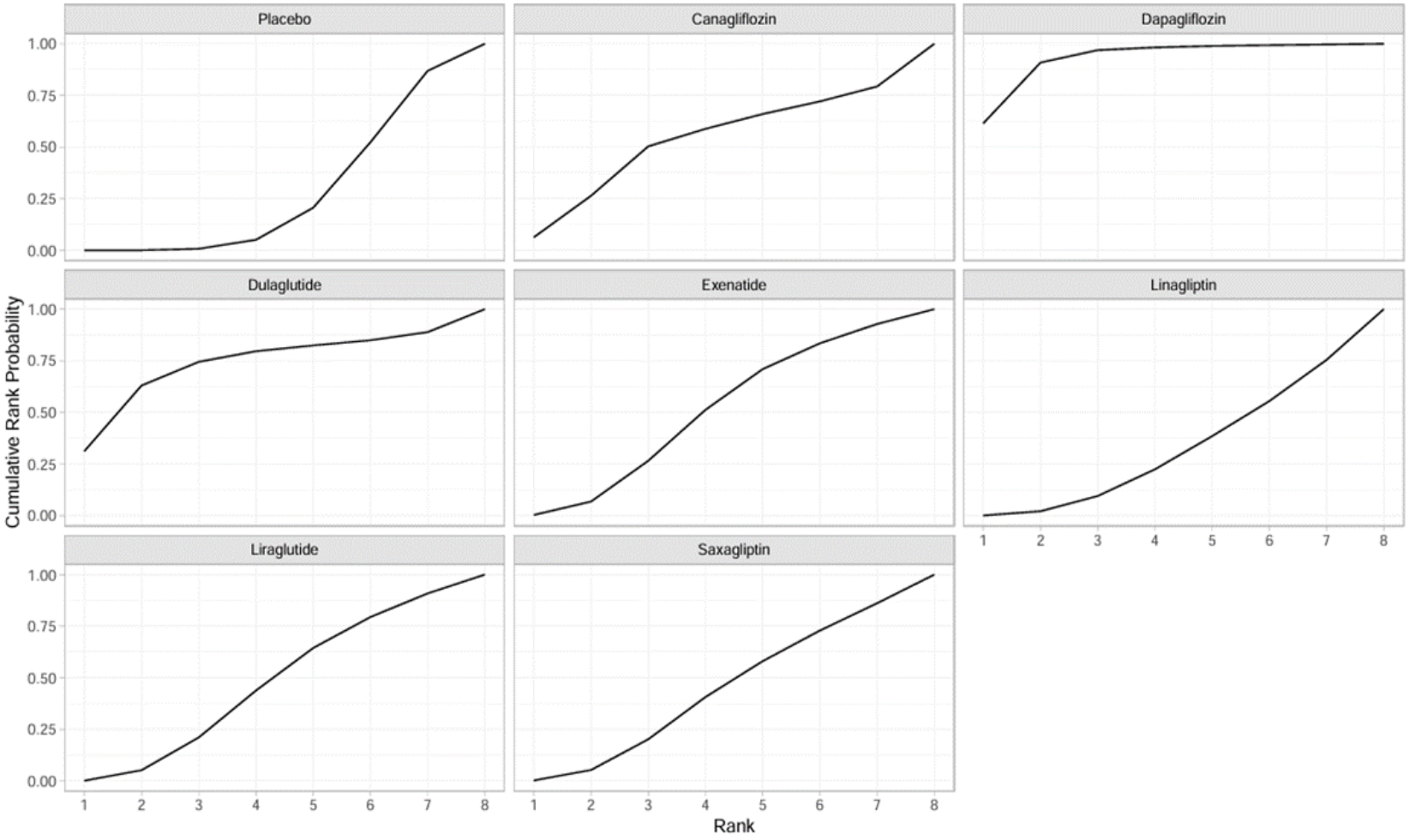
### 6.5.8. Hospitalisation for heart failure

**Figure 44: Cumulative ranking probability plots for hospitalisation for heart failure using the base case analysis. Treatments with the largest area under the curve rank the best across the range of rankings.**


Placebo
Alogliptin
Canagliflozin
Dapagliflozin
Dapagliflozin + Saxagliptin
Dulaglutide
Empagliflozin
Exenatide
Glimepiride
IDegLira
Insulin
Insulin glargine/Lixisenatide
Linagliptin
Liraglutide
Lixisenatide
Metformin type unspecified
Pioglitazone
Saxagliptin
Semaglutide; Oral
Semaglutide; Subcutaneous
Sitagliptin
Tirzepatide
Cumulative Rank Probability
0.00
0.25
0.50
0.75
1.00
Rank

### 6.5.9. Development of end-stage renal failure

**Figure 45: Cumulative ranking probability plots for development of end-stage renal failure. Treatments with the largest area under the curve rank the best across the range of rankings.**


Placebo
Canagliflozin
Dapagliflozin
Dulaglutide
Exenatide
Linagliptin
Liraglutide
Saxagliptin
Cumulative Rank Probability
1.00
0.75
0.50
0.25
0.00
1
2
3
4
5
6
7
8
Rank

1

# 7. Quality assessment

## 7.1. Risk of bias

Risk of bias and indirectness for the included studies was assessed as described in the methods chapter. Details for the assessment of each trial are provided in the review document.

The majority of the trials included in the NMA were assessed as low risk of bias. For studies where there was high or very high risk of bias, the reason varied but this was more commonly due to either bias arising from the randomisation process, bias due to deviations from the intended interventions or bias due to missing outcome data.

**Table 41: Pairwise meta-analysis risk of bias (RoB) assessment per NMA outcome - RQ1.1 - model 5**

| Study names | HbA1c change | Weight change |
|---|---|---|
| Aggarwal 2018 | Moderate | Moderate |
| Arjona Ferreira 2013A | Moderate | Moderate |
| Arjona Ferreira 2013B | Moderate | Moderate |
| Aroda 2019B | Low | NA |
| Aronoff 2000 | High | High |
| Aschner 2006 | High | NA |
| Aschner 2010 | Moderate | Moderate |
| Bailey 2012 | Low | Low |
| Banerji 1995 | High | NA |
| Barzilai 2011 | High | High |
| Bi 2013 | High | High |
| Bosi 2009 | Moderate | Moderate |
| Camerini-Davalos 1988 | Moderate | NA |
| Campbell 1994 | High | NA |
| Chakraborty 2011 | High | NA |
| Charbonnel 2005 | High | NA |
| Chen 2015 | Moderate | Moderate |
| Chen 2018B | High | High |
| Chen 2022 | Low | NA |
| Chiasson 2001 | High | High |
| Chou 2012 | Moderate | NA |
| de Boer 2017 | Low | Low |
| DeFronzo 1995 | High | High |
| DeFronzo 2008 | High | NA |
| Dejager 2007 | High | NA |
| del Prato 2003 | High | High |
| Del Prato 2011 | High | NA |
| Derosa 2004 | High | NA |

| Study names | HbA1c change | Weight change |
|---|---|---|
| Derosa 2009 | Low | NA |
| Dou 2018 | High | High |
| Erem 2014 | High | High |
| Esposito 2011 | Low | Low |
| Feng 2017 | High | High |
| Ferrannini 2010 | Moderate | Moderate |
| Foley 2009 | High | High |
| Foley 2011 | High | NA |
| Frederich 2012 | High | High |
| Gantz 2017D | Moderate | Moderate |
| Garber 2009 1.1 | High | NA |
| Goldstein 2007 | High | NA |
| Grant 1996 | High | NA |
| Guo 2014 | High | NA |
| Haak 2012 | High | High |
| Hadjadj 2016 | Low | NA |
| Hällsten 2002 | NA | NA |
| Henry 2012A | Low | Low |
| Henry 2012B | Low | Low |
| Henry 2014 | High | High |
| Inagaki 2014 | High | High |
| Inagaki 2015 | Low | NA |
| Inagaki 2022 | Moderate | Moderate |
| Ji 2014 | Moderate | Moderate |
| Ji 2016A | Moderate | Moderate |
| Ji 2017 | High | NA |
| Kahl 2019 | Moderate | Moderate |
| Kaku 2014 | Low | Low |
| Kaku 2018A | High | NA |
| Kaku 2018B | High | NA |
| Kikuchi 2012 | High | High |
| Kim 2017 | High | NA |
| Kondo 2016 | High | NA |
| Kumar 2014 | Moderate | NA |
| Lambadiari 2018 | High | High |
| Lewin 2015 | High | NA |
| Li 2019A | High | NA |
| Liu 2020 | High | High |
| Mari 2008 | High | High |
| Miyagawa 2015 | High | NA |
| Miyazaki 2002 | High | High |

| Study names | HbA1c change | Weight change |
|---|---|---|
| Moretto 2008 | Moderate | Moderate |
| Mu 2017 | High | High |
| Nauck 2016 | Moderate | Moderate |
| Pan 2012A | High | High |
| Perez 2009 | High | NA |
| Pfützner 2011A | High | NA |
| Pistrosch 2013 | High | NA |
| Pi-Sunyer 2007 | Moderate | Moderate |
| Pratley 2014 | High | High |
| Roden 2005 1.1 | NA | High |
| Roden 2015 | Moderate | Moderate |
| Rosenstock 2007A | High | High |
| Rosenstock 2016 | High | High |
| Ross 2015 | Low | Moderate |
| Russell-Jones 2012 | Low | Low |
| Scherbaum 2002 | High | High |
| Schwartz 2006 | High | NA |
| Schweizer 2007 | High | High |
| Schweizer 2009 | Moderate | Moderate |
| Shihara 2011 | NA | High |
| Sorli 2017 | High | High |
| Stenlöf 2013 | Moderate | Moderate |
| Tan 2005 | High | High |
| Tao 2018 | High | High |
| Wainstein 2012 | High | NA |
| Wang 2013 | High | High |
| Wang 2016A | High | NA |
| Wang 2022A | High | NA |
| Wolever 2000 | High | NA |
| Wu 2015 | High | High |
| Xu 2015 | High | High |
| Yamada 2020 | High | High |
| Yamanouchi 2005 | High | NA |
| Yoon 2011A | High | NA |
| Yoon 2012 | High | High |
| Yuan 2012 | High | High |
| Zhang 2020A | High | High |
| Zhou 2021 | NA | High |
| Zhou 2022 | High | NA |
| Zougrafou 2015 | High | High |

**Table 42: Pairwise meta-analysis risk of bias (RoB) assessment per NMA outcome - RQ1.2 – model 1**

| Study names | Cardiovascular mortality | 3-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Hospitalisation for heart failure | HbA1c change |
|---|---|---|---|---|---|---|
| Arturi 2017 | NA | NA | NA | NA | NA | Moderate |
| Cannon 2020 HF | NA | Low | NA | NA | Low | NA |
| Chen 2017 | NA | NA | NA | NA | NA | High |
| Green 2015 HF | NA | NA | NA | NA | Low | NA |
| Holman 2017 HF | NA | Low | NA | NA | NA | NA |
| Mahaffey 2018 HF | Low | Low | NA | NA | Low | NA |
| Marso 2016A HF | Low | Low | Low | Low | Low | NA |
| Marso 2016B HF | NA | Low | NA | NA | NA | NA |
| McMurray 2018 | Low | NA | NA | Low | Low | NA |
| Perkovic 2019 HF | NA | Low | NA | NA | Low | NA |
| Pfeffer 2015 HF | NA | NA | NA | NA | Low | NA |
| Rosenstock 2019A HF | Low | NA | NA | NA | Low | NA |
| White 2013 HF | High | High | High | High | High | NA |
| Wiviott 2019 HF | Moderate | Moderate | Moderate | Moderate | Moderate | NA |

**Table 43: Pairwise meta-analysis risk of bias (RoB) assessment per NMA outcome - RQ1.2 - model 2**

| Study names | Cardiovascular mortality | 3-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Hospitalisation for heart failure | HbA1c change | Weight change |
|---|---|---|---|---|---|---|---|
| Adel 2022 | High | NA | NA | NA | NA | High | NA |
| Arturi 2017 | NA | NA | NA | NA | NA | Moderate | NA |
| Cannon 2020 | Low | Low | Low | Low | Low | High | NA |
| Cefalu 2015 | High | NA | NA | NA | High | High | High |

| Study names | Cardiovascular mortality | 3-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Hospitalisation for heart failure | HbA1c change | Weight change |
|---|---|---|---|---|---|---|---|
| Chen 2017 | NA | NA | NA | NA | NA | High | NA |
| Del Prato 2021 | NA | NA | NA | NA | NA | Low | NA |
| Gerstein 2019A CVD | NA | Low | NA | NA | NA | NA | NA |
| Gohari 2022 | NA | NA | NA | NA | NA | Moderate | NA |
| Green 2015 | Low | Low | Low | NA | Low | High | NA |
| Holman 2017 CVD | NA | Low | NA | NA | NA | NA | NA |
| Lee 2013B | NA | NA | High | NA | NA | High | NA |
| Leiter 2014 | Moderate | NA | Moderate | Moderate | Moderate | Moderate | Moderate |
| Li 2014C | NA | NA | NA | NA | NA | Moderate | NA |
| Mahaffey 2018 CVD | Low | Low | Low | Low | Low | NA | NA |
| Nissen 2008 | Moderate | Moderate | Moderate | Moderate | Moderate | Moderate | NA |
| Oh 2021 | NA | NA | NA | NA | NA | High | High |
| Pfeffer 2015 | Low | NA | NA | NA | Low | Low | NA |
| Phrommintikul 2019 | NA | NA | Moderate | NA | NA | High | High |
| Rosenstock 2019B CVD | NA | Low | NA | NA | NA | NA | NA |
| Scirica 2013 CVD | NA | High | NA | NA | NA | NA | NA |
| Verma 2019 | NA | NA | NA | NA | NA | Low | Low |
| White 2013 | High | High | High | High | High | High | NA |
| Wilcox 2008 | High | High | High | High | High | NA | NA |
| Wiviott 2019 CVD | Moderate | Moderate | Moderate | Moderate | Moderate | NA | NA |

| Study names | Cardiovascular mortality | 3-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Hospitalisation for heart failure | HbA1c change | Weight change |
|---|---|---|---|---|---|---|---|
| Zinman 2015 | Low | Low | Low | Low | Low | Low | NA |

1

2

3 **Table 44: Pairwise meta-analysis risk of bias (RoB) assessment per NMA outcome -**
4 **RQ1.2 - model 3**

| Study names | Cardiovascular mortality | 3-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Hospitalisation for heart failure | Development of endstage kidney disease | HbA1c change | Weight change |
|---|---|---|---|---|---|---|---|---|
| Barnett 2014 | NA | NA | NA | NA | NA | NA | Low | Low |
| Cannon 2020 CKD | NA | NA | NA | NA | NA | NA | High | NA |
| Davies 2016 | Low | NA | NA | Low | NA | NA | Moderate | NA |
| Fioretto 2018 | NA | NA | NA | Low | Low | NA | Moderate | Moderate |
| Galle 2012 | NA | NA | NA | NA | NA | NA | High | NA |
| Groop 2017 | Low | NA | Low | NA | NA | NA | Low | NA |
| Grunberger 2018 | High | NA | NA | NA | High | NA | High | High |
| Hiramatsu 2018 | NA | NA | High | NA | High | NA | High | NA |
| Kimura 2023 | NA | NA | NA | NA | NA | NA | Moderate | NA |
| Kohan 2014 | High | NA | NA | NA | NA | High | High | High |
| Kothny 2015 | NA | NA | NA | NA | NA | NA | Moderate | NA |
| Li 2014C | NA | NA | NA | NA | NA | NA | Moderate | NA |
| McGill 2013 | NA | NA | High | High | NA | NA | High | NA |
| Moeinzadeh 2021 | NA | NA | NA | NA | NA | NA | High | High |

| Study names | Cardiovascular mortality | 3-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Hospitalisation for heart failure | Development of endstage kidney disease | HbA1c change | Weight change |
|---|---|---|---|---|---|---|---|---|
| Mosenzon 2019 | Low | NA | NA | NA | Low | NA | Low | NA |
| Nowicki 2011A | NA | NA | NA | NA | NA | High | High | NA |
| Perkovic 2019 | Low | Low | NA | NA | Low | Low | Low | NA |
| Pollock 2019 | NA | NA | NA | NA | NA | NA | High | NA |
| Raman 2022 | NA | NA | NA | NA | NA | NA | High | NA |
| Rosenstock 2019A CKD | NA | NA | NA | NA | Low | NA | NA | NA |
| Takahashi 2023 | NA | NA | NA | NA | NA | NA | Moderate | NA |
| Tuttle 2018 | NA | NA | NA | NA | NA | NA | High | NA |
| Wada 2022 | Moderate | Low | NA | NA | Moderate | NA | Low | NA |
| Wang 2020B | NA | NA | NA | NA | NA | NA | High | NA |
| Wiviott 2019 CKD | Moderate | Moderate | NA | NA | Moderate | NA | NA | NA |
| Yale 2013 | NA | NA | NA | NA | NA | NA | High | High |
| Zinman 2015 CKD | Low | NA | NA | NA | Low | NA | NA | NA |

1

2

**Table 45: Pairwise meta-analysis risk of bias (RoB) assessment per NMA outcome – RQ1.2 model 5 adverse events outcomes**

| Study names | Cardiovascular mortality | 3-point MACE | 4-point MACE | 5-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Unstable angina | Hospitalisation for heart failure | Development of end stage kidney disease |
|---|---|---|---|---|---|---|---|---|---|
| Abdul-Ghani 2017 | NA | NA | NA | NA | NA | Some concerns | NA | NA | NA |
| Ahren 2017 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Araki 2015B | NA | NA | NA | NA | Low | Low | NA | NA | NA |
| Arechavaleta 2011 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Aroda 2016B | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Aroda 2017 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Aroda 2019A | High | NA | NA | NA | High | High | High | High | NA |
| Aschner 2012 | NA | NA | NA | NA | High | NA | High | NA | NA |
| Attaran 2023 | NA | NA | NA | NA | NA | Some concerns | NA | NA | NA |
| Ba 2017 | NA | NA | NA | NA | NA | Low | Low | NA | NA |
| Bailey 2010 | Some concerns | NA | NA | NA | NA | NA | NA | NA | NA |
| Bajaj 2014 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Barnett 2013 | NA | NA | NA | NA | NA | Low | Low | NA | NA |
| Bergenstal 2010 | High | NA | NA | NA | NA | NA | High | NA | NA |
| Billings 2018 | NA | NA | NA | NA | Low | NA | Low | Low | NA |
| Bode 2013 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Bolli 2008 | NA | NA | NA | NA | NA | Low | NA | NA | NA |

| Study names | Cardiovascular mortality | 3-point MACE | 4-point MACE | 5-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Unstable angina | Hospitalisation for heart failure | Development of end stage kidney disease |
|---|---|---|---|---|---|---|---|---|---|
| Bosi 2007 | NA | NA | NA | NA | NA | Some concerns | NA | NA | NA |
| Buse 2004 | NA | NA | NA | NA | High | NA | NA | NA | NA |
| Buse 2011 | Some concerns | NA | NA | NA | NA | NA | NA | NA | NA |
| Buse 2020 | NA | NA | NA | NA | NA | NA | NA | Low | NA |
| Cefalu 2013 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Charpentier 2009 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Chen 2018A | Some concerns | NA | NA | NA | Some concerns | NA | NA | NA | NA |
| Civera 2008 | Some concerns | NA | NA | NA | NA | NA | NA | NA | NA |
| D'Alessio 2015 | NA | NA | NA | NA | NA | Low | NA | NA | NA |
| Dahl 2022 | NA | NA | Low | NA | NA | NA | NA | NA | NA |
| Davies 2015 | High | NA | NA | NA | NA | NA | NA | NA | High |
| Davies 2017 | NA | NA | NA | NA | High | High | NA | NA | NA |
| DeFronzo 2009 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| DeFronzo 2012 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| DeFronzo 2015 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Del Prato 2014 | High | NA | NA | NA | High | NA | NA | NA | NA |
| Diamant 2014 | Some concerns | NA | NA | NA | Some concerns | NA | NA | NA | NA |

| Study names | Cardiovascular mortality | 3-point MACE | 4-point MACE | 5-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Unstable angina | Hospitalisation for heart failure | Development of end stage kidney disease |
|---|---|---|---|---|---|---|---|---|---|
| Dungan 2016 | NA | NA | NA | NA | NA | Low | NA | NA | NA |
| Ferrannini 2009 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Fonseca 2007 | Some concerns | NA | NA | NA | NA | NA | NA | NA | NA |
| Frias 2016 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Frias 2021 | Some concerns | NA | NA | NA | Some concerns | NA | NA | NA | NA |
| Frias 2023 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Gadde 2017 | NA | NA | NA | NA | High | NA | NA | NA | NA |
| Gallwitz 2012A | Low | NA | NA | NA | Low | Low | Low | Low | NA |
| Gao 2023 | Some concerns | NA | Some concerns | NA | Some concerns | Some concerns | NA | Some concerns | NA |
| Garvey 2023 | NA | Low | NA | NA | NA | NA | NA | NA | NA |
| Gerstein 2019A | Low | Low | NA | NA | Low | Low | Low | Low | Low |
| Giorgino 2015 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Gough 2014 | Low | Low | NA | NA | Low | NA | NA | NA | NA |
| Group 2022 | Some concerns | Some concerns | NA | NA | NA | NA | Some concerns | Some concerns | NA |
| Gu 2019 | NA | NA | NA | NA | Low | NA | NA | NA | NA |
| Göke 2010 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Hao 2022 | NA | NA | NA | NA | NA | NA | High | NA | NA |
| Haring 2013 | High | NA | NA | NA | NA | NA | NA | NA | NA |

| Study names | Cardiovascular mortality | 3-point MACE | 4-point MACE | 5-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Unstable angina | Hospitalisation for heart failure | Development of end stage kidney disease |
|---|---|---|---|---|---|---|---|---|---|
| Henriksen 2011 | NA | NA | NA | NA | Some concerns | NA | NA | NA | NA |
| Holland er 2009 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Holland er 2018 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Holman 2017 | Low | Low | NA | NA | NA | NA | Low | Low | Low |
| Home 2015 | NA | High | NA | NA | NA | NA | NA | NA | NA |
| Husain 2019 | Low | Low | NA | Low | Low | Low | Low | Low | NA |
| Inagaki 2012 | Low | NA | NA | NA | NA | Low | NA | NA | NA |
| Ji 2021A | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Joubert 2021 | NA | NA | NA | NA | NA | NA | NA | Some concerns | NA |
| Kawamori 2018 | Low | NA | NA | NA | NA | Low | NA | NA | NA |
| Kellerer 2022 | NA | NA | NA | NA | NA | NA | Some concerns | NA | NA |
| Kooy 2009 | Some concerns | NA | NA | NA | NA | NA | NA | Some concerns | NA |
| Koyama 2014 | NA | NA | NA | NA | High | High | NA | NA | NA |
| Langenfeld 2005 | NA | NA | NA | NA | NA | NA | NA | High | NA |
| Ledesma 2019 | Low | NA | Low | NA | Low | Low | NA | Low | NA |
| Lingvay 2016 | Some concerns | NA | NA | NA | NA | Some concerns | NA | NA | NA |
| Lingvay 2019 | Low | NA | NA | NA | NA | NA | NA | NA | NA |

| Study names | Cardiovascular mortality | 3-point MACE | 4-point MACE | 5-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Unstable angina | Hospitalisation for heart failure | Development of end stage kidney disease |
|---|---|---|---|---|---|---|---|---|---|
| Ludvik 2018 | NA | NA | NA | NA | Low | NA | Low | NA | NA |
| Ludvik 2021 | Low | NA | Low | NA | NA | NA | NA | NA | NA |
| Mahaffey 2018 | Low | Low | NA | NA | Low | Low | NA | Low | Low |
| Marso 2016A | Low | Low | NA | NA | Low | Low | Low | Low | Low |
| Marso 2016B | Low | NA | NA | Low | Low | Low | Low | Low | Low |
| Mathieu 2014 | NA | NA | NA | NA | NA | Some concerns | NA | NA | NA |
| Matthews 2005 | NA | NA | NA | NA | High | NA | NA | NA | NA |
| Mazzone 2006 | NA | High | NA | NA | High | High | NA | High | NA |
| Morikawa 2011 | NA | NA | NA | NA | NA | NA | High | NA | NA |
| Muller-Wieland 2018 | NA | NA | NA | NA | NA | NA | NA | Low | NA |
| Nauck 2007B | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Nauck 2009A | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Nauck 2014 Dulaglutide v Sitagliptin | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Pan 2012B | NA | NA | NA | NA | NA | Some concerns | NA | NA | NA |
| Pan 2014 | NA | NA | NA | NA | Low | Low | NA | NA | NA |
| Pf?tzner 2005 | NA | NA | NA | NA | NA | NA | NA | High | NA |

| Study names | Cardiovascular mortality | 3-point MACE | 4-point MACE | 5-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Unstable angina | Hospitalisation for heart failure | Development of end stage kidney disease |
|---|---|---|---|---|---|---|---|---|---|
| Pf?tzner 2011B | NA | NA | NA | NA | NA | NA | NA | Some concerns | NA |
| Philis-Tsimikas 2019 | Low | Low | NA | NA | Low | NA | NA | NA | NA |
| Pieber 2019 | Low | NA | NA | NA | NA | NA | NA | Low | NA |
| Pinget 2013 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Pozzilli 2017 | NA | NA | NA | NA | Low | Low | Low | NA | NA |
| Pratley 2009A | NA | NA | NA | NA | Low | NA | NA | Low | NA |
| Pratley 2010 | Some concerns | NA | NA | NA | NA | NA | NA | NA | NA |
| Pratley 2018A | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Pratley 2018B | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Pratley 2019 | Low | NA | NA | NA | Low | Low | Low | NA | NA |
| Puntha kee 2012 | High | High | NA | NA | High | High | NA | High | NA |
| Raz 2008 | Some concerns | NA | NA | NA | NA | NA | NA | NA | NA |
| Riddle 1998 | NA | NA | NA | NA | High | High | NA | NA | NA |
| Riddle 2013A | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Riddle 2013B | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Roberts 2005 | NA | NA | NA | NA | High | NA | NA | NA | NA |
| Rodbard 2017 | NA | NA | NA | NA | Low | NA | NA | NA | NA |
| Rodbard 2018 | NA | NA | NA | NA | NA | Low | NA | Low | NA |
| Rodbard 2019 | Low | NA | NA | NA | NA | NA | NA | Low | NA |

| Study names | Cardiovascular mortality | 3-point MACE | 4-point MACE | 5-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Unstable angina | Hospitalisation for heart failure | Development of end stage kidney disease |
|---|---|---|---|---|---|---|---|---|---|
| Rosenstock 2009B | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Rosenstock 2014A | Some concerns | NA | NA | NA | NA | NA | NA | NA | NA |
| Rosenstock 2016A | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Rosenstock 2016B | Some concerns | NA | NA | NA | NA | Some concerns | Some concerns | Some concerns | NA |
| Rosenstock 2019A | Low | Low | Low | NA | Low | Low | Low | Low | Low |
| Rosenstock 2019B | Low | Low | Low | NA | Low | Low | Low | Low | NA |
| Rosenstock 2019C | Low | NA | NA | NA | Low | Low | Low | Low | NA |
| Rosenstock 2019D | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Roussel 2019 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Schernthaner 2013 | High | NA | NA | NA | NA | NA | NA | NA | NA |
| Schernthaner 2015A | Some concerns | NA | NA | NA | NA | NA | NA | NA | NA |
| Scirica 2013 | High | High | NA | NA | High | High | High | High | High |
| Seino 2012 | NA | NA | NA | NA | NA | Low | NA | NA | NA |
| Shankar 2017A | NA | NA | NA | NA | Some concerns | NA | NA | NA | NA |
| Sone 2019 | NA | NA | NA | NA | NA | NA | Low | NA | NA |
| Strain 2013 | Low | NA | NA | NA | NA | NA | NA | NA | NA |

| Study names | Cardiovascular mortality | 3-point MACE | 4-point MACE | 5-point MACE | Non-fatal myocardial infarction | Non-fatal stroke | Unstable angina | Hospitalisation for heart failure | Development of end stage kidney disease |
|---|---|---|---|---|---|---|---|---|---|
| Strojek 2011 | Low | NA | NA | NA | NA | Low | NA | NA | NA |
| Thrasher 2014 | NA | NA | NA | NA | Some concerns | NA | NA | NA | NA |
| Vianna 2018 | Some concerns | NA | NA | NA | NA | Some concerns | NA | NA | NA |
| Vilsboll 2010 | NA | NA | NA | NA | Some concerns | NA | Some concerns | NA | NA |
| Wang 2022B | NA | NA | NA | NA | NA | Some concerns | Some concerns | NA | NA |
| Watada 2019 | NA | NA | NA | NA | Low | NA | NA | NA | NA |
| Webb 2020 | NA | NA | NA | NA | Low | NA | NA | NA | NA |
| Wilding 2012 | Low | NA | NA | NA | NA | NA | NA | NA | NA |
| Wiviott 2019 | Some concerns | Some concerns | NA | NA | Some concerns | Some concerns | Some concerns | Some concerns | Some concerns |
| Wysham 2014 52 weeks | Some concerns | NA | NA | NA | NA | NA | NA | NA | NA |
| Xu 2017 | NA | NA | NA | NA | High | NA | High | NA | NA |
| Yang 2011 | NA | NA | NA | NA | NA | Some concerns | NA | NA | NA |
| Yang 2015 | NA | NA | NA | NA | NA | High | NA | NA | NA |
| Yang 2018A | NA | NA | NA | NA | Low | NA | NA | NA | Low |
| Yki-Järvinen 2013 | High | NA | NA | High | NA | NA | NA | NA | NA |
| Zang 2016 | NA | NA | NA | NA | NA | Low | NA | NA | NA |
| Zinman 2019B | NA | NA | NA | NA | Some concerns | Some concerns | NA | Some concerns | NA |

**Table 46: Pairwise meta-analysis risk of bias (RoB) assessment per NMA outcome – RQ1.2 model 5 HbA1c and weight change outcomes**

| Study names | HbA1c change | HbA1c change (regression) | Weight change |
|---|---|---|---|
| Abreu 2019 | High | High | High |
| Ahmann 2018 | High | NA | NA |
| Ahren 2013 | Moderate | NA | NA |
| Ahren 2017 | Low | Low | Low |
| Ando 2021 | High | High | High |
| Araki 2015A | Moderate | Moderate | Moderate |
| Arechavaleta 2011 | Low | Low | Low |
| Aroda 2016B | Low | Low | Low |
| Aroda 2019A | Moderate | Moderate | High |
| Aschner 2012 | High | High | High |
| Attaran 2023 | Moderate | Moderate | NA |
| Avilés-Santa 1999 | Moderate | NA | NA |
| Babar 2021 | High | NA | NA |
| Bae 2021 | Moderate | Moderate | NA |
| Bailey 2010 | Moderate | Moderate | NA |
| Barnett 2013 | Low | Low | Low |
| Bergenstal 2009 | Moderate | Moderate | Low |
| Bergenstal 2010 | Moderate | Moderate | Moderate |
| Berndt-Zipfel 2013 | High | High | High |
| Bizino 2019 | NA | NA | Low |
| Blonde 2015 | Moderate | Moderate | Moderate |
| Bode 2013 | Low | Low | NA |
| Bolinder 2012 | Moderate | Moderate | Moderate |
| Bolli 2008 | Low | Low | Low |
| Bolli 2014 | High | High | High |
| Bosi 2007 | Moderate | Moderate | Moderate |
| Brown 2020 | NA | NA | Low |
| Bunck 2009 | Moderate | Moderate | Moderate |
| Buse 2004 | High | High | NA |
| Buse 2011 | High | High | NA |
| Camerini-Davalos 1994 | High | High | NA |
| Charbonnel 2006 | High | High | NA |
| Charbonnel 2013 | High | High | NA |
| Chen 2016 | High | High | NA |
| Chen 2018A | Moderate | Moderate | Moderate |
| Cho 2019 | Moderate | NA | NA |

| Study names | HbA1c change | HbA1c change (regression) | Weight change |
|---|---|---|---|
| Civera 2008 | Moderate | Moderate | Moderate |
| Cusi 2019 | High | High | High |
| da Silva 2016 | High | High | High |
| Dagogo-Jack 2017 | Low | Low | Low |
| Dahl 2022 | NA | NA | Low |
| D'Alessio 2015 | Low | Low | Low |
| Davies 2009 | Moderate | Moderate | Moderate |
| Davies 2013 | Moderate | Moderate | Moderate |
| Davies 2015 | High | NA | High |
| Davies 2017 | High | High | High |
| Davies 2021 | Low | Low | Low |
| DeFronzo 2005 | Moderate | Moderate | Moderate |
| DeFronzo 2009 | High | High | NA |
| DeFronzo 2012 | High | High | NA |
| DeFronzo 2015 | Low | NA | NA |
| Del Prato 2014 | High | High | NA |
| DePaoli 2014 | High | High | NA |
| Derosa 2010A | High | High | High |
| Derosa 2010B | High | High | High |
| Derosa 2011B | High | High | High |
| Derosa 2012A | High | High | High |
| Derosa 2012B | High | High | High |
| Derosa 2012C | High | High | High |
| Derosa 2014B | High | High | High |
| Dorkhan 2009 | High | High | NA |
| Ferdinand 2019 | Low | Low | Low |
| Fernandez 2008 | High | High | NA |
| Ferrannini 2009 | High | High | NA |
| Filozof 2010a | High | High | NA |
| Fonseca 2007 | Moderate | Moderate | Moderate |
| Fonseca 2013 | Low | Low | Low |
| Forst 2014 | High | High | High |
| Forst 2015 | High | High | NA |
| Frias 2016 | High | High | High |
| Frias 2018 | Low | Low | Low |
| Frias 2020 | High | High | High |
| Frias 2023 | Moderate | Moderate | Low |
| Gadde 2017 | High | High | High |
| Galindo 2023 | High | High | High |
| Gallwitz 2012B | Low | NA | Low |
| Gao 2023 | Moderate | Moderate | Moderate |

| Study names | HbA1c change | HbA1c change (regression) | Weight change |
|---|---|---|---|
| Garvey 2023 | Low | Low | NA |
| Genovese 2013 | Moderate | Moderate | Moderate |
| Gerstein 2019A | Low | Low | NA |
| Giorgino 2015 | Low | Low | Low |
| Giugliano 1993 | Moderate | Moderate | NA |
| Göke 2010 | High | High | High |
| Goodman 2009 | High | High | NA |
| Gough 2014 | Low | Low | Low |
| Gram 2011 | Moderate | Moderate | Moderate |
| Grey 2014 | Moderate | Moderate | Moderate |
| Group 2022 | High | High | NA |
| Gu 2019 | Low | Low | Low |
| Guja 2017 | Low | Low | Low |
| Gullaksen 2023 | NA | NA | High |
| Guo 2020 | Low | Low | Low |
| Gurkan 2014 | Moderate | Moderate | Moderate |
| Guzman 2017 | High | High | High |
| Handelsman 2019 | High | High | NA |
| Hanefeld 2011 | Moderate | Moderate | NA |
| Hao 2022 | High | High | High |
| Haring 2013 | Moderate | Moderate | Moderate |
| Haring 2014 | High | High | High |
| Hartemann-Heurtier 2009 | High | High | High |
| Hattori 2018 | High | NA | NA |
| Heise 2022 | NA | NA | Moderate |
| Hermansen 2007 - Stratum 1 | High | High | High |
| Hermansen 2007 - Stratum 2 | Low | Low | Low |
| Hollander 2009 | High | High | High |
| Hollander 2018 | High | High | High |
| Home 2015 | Moderate | Moderate | Moderate |
| Hong 2012 | Moderate | Moderate | Moderate |
| Hong 2023 | Moderate | Moderate | NA |
| Iacobellis 2017 | High | High | NA |
| Iacobellis 2020 | Moderate | Moderate | Moderate |
| Iijima 2023 | Moderate | Moderate | Moderate |
| Ikonomidis 2020 | Moderate | Moderate | Moderate |
| Inagaki 2012 | Low | Low | NA |
| Inagaki 2013 | Moderate | NA | NA |
| Ji 2016B | High | High | High |
| Ji 2023 | Low | Low | Low |
| Joubert 2021 | Moderate | Moderate | Moderate |

| Study names | HbA1c change | HbA1c change (regression) | Weight change |
|---|---|---|---|
| Kadowaki 2011 | High | High | High |
| Kadowaki 2017 | Low | Low | Low |
| Kaku 2009A | Moderate | Moderate | NA |
| Kanazawa 2010 | High | High | High |
| Kang 2021 | High | High | High |
| Kendall 2005 | High | NA | NA |
| Kesavadev 2017 | High | High | NA |
| Khaloo 2019 | High | High | High |
| Khan 2022 | High | High | High |
| Kim 2020 | Moderate | Moderate | NA |
| Kinoshita 2020 | Low | Low | Low |
| Komorizono 2020 | Low | Low | Low |
| Kothny 2013 | Low | Low | NA |
| Koyama 2014 | High | High | NA |
| Langenfeld 2005 | High | NA | NA |
| Lavalle-Gonzalez 2013A | Low | Low | Low |
| Lavalle-Gonzalez 2013B | Low | Low | Low |
| Lee 2022 | High | NA | NA |
| Li 2014A | High | High | High |
| Li 2014B | High | High | NA |
| Li 2017 | Moderate | Moderate | High |
| Lind 2015 | Low | Low | Low |
| Lingvay 2016 | Moderate | NA | Moderate |
| Lingvay 2019 | Low | NA | NA |
| Liu 2013 | Moderate | Moderate | Moderate |
| Liu 2021 | Low | Low | Low |
| Liutkus 2010 | Moderate | Moderate | Moderate |
| Ludvik 2018 | Low | Low | Low |
| Ludvik 2021 | Low | Low | Low |
| Lundby-Christensen 2016 | Low | Low | Low |
| Macauley 2015 | High | High | NA |
| Mahaffey 2018 | Low | NA | NA |
| Marre 2009 | Moderate | Moderate | Moderate |
| Mathieu 2014 | Moderate | Moderate | Moderate |
| Mathieu 2015A | Low | Low | Low |
| Mathieu 2015B | Low | NA | NA |
| Matthews 2010 | NA | NA | Moderate |
| Mattoo 2005 | Low | Low | NA |
| McCluskey 2004 | High | High | NA |
| Moon 2014 | High | High | High |
| Morikawa 2011 | High | High | NA |

| Study names | HbA1c change | HbA1c change (regression) | Weight change |
|---|---|---|---|
| Moses 2014 | Low | Low | Low |
| Moses 2017 | Moderate | Moderate | NA |
| Muller-Wieland 2018 | Low | Low | Low |
| Nahra 2021 | Moderate | Moderate | NA |
| Nakaguchi 2020 | Low | Low | Low |
| Nauck 2007A | Moderate | Moderate | Moderate |
| Nauck 2007B | High | High | High |
| Nauck 2009A | Low | Low | NA |
| Nauck 2009B | High | High | NA |
| Nauck 2011 | High | High | High |
| Nauck 2014 Dulaglutide v Placebo | Moderate | Moderate | NA |
| Nauck 2014 Dulaglutide v Sitagliptin | Moderate | Moderate | High |
| Nauck 2014 Sitagliptin v Placebo | Moderate | Moderate | NA |
| Nesti 2022 | NA | NA | High |
| Ning 2016 | Low | Low | NA |
| Nogueira 2014 | High | High | High |
| Ohira 2014A | High | High | High |
| Ohira 2014B | High | High | High |
| Owens 2011 | Moderate | Moderate | Moderate |
| Pan 2012B | Moderate | Moderate | NA |
| Papathanassiou 2009 | High | High | High |
| Park 2011 | High | High | NA |
| Park 2014 | High | High | NA |
| Park 2023 | Low | Low | Low |
| Pasquel 2021 | High | High | High |
| Petrica 2011 | High | High | NA |
| Pf?tzner 2005 | High | High | NA |
| Pf?tzner 2011B | Moderate | Moderate | Moderate |
| Pieber 2019 | Low | Low | Low |
| Pozzilli 2017 | Moderate | Moderate | Moderate |
| Pratley 2010 | Moderate | Moderate | Moderate |
| Pratley 2018A | High | High | High |
| Pratley 2018B | Low | Low | Low |
| Pratley 2019 | High | High | NA |
| Punthakee 2012 | High | High | High |
| Raz 2008 | Moderate | Moderate | NA |
| Ridderstrale 2014 | Low | Low | NA |
| Riddle 1998 | High | High | High |
| Riddle 2013A | Low | Low | Low |

| Study names | HbA1c change | HbA1c change (regression) | Weight change |
|---|---|---|---|
| Riddle 2013B | Low | Low | Low |
| Roberts 2005 | High | High | High |
| Roden 2005 1.2 | NA | NA | High |
| Rosenstock 2006 | High | High | High |
| Rosenstock 2009B | High | High | High |
| Rosenstock 2012 | Moderate | Moderate | Moderate |
| Rosenstock 2014A | Moderate | Moderate | Moderate |
| Rosenstock 2014B | Low | Low | Low |
| Rosenstock 2015A | Moderate | Moderate | Moderate |
| Rosenstock 2015B | High | NA | NA |
| Rosenstock 2019D | Low | Low | NA |
| Roussel 2019 | Low | Low | Low |
| Russell-Jones 2009 | Low | Low | Low |
| Sathyanarayana 2011 | High | High | High |
| Savvidou 2016 | High | High | High |
| Scirica 2013 | High | High | High |
| Scott 2018 | Low | Low | NA |
| Seino 2021 | Low | Low | Low |
| Skrivanek 2014 | High | High | NA |
| Sone 2019 | Moderate | Moderate | Moderate |
| Sridhar 2013 | High | High | High |
| Su 2014 | High | High | NA |
| Takihata 2013 | Low | Low | Low |
| Tan 2004 | Low | Low | NA |
| Tanaka 2017 | High | High | High |
| Tanaka 2019 | Low | Low | NA |
| Taskinen 2011 | High | High | High |
| Thrasher 2014 | High | High | High |
| Tripathy 2013 | Moderate | Moderate | Moderate |
| Umpierrez 2006 | High | High | NA |
| Vähätalo 2007 | High | NA | NA |
| van der Meer 2009 | Moderate | Moderate | Moderate |
| van Gaal 2014 | High | High | NA |
| Vanderheiden 2016A | Moderate | Moderate | Moderate |
| Vianna 2018 | Moderate | Moderate | High |
| Vilsboll 2010 | High | High | Moderate |
| W?gner 2019 | Low | Low | Low |
| Wang 2016B | Moderate | Moderate | Moderate |
| Wang 2017 | Moderate | Moderate | Moderate |
| Wang 2019B | Low | Low | Low |
| Wang 2020A | High | High | High |

| Study names | HbA1c change | HbA1c change (regression) | Weight change |
|---|---|---|---|
| Wang 2020C | High | High | NA |
| Wang 2023 | Low | Low | Low |
| Webb 2020 | Low | Low | Low |
| Wilding 2012 | Moderate | Moderate | Moderate |
| Wu 2014 | High | High | NA |
| Wysham 2014 26 weeks | High | High | High |
| Xiao 2015 | High | High | NA |
| Xiao 2016 | High | High | NA |
| Xu 2017 | High | High | Low |
| Yabe 2020 | Moderate | Moderate | Moderate |
| Yabe 2023 | Low | Low | Low |
| Yan 2019 | Low | Low | Low |
| Yang 2018A | High | High | High |
| Yang 2021 | Moderate | Moderate | NA |
| Yki-Järvinen 2013 | Moderate | Moderate | NA |
| Yokoyama 2014 | High | High | High |
| Zhang 2020B | NA | NA | High |
| Zhao 2017 | High | High | High |

## 7.2. GRADE assessment

The quality of evidence from the NMA was assessed using a modified version of the GRADE approach to quality rating. Each GRADE domain was rated as 'not serious', 'serious' or 'very serious' and an overall quality rating was derived for the evidence from the NMA as whole. For a description of how the GRADE criteria were applied to the NMA, see the methods document. The summary for the effectiveness evidence for the NMA can be found in reports E1 and F1.

# 8. Discussion

For a full discussion of results, please refer to the committee's discussion of evidence.

# 9. Conclusions

Please refer please refer to the committee's discussion of evidence. for conclusions of this analysis and the economic analysis.

# 10. References


1. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Medical Decision Making. 2013; 33(5):641-656

2. Gunhan BK, Rover C, Friede T. Random-effects meta-analysis of few studies involving rare events. Res Synth Methods. 2020; 11(1):74-90

3. Skoetz N, Goldkuhle M, van Dalen EC, Akl EA, Trivella M, Mustafa RA et al. GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and Evidence Profiles. Journal of Clinical Epidemiology. 2020; 118:124-131

4. Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Medical Research Methodology. 2010; 10:54

# Appendices

## Appendix A NMA program code

## A.1 R code

### A.1.1 Fixed effects model:

```
library(readxl)

library(tidyverse)

library(multinma)

library(bayesplot)

library(ggplot2)

options(mc.cores = parallel::detectCores())


######### Functions ##########


# This function generates a league table from multinma relative
effects

 get.league <- function(nma, ume=NULL, digits=2, treatments,
expon=FALSE) {

  rels <- as.array(relative_effects(nma, all_contrasts = TRUE))


  # For NMA results (lower left triangle)

  med <- apply(rels, MARGIN=c(3), median)

  l95 <- apply(rels, MARGIN=c(3), FUN=function(x) quantile(x,
probs=0.025))

  u95 <- apply(rels, MARGIN=c(3), FUN=function(x) quantile(x,
probs=0.975))


  if (expon==TRUE) {

    med <- exp(med)

    l95 <- exp(l95)

    u95 <- exp(u95)
```

```
  }

  out.str <- vector()
  for (i in seq_along(med)) {
    out.str <- append(out.str, paste0(round(med[i], digits),
                                      " (", round(l95[i], digits),
", ",
                                      round(u95[i], digits), ")"
    ))
  }

  mat <- matrix(NA, nrow=length(treatments),
ncol=length(treatments),
                dimnames=list(treatments, treatments))
  mat[lower.tri(mat, diag=FALSE)] <- out.str

  # For UME results (upper right triangle)
  if (!is.null(ume)) {
    sum.ume <- summary(ume)$summary
    sum.ume <- sum.ume[grepl("^d\\[", sum.ume$parameter),]

    sum.ume <- sum.ume %>%
      mutate(
        t2=gsub("(^d\\[)(.+)( vs\\..+)", "\\2", parameter),
        t1=gsub("(^d\\[)(.+ vs\\. )(.+)(\\])", "\\3", parameter)
      )

    if (expon==TRUE) {
      sum.ume$`2.5%` <- exp(sum.ume$`2.5%`)
      sum.ume$`50%` <- exp(sum.ume$`50%`)
      sum.ume$`97.5%` <- exp(sum.ume$`97.5%`)
```

```
    }

    for (i in 1:(length(treatments)-1)) {
      for (k in 2:length(treatments)) {
        sub <- subset(sum.ume, t2==treatments[k] &
t1==treatments[i])

        if (nrow(sub)>0) {
          mat[i,k] <- paste0(round(sub$`50%`, digits),
                             " (", round(sub$`2.5%`, digits), ", ",
                             round(sub$`97.5%`, digits), ")"
          )
        }
      }
    }
  }

  return(mat)
}

######################## Data into multinma ######################

# CONTRAST DATA (logHRs)
# Note that we want to be analysing HRs on the log scale
# set_agd_contrast = set aggregate contrast data
hr.net <- set_agd_contrast(hr.df,
                           study=parent_study_name,
                           trt=trt,
                           y=lHR,
                           se=se.lHR,
                           sample_size=n)
```

```
print(hr.net)
plot(hr.net, weight_nodes=TRUE, nudge=0.2) +
  ggplot2::theme(legend.position = "bottom",
                 legend.box = "vertical")

# ARM DATA (r and n)
# set_agd_arm = set aggregate arm data
rn.net <- set_agd_arm(rn.df,
                      study=parent_study_name,
                      trt=trt,
                      r=r,
                      n=n,
                      sample_size=n)

print(rn.net)
plot(rn.net, weight_nodes=TRUE, nudge=0.2) +
  ggplot2::theme(legend.position = "bottom",
                 legend.box = "vertical")

# COMBINE CONTRAST AND ARM DATA
comb.net <- combine_network(hr.net, rn.net,
                            trt_ref="Placebo")

print(comb.net)
plot(comb.net, weight_nodes=TRUE, nudge=0.1) +
  ggplot2::theme(legend.position = "bottom",
                 legend.box = "vertical")

####################### Run NMA ####################
```

```
nma.fe <- nma(comb.net,
              consistency="consistency",
              trt_effects="fixed",
              regression = ~offset(log(time/52)),
              link="cloglog",
              prior_intercept = normal(0,100), # Default vague prior
is reasonable for logHR scale
              prior_trt = normal(0, 2.82) # Prior from Gunhan et al.
2019 on Weakly Informative Priors))
)
dic.fe <- dic(nma.fe)


plot(relative_effects(nma.fe), .width=c(0,0.95))


nma.re <- nma(comb.net, consistency="consistency",
              trt_effects="random",
              regression = ~offset(log(time/52)),
              link="cloglog",
              iter=6000,
              adapt_delta=0.99, # Can set this higher to improve
convergence - useful if you get warnings about divergent transitions
              prior_intercept = normal(0,100), # Default vague prior
is reasonable for logHR scale
              prior_trt = normal(0, 2.82), # Prior from Gunhan et
al. 2019 on Weakly Informative Priors))
              prior_het = half_normal(scale=5) # Default vague prior
is reasonable for logHR scale
)
dic.re <- dic(nma.re)


############## Check for consistency ##############
```

```
ume.fe <- nma(comb.net, consistency="ume",
              trt_effects="fixed",
              regression = ~offset(log(time/52)),
              link="cloglog",
              prior_intercept = normal(0,100), # Default vague prior
is reasonable for logHR scale
              prior_trt = normal(0, 2.82) # Prior from Gunhan et al.
2019 on Weakly Informative Priors))
)
dic.ume <- dic(ume.fe)


plot(dic.fe)
plot(dic.fe, dic.ume, show_uncertainty = FALSE)


arrange(dic.fe$pointwise$agd_arm, desc(resdev))


res.ume <- dic(ume.fe)$pointwise$agd_arm
res.fe <- dic(nma.fe)$pointwise$agd_arm %>%
  mutate(umedev=res.ume$resdev,
         ratio=resdev/umedev) %>%
  arrange(desc(ratio))


incon.study <- unique(res.fe$.study[res.fe$ratio>1.5])
view(long.df[long.df$parent_study_name %in% incon.study,])


######################## Model outputs  ######################


nma.selected <- nma.fe


rels <- relative_effects(nma.selected,
                         trt_ref="Placebo")
```

```
plot(rels, ref_line=0, .width=c(0,0.95))

leaguemat <- get.league(nma=nma.selected, # The NMA model
                        digits=2, # The number of decimal places
                        treatments=comb.net$treatments, # A vector
of treatment names
                        expon=FALSE # Results on log scale
)

leaguemat <- get.league(nma=nma.selected, # The NMA model
                        ume=ume.fe, # The UME model
                        digits=2, # The number of decimal places
                        treatments=comb.net$treatments, # A vector
of treatment names
                        expon=TRUE # Results on HR scale
)




ranks <- posterior_ranks(nma.selected,
                         lower_better = TRUE)

print(ranks)

rankprobs <- posterior_rank_probs(nma.selected, lower_better = TRUE)
plot(rankprobs)

cumranks <- posterior_rank_probs(nma.selected,
                                 lower_better = TRUE,
                                 cumulative=TRUE)
```

```
plot(cumranks)
```

### A.1.2 Random effects model:

```
library(readxl)

library(tidyverse)

library(multinma)

library(bayesplot)

library(ggplot2)

options(mc.cores = parallel::detectCores())


######### Functions ##########


# This function generates a league table from multinma relative
effects


  rels <- as.array(relative_effects(nma, all_contrasts = TRUE))


  # For NMA results (lower left triangle)

  med <- apply(rels, MARGIN=c(3), median)

  l95 <- apply(rels, MARGIN=c(3), FUN=function(x) quantile(x,
probs=0.025))

  u95 <- apply(rels, MARGIN=c(3), FUN=function(x) quantile(x,
probs=0.975))


  if (expon==TRUE) {

    med <- exp(med)

    l95 <- exp(l95)

    u95 <- exp(u95)

  }


  out.str <- vector()
```

```
  for (i in seq_along(med)) {
    out.str <- append(out.str, paste0(round(med[i], digits),
                                      " (", round(l95[i], digits),
", ",
                                      round(u95[i], digits), ")"
    ))
  }

  mat <- matrix(NA, nrow=length(treatments),
ncol=length(treatments),
                dimnames=list(treatments, treatments))
  mat[lower.tri(mat, diag=FALSE)] <- out.str

  # For UME results (upper right triangle)
  if (!is.null(ume)) {
    sum.ume <- summary(ume)$summary
    sum.ume <- sum.ume[grepl("^d\\[", sum.ume$parameter),]

    sum.ume <- sum.ume %>%
      mutate(
        t2=gsub("(^d\\[)(.+)( vs\\..+)", "\\2", parameter),
        t1=gsub("(^d\\[)(.+ vs\\. )(.+)(\\])", "\\3", parameter)
      )

    if (expon==TRUE) {
      sum.ume$`2.5%` <- exp(sum.ume$`2.5%`)
      sum.ume$`50%` <- exp(sum.ume$`50%`)
      sum.ume$`97.5%` <- exp(sum.ume$`97.5%`)
    }

    for (i in 1:(length(treatments)-1)) {
```

```
      for (k in 2:length(treatments)) {
        sub <- subset(sum.ume, t2==treatments[k] &
t1==treatments[i])

        if (nrow(sub)>0) {
          mat[i,k] <- paste0(round(sub$`50%`, digits),
                             " (", round(sub$`2.5%`, digits), ", ",
                             round(sub$`97.5%`, digits), ")"
          )
        }
      }
    }
  }

  return(mat)
}

######################## Data into multinma ######################

# CONTRAST DATA (logHRs)
# Note that we want to be analysing HRs on the log scale
# set_agd_contrast = set aggregate contrast data
hr.net <- set_agd_contrast(hr.df,
                           study=parent_study_name,
                           trt=trt,
                           y=lHR,
                           se=se.lHR,
                           sample_size=n)

print(hr.net)
plot(hr.net, weight_nodes=TRUE, nudge=0.2) +
```

```
  ggplot2::theme(legend.position = "bottom",
                 legend.box = "vertical")

# ARM DATA (r and n)
# set_agd_arm = set aggregate arm data
rn.net <- set_agd_arm(rn.df,
                      study=parent_study_name,
                      trt=trt,
                      r=r,
                      n=n,
                      sample_size=n)

print(rn.net)
plot(rn.net, weight_nodes=TRUE, nudge=0.2) +
  ggplot2::theme(legend.position = "bottom",
                 legend.box = "vertical")

# COMBINE CONTRAST AND ARM DATA
comb.net <- combine_network(hr.net, rn.net,
                            trt_ref="Placebo")

print(comb.net)
plot(comb.net, weight_nodes=TRUE, nudge=0.1) +
  ggplot2::theme(legend.position = "bottom",
                 legend.box = "vertical")

####################### Run NMA ######################

nma.fe <- nma(comb.net,
              consistency="consistency",
```

```
              trt_effects="fixed",

              regression = ~offset(log(time/52)),

              link="cloglog",

              prior_intercept = normal(0,100), # Default vague prior
is reasonable for logHR scale

              prior_trt = normal(0, 2.82) # Prior from Gunhan et al.
2019 on Weakly Informative Priors))

)

dic.fe <- dic(nma.fe)


plot(relative_effects(nma.fe), .width=c(0,0.95))


nma.re <- nma(comb.net, consistency="consistency",

              trt_effects="random",

              regression = ~offset(log(time/52)),

              link="cloglog",

              iter=6000,

              adapt_delta=0.99, # Can set this higher to improve
convergence - useful if you get warnings about divergent transitions

              prior_intercept = normal(0,100), # Default vague prior
is reasonable for logHR scale

              prior_trt = normal(0, 2.82), # Prior from Gunhan et
al. 2019 on Weakly Informative Priors))

              prior_het = half_normal(scale=5) # Default vague prior
is reasonable for logHR scale

)

dic.re <- dic(nma.re)


############## Check for consistency ##############


ume.re <- nma(comb.net, consistency="ume",

              trt_effects="random",

              regression = ~offset(log(time/52)),
```

```
              link="cloglog",
              prior_intercept = normal(0,100), # Default vague prior
is reasonable for logHR scale
              prior_trt = normal(0, 2.82) # Prior from Gunhan et al.
2019 on Weakly Informative Priors))
)
dic.ume <- dic(ume.re)

plot(dic.re)
plot(dic.re, dic.ume, show_uncertainty = FALSE)

arrange(dic.re$pointwise$agd_arm, desc(resdev))

res.ume <- dic(ume.re)$pointwise$agd_arm
res.re <- dic(nma.re)$pointwise$agd_arm %>%
  mutate(umedev=res.ume$resdev,
         ratio=resdev/umedev) %>%
  arrange(desc(ratio))

incon.study <- unique(res.re$.study[res.re$ratio>1.5])
view(long.df[long.df$parent_study_name %in% incon.study,])

######################## Model outputs  ####################

nma.selected <- nma.re

rels <- relative_effects(nma.selected,
                         trt_ref="Placebo")
plot(rels, ref_line=0, .width=c(0,0.95))

leaguemat <- get.league(nma=nma.selected, # The NMA model
```

```
                        digits=2, # The number of decimal places
                        treatments=comb.net$treatments, # A vector
of treatment names
                        expon=FALSE # Results on log scale
)

leaguemat <- get.league(nma=nma.selected, # The NMA model
                        ume=ume.re, # The UME model
                        digits=2, # The number of decimal places
                        treatments=comb.net$treatments, # A vector
of treatment names
                        expon=TRUE # Results on HR scale
)




ranks <- posterior_ranks(nma.selected,
                         lower_better = TRUE)

print(ranks)

rankprobs <- posterior_rank_probs(nma.selected, lower_better = TRUE)
plot(rankprobs)

cumranks <- posterior_rank_probs(nma.selected,
                                 lower_better = TRUE,
                                 cumulative=TRUE)
plot(cumranks)
```

# Appendix B Baseline risk tables

Bolded rows are the selected proportion for modelling the baseline risk. The decision rules for selection of baseline risk values include:

1. The value has to be reported later than 2 years – this ensures that it is a true reflection of the outcomes of interest.

2. Timepoint selection:

    a. Is a timepoint reported for all population models? Choose the value closest to this time – this allows the values to be comparable between the different models

    b. Where available, data points where there are multiple values for a timepoint (+/- 2 months) will be prioritised over others – this means that the consistency of values at that timepoint can allow for more validation in the final result.

3. The value from a study with the lowest risk of bias will be used.

4. After other rules have been applied, the study from the latest time point will be used.

## B.1 Model 1: People with type 2 diabetes and heart failure

**Table 47: Risk of cardiovascular mortality events reported in trials that informed baseline risk for the placebo arm in model 1**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| **Marso 2016A** | **46** | **88/832** | **10.6%** | **Selected as Marso 2016A was the lowest risk of bias study at the latest time point.** |
| McMurray 2018 | 12 | 4/126 | 3.2% | Ignore as short follow-up – unlikely to have captured events |
| White 2013 | 18 | 69/762 | 9.1% | Ignore as short follow-up – unlikely to have captured events |
| Wiviott 2019 | 50 | 74/872 | 8.5% | NA |

**Table 48: Risk of 3-item MACE events reported in trials that informed baseline risk for the placebo arm in model 1**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Cannon 2020 | 36 | 94/671 | 14.0% | NA |
| **Holman 2017** | **38** | **237/1228** | **19.3%** | **Selected as multiple reports around 37 months. Both low risk of bias.** |

| | | | | |
|---|---|---|---|---|
| | | | | **Latest reporting by Holman 2017. Allows for better comparison between all populations than using a longer timepoint (for example: Marso 2016A).** |
| Marso 2016A | 46 | 170/832 | 20.4% | NA |
| Marso 2016B | 25 | 34/288 | 11.8% | NA |
| White 2013 | 18 | 131/762 | 17.2% | Ignore as short follow-up – unlikely to have captured events |
| Wiviott 2019 | 50 | 151/872 | 17.3% | NA |

**Table 49: Risk of non-fatal myocardial infarction events reported in trials that informed baseline risk for the placebo arm in model 1**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| **Marso 2016A** | **46** | **71/832** | **8.5%** | **Selected as Marso 2016A was the lowest risk of bias study at the latest time point.** |
| White 2013 | 18 | 66/762 | 8.7% | Ignore as short follow-up – unlikely to have captured events |
| Wiviott 2019 | 50 | 76/872 | 8.7% | NA |

**Table 50: Risk of non-fatal stroke events reported in trials that informed baseline risk for the placebo arm in model 1**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| **Marso 2016A** | **46** | **30/832** | **3.6%** | **Selected as Marso 2016A was the lowest risk of bias study at the latest time point.** |
| McMurray 2018 | 12 | 4/126 | 3.2% | Ignore as short follow-up – unlikely to have captured events |
| White 2013 | 18 | 6/762 | 0.8% | Ignore as short follow-up – unlikely to have captured events |
| Wiviott 2019 | 50 | 34/872 | 2.8% | NA |

**Table 51: Risk of unstable angina events reported in trials that informed baseline risk for the placebo arm in model 1**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| **Marso 2016A** | **46** | **30/832** | **3.6%** | **Selected as Marso 2016A was the lowest risk of bias study at the latest time point.** |
| White 2013 | 18 | 11/762 | 1.4% | Ignore as short follow-up – unlikely to have captured events |

**Table 52: Risk of hospitalisation for heart failure events reported in trials that informed baseline risk for the placebo arm in model 1**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Cannon 2020 | 36 | 55/672 | 8.2% | NA |
| Green 2015 | 36 | 94/1340 | 7.0% | NA |
| **Marso 2016A** | **46** | **108/832** | **13.0%** | **Selected as Marso 2016A reflected the lowest risk of bias at the latest timepoint that also allowed for the best comparison with the higher risk group to maintain consistency with previous comparisons.** |
| McMurray 2018 | 12 | 10/126 | 7.9% | Ignore as short follow-up – unlikely to have captured events |
| Pfeffer 2015 | 25 | 69/676 | 10.2% | NA |
| Rosenstock 2019A | 26 | 122/921 | 13.2% | NA |
| White 2013 | 18 | 65/762 | 8.5% | Ignore as short follow-up – unlikely to have captured events |
| Wiviott 2019 | 50 | 115/872 | 13.2% | NA |

## B.2 Model 2: People with type 2 diabetes and atherosclerotic cardiovascular disease

**Table 53: Risk of cardiovascular mortality events reported in trials that informed baseline risk for the placebo arm in model 2**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Cannon 2020 | 36 | 184/2745 | 6.7% | NA |
| Cefalu 2015 | 12 | 2/462 | 0.4% | Ignore as short follow-up – unlikely to have captured events |
| Green 2015 | 36 | 366/7339 | 5.0% | NA |
| Leiter 2014 | 12 | 1/483 | 0.2% | Ignore as short follow-up – unlikely to have captured events |
| Pfeffer 2015 | 25 | 158/3034 | 5.2% | NA |
| White 2013 | 18 | 130/2679 | 4.9% | Ignore as short follow-up – unlikely to have captured events |
| Wilcox 2008 | 36 | 136/2633 | 5.2% | NA |
| Wiviott 2019 | 50 | 163/3500 | 4.7% | NA |
| **Zinman 2015** | **37** | **137/2333** | **5.9%** | **Selected as Zinman 2015 had the lowest risk of bias at the latest timepoint while being comparable to other population groups (chronic kidney disease).** |

**Table 54: Risk of 3-item MACE events reported in trials that informed baseline risk for the placebo arm in model 2**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Cannon 2020 | 36 | 327/2745 | 11.9% | NA |
| Gerstein 2019A | 65 | 663/4952 | 13.4% | NA |
| Green 2015 | 36 | 746/7339 | 10.2% | NA |
| **Holman 2017** | **38** | **786/5388** | **14.6%** | **Selected as Holman 2017 is the latest timepoint out of those reported around 37 months that are of low risk of bias.** |
| Scirica 2013 | 25 | 550/6465 | 8.5% | NA |
| White 2013 | 18 | 316/2679 | 11.8% | Ignore as short follow-up – unlikely to have captured events |

| | | | | |
|---|---|---|---|---|
| Wilcox 2008 | 36 | 313/2633 | 11.9% | NA |
| Wiviott 2019 | 50 | 537/3500 | 15.3% | NA |
| Zinman 2015 | 37 | 282/2333 | 12.1% | NA |

**Table 55: Risk of non-fatal myocardial infarction events reported in trials that informed baseline risk for the placebo arm in model 2**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Cannon 2020 | 36 | 148/2747 | 5.4% | NA |
| Green 2015 | 36 | 302/7339 | 4.1% | NA |
| Lee 2013B | 12 | 1/61 | 1.6% | Ignore as short follow-up – unlikely to have captured events |
| Leiter 2014 | 12 | 1/483 | 0.2% | Ignore as short follow-up – unlikely to have captured events |
| Pfeffer 2015 | 25 | 247/3034 | 8.1% | NA |
| White 2013 | 18 | 173/2679 | 6.5% | Ignore as short follow-up – unlikely to have captured events |
| Wilcox 2008 | 36 | 144/2633 | 5.5% | NA |
| Wiviott 2019 | 50 | 321/3500 | 9.2% | NA |
| **Zinman 2015** | **37** | **121/2333** | **5.2%** | **Selected as it was of low risk of bias and the latest time point out of the studies reported around 36 months.** |

**Table 56: Risk of non-fatal stroke events reported in trials that informed baseline risk for the placebo arm in model 2**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Cannon 2020 | 36 | 78/2747 | 2.8% | NA |
| Pfeffer 2015 | 25 | 49/3034 | 1.6% | NA |
| White 2013 | 18 | 32/2679 | 1.2% | Ignore as short follow-up – unlikely to have captured events |
| Wilcox 2008 | 36 | 107/2633 | 4.1% | NA |
| Wiviott 2019 | 50 | 142/3500 | 4.1% | NA |
| **Zinman 2015** | **37** | **60/2333** | **2.6%** | **Selected as it was of low risk of bias and the latest time point out of the studies** |

| | | | | |
|---|---|---|---|---|
| | | | | **reported around 36 months.** |

**Table 57: Risk of unstable angina events reported in trials that informed baseline risk for the placebo arm in model 2**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Cannon 2020 | 36 | 89/2745 | 3.2% | NA |
| Cefalu 2015 | 12 | 7/462 | 1.5% | Ignore as short follow-up – unlikely to have captured events |
| Green 2015 | 36 | 129/7339 | 1.8% | NA |
| Pfeffer 2015 | 25 | 10/3034 | 0.3% | NA |
| White 2013 | 18 | 47/2679 | 1.8% | Ignore as short follow-up – unlikely to have captured events |
| **Zinman 2015** | **37** | **66/2333** | **2.8%** | **Selected as it was of low risk of bias and the latest time point out of the studies reported around 36 months.** |

**Table 58: Risk of hospitalisation for heart failure events reported in trials that informed baseline risk for the placebo arm in model 2**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Cannon 2020 | 36 | 99/2747 | 3.6% | NA |
| Cefalu 2015 | 12 | 1/462 | 0.2% | Ignore as short follow-up – unlikely to have captured events |
| Green 2015 | 36 | 229/7339 | 3.1% | NA |
| Pfeffer 2015 | 25 | 127/3034 | 4.2% | NA |
| White 2013 | 18 | 89/2679 | 3.3% | Ignore as short follow-up – unlikely to have captured events |
| Wilcox 2008 | 36 | 108/2633 | 4.1% | NA |
| Wiviott 2019 | 50 | 192/3500 | 5.5% | NA |
| **Zinman 2015** | **37** | **95/2333** | **4.1%** | **Selected as it was of low risk of bias and the latest time point out of the studies reported around 36 months.** |

## B.3 Model 3: People with type 2 diabetes and chronic kidney disease

**Table 59: Risk of cardiovascular mortality events reported in trials that informed baseline risk for the placebo arm in model 3**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comments |
|---|---|---|---|---|
| Kohan 2014 | 24 | 3/84 | 3.6% | Unlikely to be a plausible measure of baseline rate due to small sample size. |
| Perkovic 2019 | 31 | 140/2199 | 6.4% | NA |
| Wada 2022 | 24 | 1/154 | 0.7% | Unlikely to be a plausible measure of baseline rate due to small sample size. |
| Wiviott 2019 | 50 | 138/2940 | 4.7% | NA |
| **Zinman 2015** | **37** | **65/752** | **8.6%** | **Selected as Zinman 2015 was reported at the latest time point of the studies with the lowest risk of bias.** |

**Table 60: Risk of 3-item MACE events reported in trials that informed baseline risk for the placebo arm in model 3**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comments |
|---|---|---|---|---|
| **Perkovic 2019** | **31** | **253/2199** | **11.5%** | **Selected as Perkovic 2019 was reported at the latest time point of the studies with the lowest risk of bias.** |
| Wiviott 2019 | 50 | 371/2940 | 12.6% | NA |

**Table 61: Risk of non-fatal myocardial infarction events reported in trials that informed baseline risk for the placebo arm in model 3**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comments |
|---|---|---|---|---|
| McGill 2013 | 12 | 2/65 | 3.1% | Ignore as short follow-up – unlikely to have captured events |

**Table 62: Risk of non-fatal stroke events reported in trials that informed baseline risk for the placebo arm in model 3**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comments |
|---|---|---|---|---|
| McGill 2013 | 12 | 1/65 | 1.5% | Ignore as short follow-up – unlikely to have captured events |

**Table 63: Risk of hospitalisation for heart failure events reported in trials that informed baseline risk for the placebo arm in model 3**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comments |
|---|---|---|---|---|
| Grunberger 2018 | 12 | 1/154 | 0.6% | Ignore as short follow-up – unlikely to have captured events |
| Perkovic 2019 | 31 | 141/2199 | 6.4% | NA |
| Rosenstock 2019A | 26 | 188/2074 | 9.1% | NA |
| Wada 2022 | 24 | 3/154 | 2.0% | Unlikely to be a plausible measure of baseline rate due to small sample size. |
| Wiviott 2019 | 50 | 166/2940 | 5.7% | NA |
| **Zinman 2015** | **37** | **53/752** | **7.1%** | **Zinman 2015 was reported at the latest time point of the studies with the lowest risk of bias.** |

**Table 64: Risk of development of end-stage renal failure events reported in trials that informed baseline risk for the placebo arm in model 3**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comments |
|---|---|---|---|---|
| Kohan 2014 | 24 | 2/84 | 2.4% | Unlikely to be a plausible measure of baseline rate due to small sample size. |
| Nowicki 2011A | 12 | 2/85 | 2.4% | Ignore as short follow-up – unlikely to have captured events |
| **Perkovic 2019** | **31** | **165/2199** | **7.5%** | **Only remaining study.** |

## B.4 Model 5: People with type 2 diabetes and higher cardiovascular risk

**Table 65: Risk of cardiovascular mortality events reported in trials that informed baseline risk for the placebo arm in model 5**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Gerstein 2019A | 65 | 346/4952 | 7.0% | NA |
| Holman 2017 | 38 | 383/7396 | 5.2% | NA |
| Husain 2019 | 16 | 30/1592 | 1.9% | Ignore as short follow-up – unlikely to have captured events |
| Kooy 2009 | 52 | 1/194 | 0.5% | Unlikely to be a plausible measure of baseline rate due to small sample size. Inconsistent with other studies. |
| **Marso 2016A** | **46** | **278/4672** | **6.0%** | **Selected as Marso 2016A was reported at a comparable timepoint to other population groups (unlike Gerstein 2019A) and out of studies with the lowest risk of bias, it was the one at the latest timepoint possible.** |
| Marso 2016B | 25 | 46/1649 | 2.8% | NA |
| Rosenstock 2019A | 26 | 264/3485 | 7.6% | NA |
| Scirica 2013 | 25 | 260/8212 | 3.2% | NA |
| Wiviott 2019 | 50 | 249/8578 | 2.9% | NA |
| Yki-Järvinen 2013 | 14 | 1/630 | 0.2% | Ignore as short follow-up – unlikely to have captured events |

**Table 66: Risk of 3-item MACE events reported in trials that informed baseline risk for the placebo arm in model 5**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Garvey 2023 | 18 | 7/623 | 1.1% | Ignore as short follow-up – unlikely to have captured MACE events |
| Gerstein 2019A | 65 | 663/4952 | 13.4% | NA |
| **Holman 2017** | **38** | **905/7396** | **12.2%** | **Selected as Holman 2017 was reported at a comparable timepoint to other population groups** |

| | | | | |
|---|---|---|---|---|
| | | | | **(unlike Gerstein 2019A and Rosenstock 2019A) and out of studies with the lowest risk of bias, it was the one at the latest timepoint possible.** |
| Home 2015 | 12 | 10/115 | 8.7% | Ignore as short follow-up – unlikely to have captured events |
| Husain 2019 | 16 | 76/1592 | 4.8% | Ignore as short follow-up – unlikely to have captured events |
| Rosenstock 2019A | 46 | 420/3485 | 12.1% | NA |
| Wiviott 2019 | 50 | 803/8578 | 9.4% | NA |

**Table 67: Risk of 4-item MACE events reported in trials that informed baseline risk for the placebo arm in model 5**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Dahl 2022 | 11 | 1/120 | 0.8% | Ignore as short follow-up – unlikely to have captured events |
| **Rosenstock 2019A** | **26** | **459/3486** | **13.2%** | **Only remaining study** |

**Table 68: Risk of 5-item MACE events reported in trials that informed baseline risk for the placebo arm in model 5**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Husain 2019 | 16 | 100/1592 | 6.3% | Ignore as short follow-up – unlikely to have captured events |
| **Marso 2016B** | **25** | **254/1649** | **15.4%** | **Only remaining study** |
| Yki-Järvinen 2013 | 14 | 11/630 | 0.2% | Ignore as short follow-up – unlikely to have captured events |

**Table 69: Risk of non-fatal myocardial infarction events reported in trials that informed baseline risk for the placebo arm in model 5**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Gerstein 2019A | 65 | 212/4952 | 4.3% | NA |

| | | | | |
|---|---|---|---|---|
| Husain 2019 | 16 | 31/1592 | 1.9% | Ignore as short follow-up – unlikely to have captured events |
| **Marso 2016A** | **46** | **317/4672** | **6.8%** | **Selected as Marso 2016A was reported at a comparable timepoint to other population groups (unlike Gerstein 2019A) and out of studies with the lowest risk of bias, it was the one at the latest timepoint possible.** |
| Marso 2016B | 25 | 64/1649 | 3.9% | NA |
| Rosenstock 2019A | 26 | 135/3485 | 3.9% | NA |
| Scirica 2013 | 25 | 278/8173 | 3.4% | NA |
| Wiviott 2019 | 50 | 441/8578 | 5.1% | NA |
| Zinman 2019B | 12 | 2/184 | 1.1% | Ignore as short follow-up – unlikely to have captured events |

**Table 70: Risk of non-fatal stroke events reported in trials that informed baseline risk for the placebo arm in model 5**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Gerstein 2019A | 65 | 175/4952 | 3.5% | NA |
| Husain 2019 | 16 | 16/1592 | 1.0% | Ignore as short follow-up – unlikely to have captured events |
| Kawamori 2018 | 12 | 1/93 | 1.1% | Ignore as short follow-up – unlikely to have captured events |
| **Marso 2016A** | **46** | **177/4672** | **3.8%** | **Selected as Marso 2016A was reported at a comparable timepoint to other population groups (unlike Gerstein 2019A) and out of studies with the lowest risk of bias, it was the one at the latest timepoint possible.** |
| Marso 2016B | 25 | 44/1649 | 2.7% | NA |
| Pratley 2019 | 12 | 1/142 | 0.7% | Ignore as short follow-up – unlikely to have captured events |
| Rosenstock 2019A | 26 | 73/3485 | 2.1% | NA |
| Scirica 2013 | 25 | 141/8173 | 1.7% | NA |

| | | | | |
|---|---|---|---|---|
| Wiviott 2019 | 50 | 231/8578 | 2.7% | NA |
| Zinman 2019B | 12 | 3/184 | 1.6% | Ignore as short follow-up – unlikely to have captured events |

**Table 71: Risk of unstable angina events reported in trials that informed baseline risk for the placebo arm in model 5**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Gerstein 2019A | 65 | 77/4952 | 1.6% | NA |
| Holman 2017 | 38 | 151/7396 | 2.0% | NA |
| Husain 2019 | 16 | 7/1592 | 0.4% | Ignore as short follow-up – unlikely to have captured events |
| **Marso 2016A** | **46** | **124/4672** | **2.7%** | **Selected as Marso 2016A was reported at a comparable timepoint to other population groups (unlike Gerstein 2019A) and out of studies with the lowest risk of bias, it was the one at the latest timepoint possible.** |
| Marso 2016B | 25 | 27/1649 | 1.6% | NA |
| Rosenstock 2019A | 26 | 47/3485 | 1.3% | NA |
| Scirica 2013 | 25 | 81/8212 | 1.0% | NA |
| Sone 2019 | 12 | 1/90 | 1.1% | Ignore as short follow-up – unlikely to have captured events |
| Wiviott 2019 | 50 | 238/8578 | 2.8% | NA |

**Table 72: Risk of hospitalisation for heart failure events reported in trials that informed baseline risk for the placebo arm in model 5**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Gerstein 2019A | 65 | 226/4952 | 4.6% | NA |
| Holman 2017 | 38 | 231/7396 | 3.1% | NA |
| Husain 2019 | 16 | 24/1592 | 1.5% | Ignore as short follow-up – unlikely to have captured events |
| Kooy 2009 | 52 | 4/194 | 2.1% | Unlikely to be a plausible measure of baseline rate due to small sample size. |
| **Marso 2016A** | **46** | **248/4672** | **5.3%** | **Selected as Marso 2016A was reported at a** |

| | | | | |
|---|---|---|---|---|
| | | | | **comparable timepoint to other population groups (unlike Gerstein 2019A) and out of studies with the lowest risk of bias, it was the one at the latest timepoint possible.** |
| Marso 2016B | 25 | 54/1649 | 3.3% | NA |
| Rosenstock 2019A | 26 | 226/3485 | 6.5% | NA |
| Scirica 2013 | 25 | 228/8173 | 2.8% | NA |
| Wiviott 2019 | 50 | 286/8578 | 3.3% | NA |

**Table 73: Risk of development of end-stage renal failure events reported in trials that informed baseline risk for the placebo arm in model 5**

| Trial name | Timepoint | Number of events / Total randomised | Proportion | Comment |
|---|---|---|---|---|
| Gerstein 2019A | 65 | 6/4952 | 0.1% | NA |
| **Holman 2017** | **38** | **65/7396** | **0.9%** | **Selected as Holman 2017 was reported at a comparable timepoint to the chronic kidney disease group (unlike Gerstein 2019A and Marso 2016A) and out of studies with the lowest risk of bias, it was the one at the latest timepoint possible.** |
| Marso 2016A | 46 | 64/4672 | 1.4% | NA |
| Rosenstock 2019A | 26 | 64/3485 | 1.8% | NA |
| Scirica 2013 | 25 | 55/8212 | 0.7% | NA |
| Wiviott 2019 | 50 | 19/8578 | 0.2% | NA |