National Institute for Health and Care Excellence

Final

Type 2 diabetes in adults: management

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

NICE guideline

Evidence reviews underpinning recommendations 1.9.1 to 1.9.5, 1.10.1 to 1.18.4, 1.19.1 to 1.19.2, 1.20.1 to 1.20.2, 1.21.3 to 1.31.1 and recommendations for research in the NICE guideline

February 2026

Final

This evidence review was developed by NICE

NICE accredited
www.nice.org.uk/accreditation

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

© NICE 2026. All rights reserved. Subject to Notice of rights.

ISBN: 978-1-4731-9272-0

Contents

1. Introduction 7
2. Study selection 8
2.1. Population 8
2.2. Interventions and their comparability 8
2.3. Outcome measures 10
3. Statistical methods 11
3.1. Synthesis methods 11
3.1.1. Priors 11
3.1.2. Convergence 11
3.1.3. Methods of sensitivity analyses, subgroup analyses and meta-regression 11
3.1.4. Between study heterogeneity 12
3.1.5. Baseline model and data 12
3.2. Summary measures and reference treatment 13
3.3. Methods of assessing inconsistency 14
3.4. Model comparison 14
3.5. Assessing clinical importance 14
4. Outcomes – model 5 – high cardiovascular risk 15
4.1. Cardiovascular mortality 15
4.2. 3-item MACE 16
4.3. 4-item MACE 17
4.4. 5-item MACE 18
4.5. Non-fatal myocardial infarction 19
4.6. Non-fatal stroke 20
4.7. Unstable angina 21
4.8. Hospitalisation for heart failure 22
4.9. Development of end-stage renal failure 23
5. Model fit – model 5 – high cardiovascular risk 24
5.1. Cardiovascular mortality 24
5.2. 3-item MACE 27
5.3. 4-item MACE 30
5.4. 5-item MACE 33
5.5. Non-fatal myocardial infarction 36
5.6. Non-fatal stroke 39
5.7. Unstable angina 42
5.8. Hospitalisation for heart failure 45
5.9. Development of end-stage renal failure 48
6. Results – model 5 – high cardiovascular risk 51

6.1. Relative effectiveness matrices 51
6.1.1. Cardiovascular mortality 53
6.1.2. 3-item MACE 63
6.1.3. 4-item MACE 65
6.1.4. 5-item MACE 65
6.1.5. Non-fatal myocardial infarction 66
6.1.6. Non-fatal stroke 69
6.1.7. Unstable angina 75
6.1.8. Hospitalisation for heart failure 77
6.1.9. Development of end-stage renal failure 82
6.2. Absolute effect tables 83
6.2.1. Cardiovascular mortality 83
6.2.2. 3-item MACE 85
6.2.3. 4-item MACE 86
6.2.4. 5-item MACE 86
6.2.5. Non-fatal myocardial infarction 86
6.2.6. Non-fatal stroke 88
6.2.7. Unstable angina 89
6.2.8. Hospitalisation for heart failure 91
6.2.9. Development of end-stage renal failure 92
6.3. Rank tables 93
6.3.1. Cardiovascular mortality 93
6.3.2. 3-item MACE 94
6.3.3. 4-item MACE 94
6.3.4. 5-item MACE 94
6.3.5. Non-fatal myocardial infarction 95
6.3.6. Non-fatal stroke 95
6.3.7. Unstable angina 96
6.3.8. Hospitalisation for heart failure 97
6.3.9. Development of end-stage renal failure 97
6.4. Relative effectiveness plots 98
6.4.1. Cardiovascular mortality 98
6.4.2. 3-item MACE 99
6.4.3. 4-item MACE 100
6.4.4. 5-item MACE 101
6.4.5. Non-fatal myocardial infarction 102
6.4.6. Non-fatal stroke 103
6.4.7. Unstable angina 104
6.4.8. Hospitalisation for heart failure 105
6.4.9. Development of end-stage renal failure 106

6.5. Cumulative ranking probability plots 107
6.5.1. Cardiovascular mortality 107
6.5.2. 3-item MACE 108
6.5.3. 4-item MACE 109
6.5.4. 5-item MACE 110
6.5.5. Non-fatal myocardial infarction 111
6.5.6. Non-fatal stroke 112
6.5.7. Unstable angina 113
6.5.8. Hospitalisation for heart failure 114
6.5.9. Development of end-stage renal failure 115
7. Quality assessment 116
7.1. Risk of bias 116
7.2. GRADE assessment 136
8. Discussion 137
9. Conclusions 138
10. References 139

Appendices 140
Appendix A NMA program code 140
Appendix B Baseline risk tables 153

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.

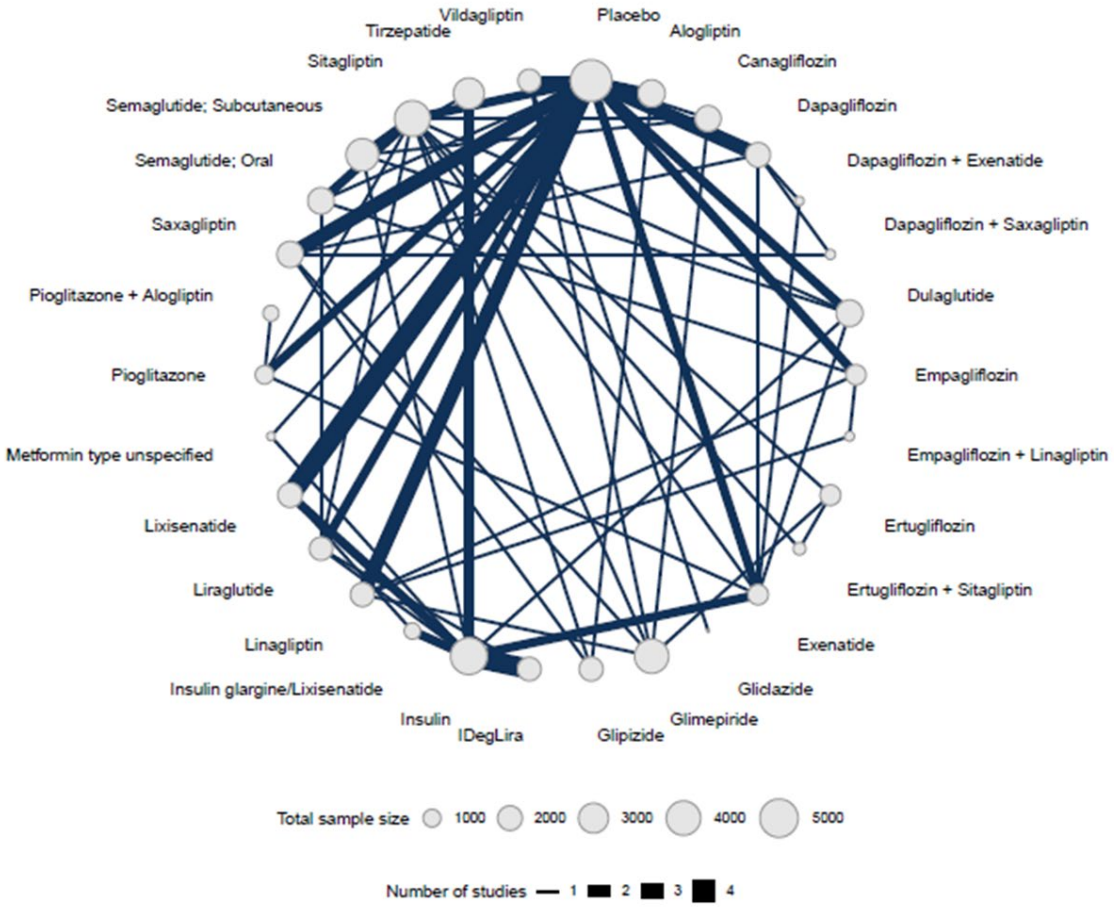
3.5. Assessing clinical importance

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

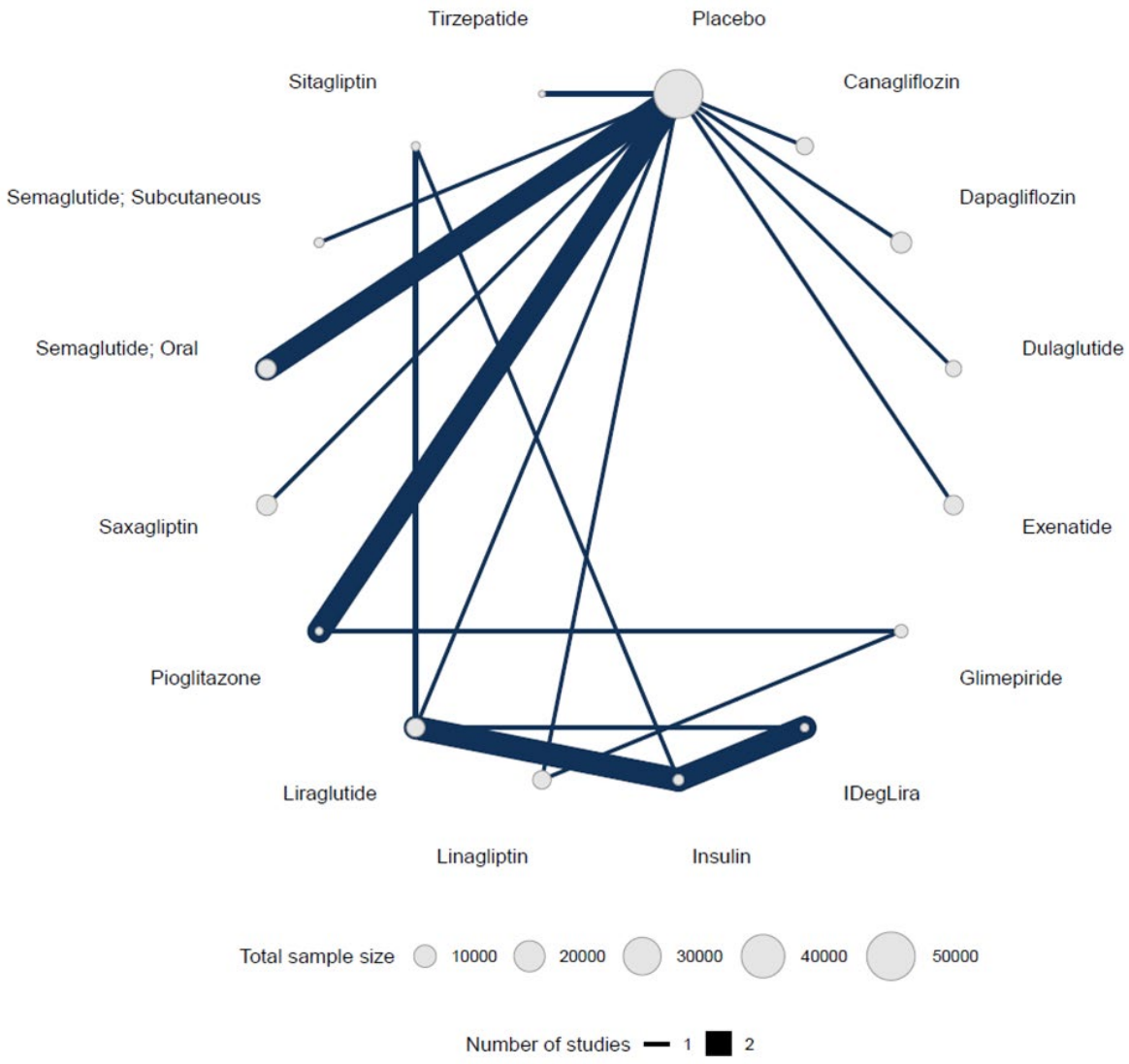
4.1. Cardiovascular mortality

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.



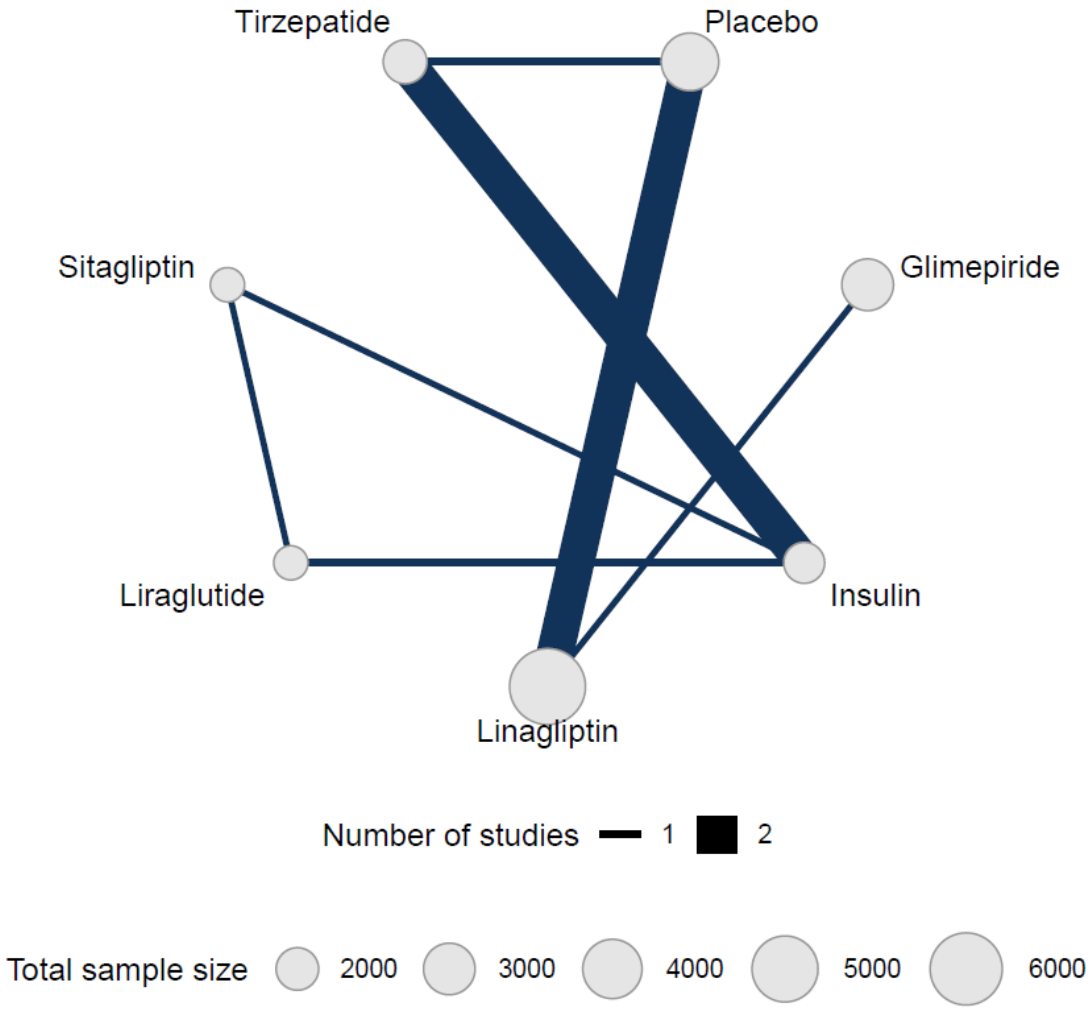
4.2. 3-item MACE

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.



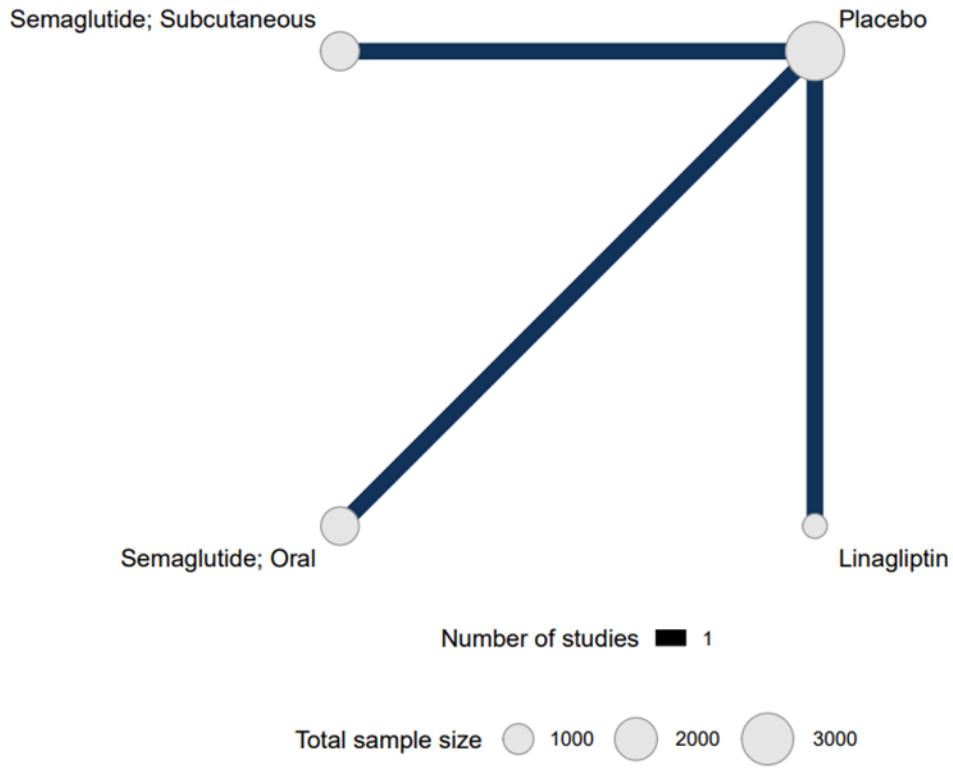
4.3. 4-item MACE

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.



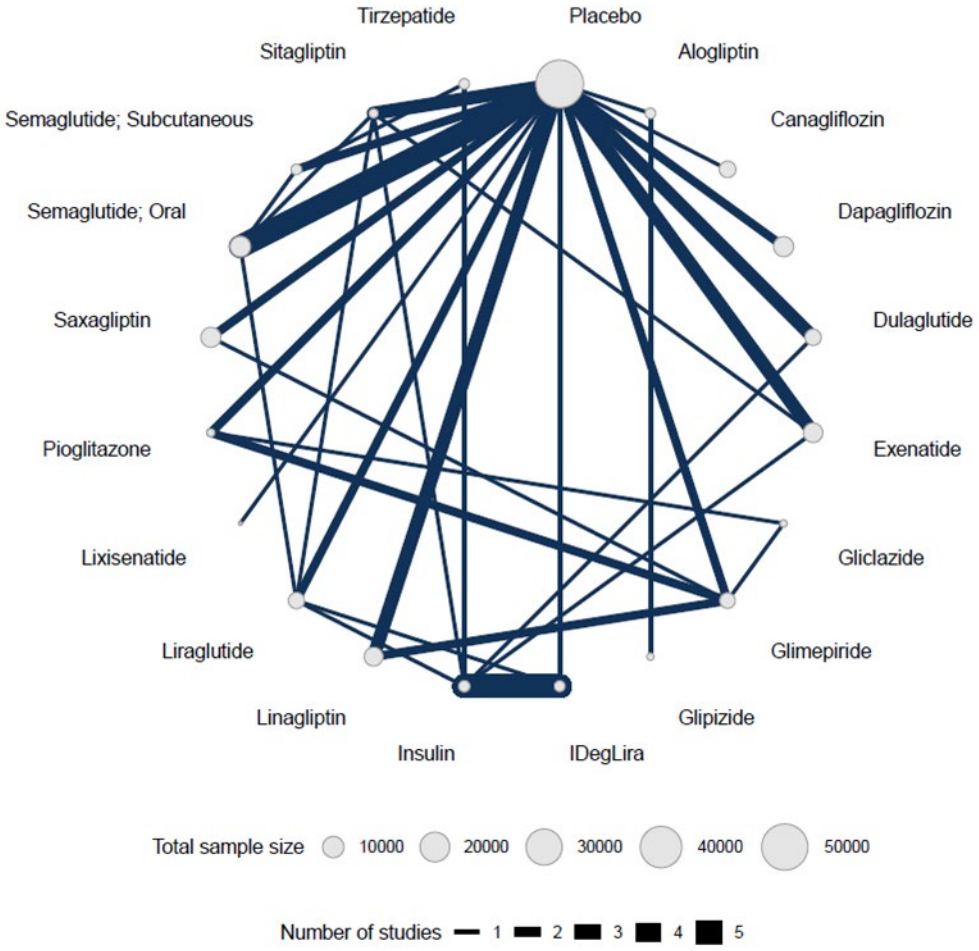
4.4. 5-item MACE

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.



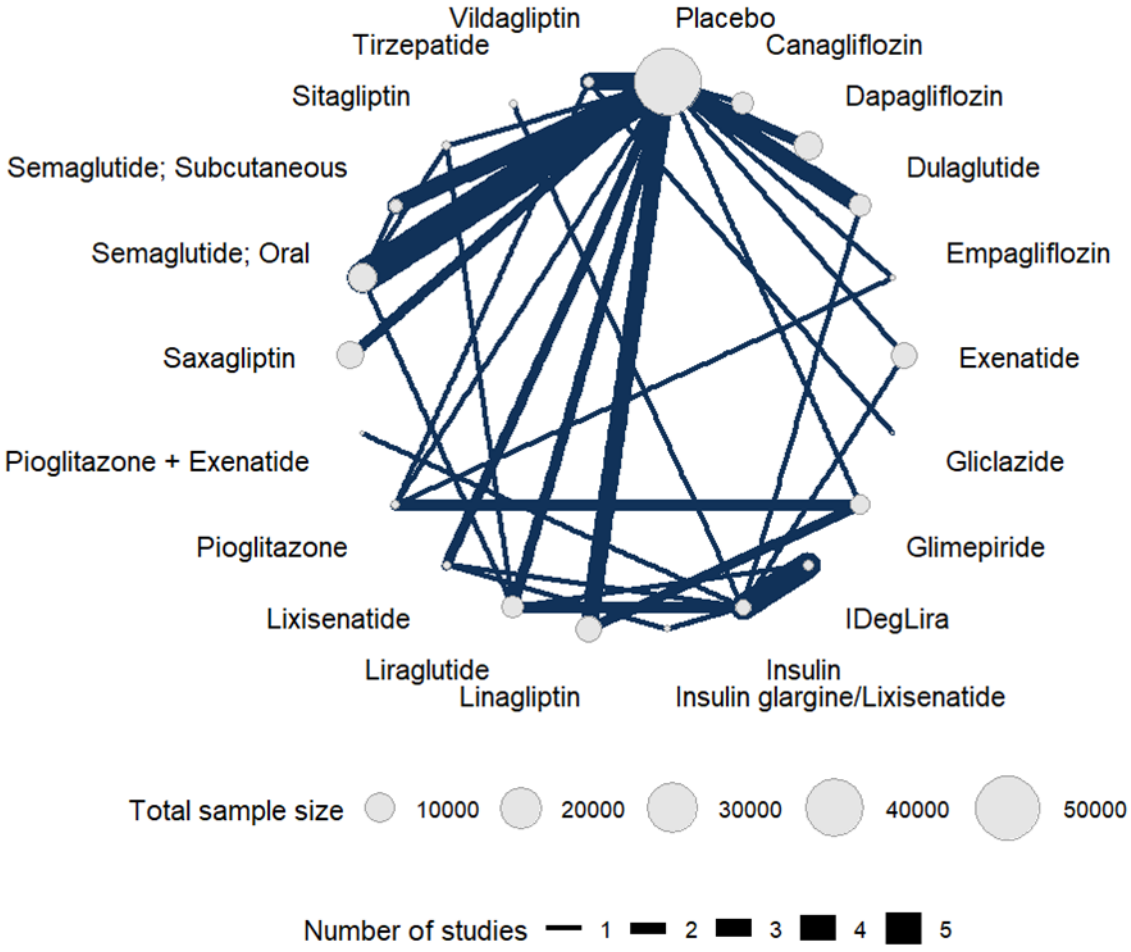
4.5. Non-fatal myocardial infarction

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.



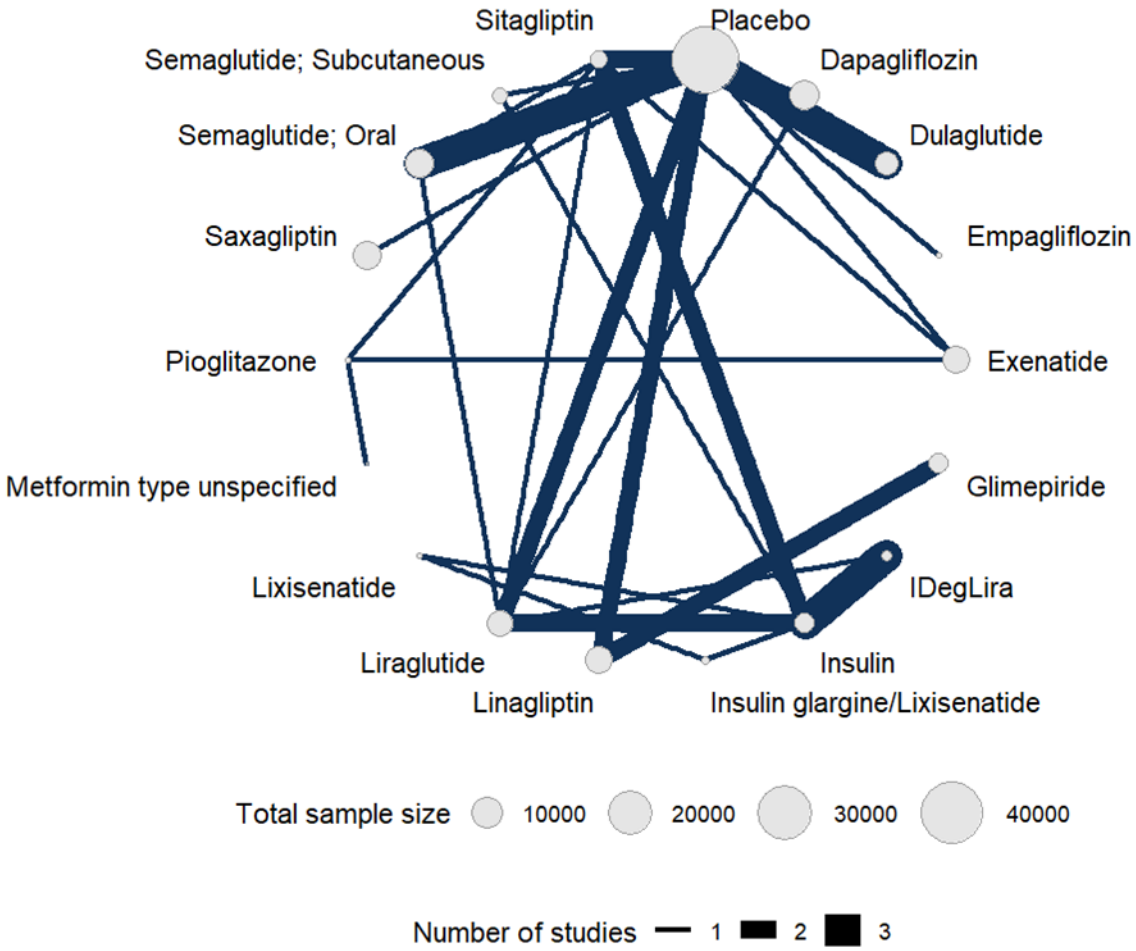
4.6. Non-fatal stroke

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.



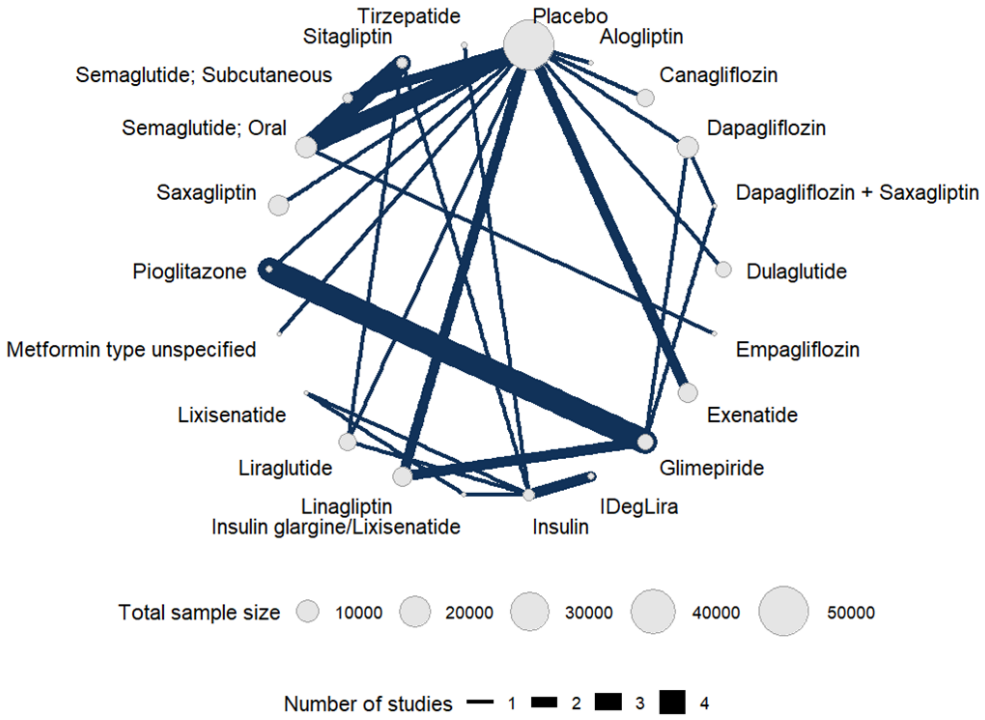
4.7. Unstable angina

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.



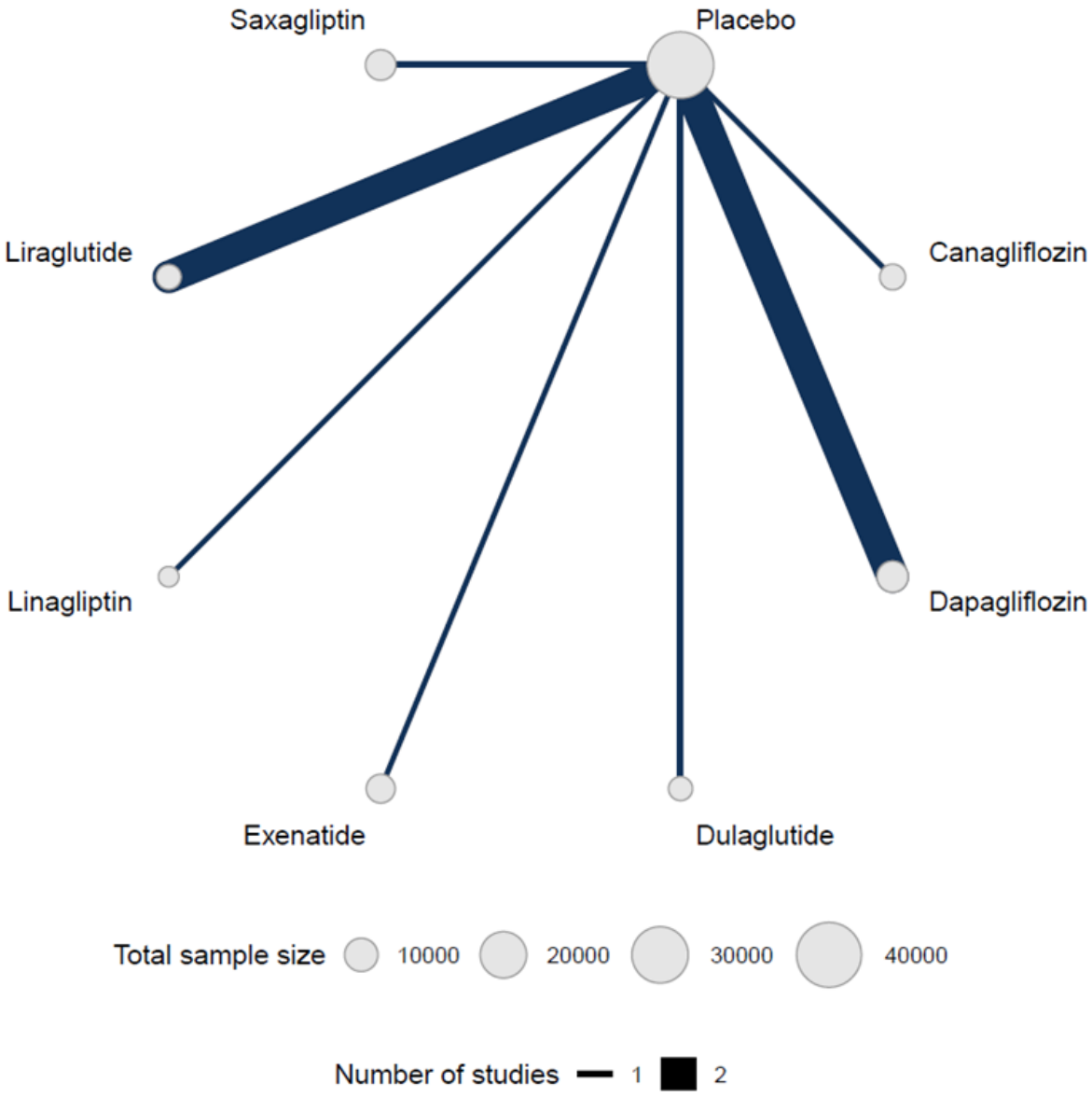
4.8. Hospitalisation for heart failure

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*	241.9	231.0	223.4
Posterior distribution (pD)	102.0	110.2	110.7
Deviance information criterion (DIC)	343.9	341.1	334.1
Between trial standard deviation (95% credible intervals)	-	0.41 (0.03, 1.00)	-
*Compared to 204 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

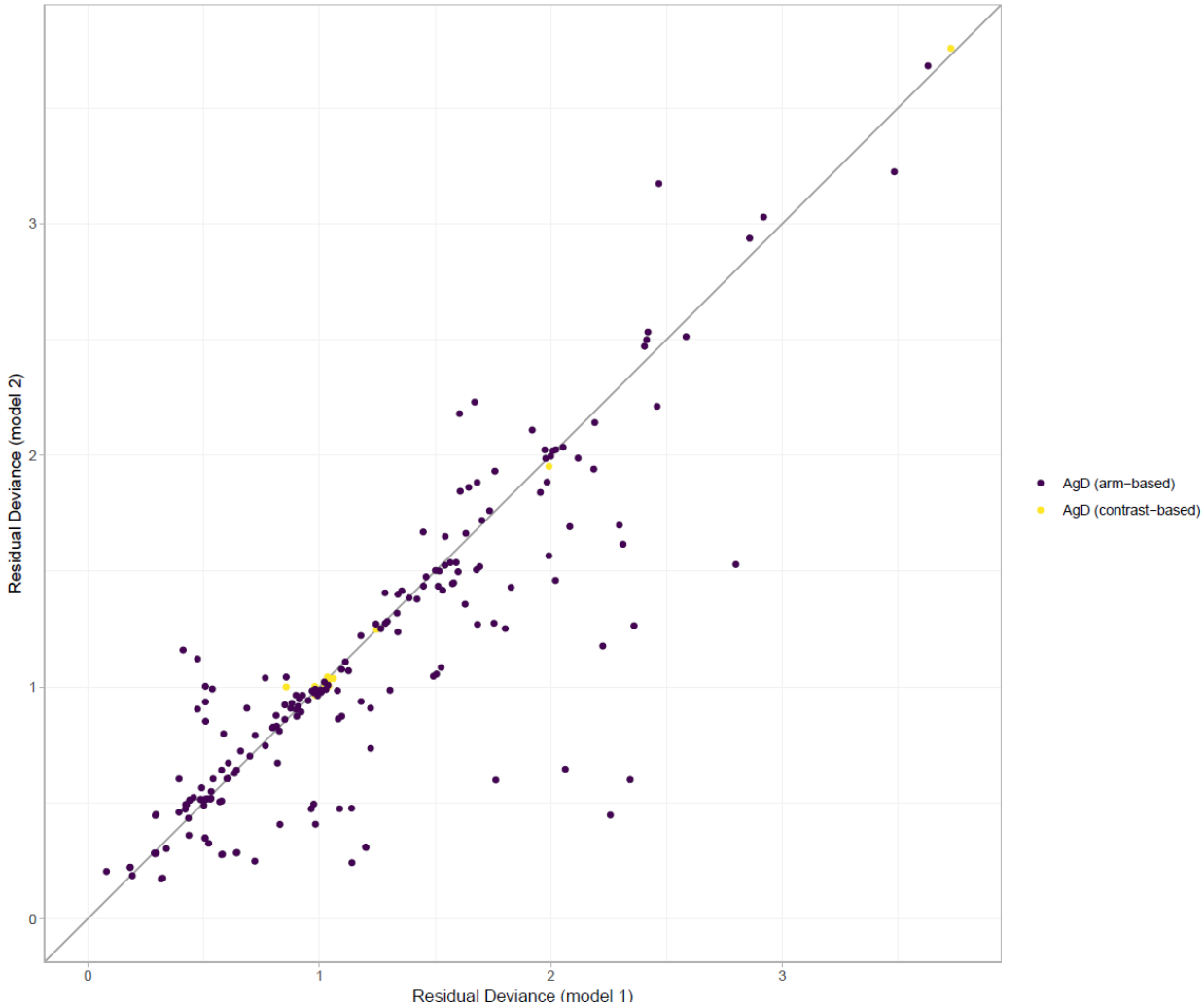
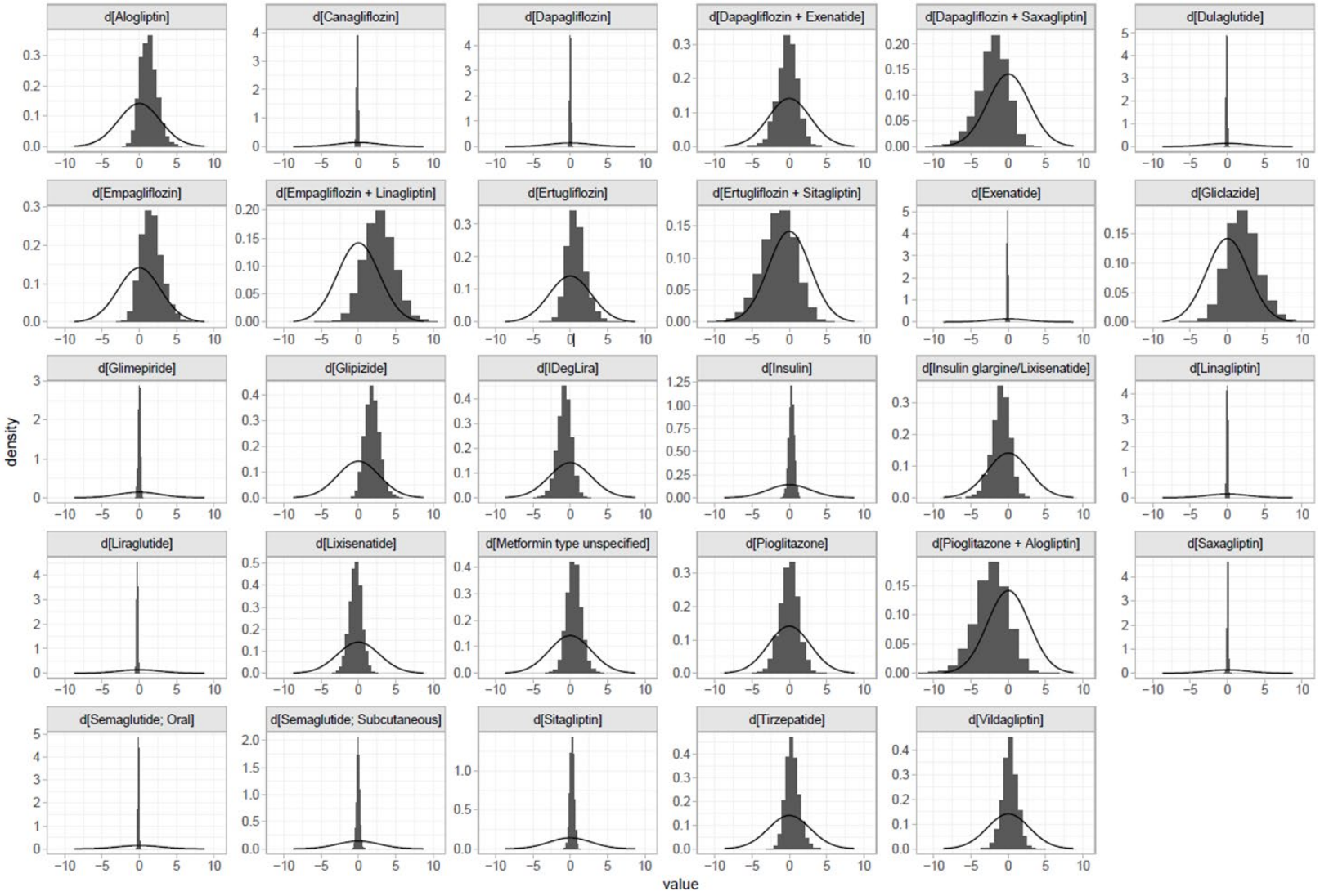


Figure 11: Prior and posterior distributions for cardiovascular mortality for the base case



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*	28.4	27.6	26.1
Posterior distribution (pD)	22.3	23.3	22.7
Deviance information criterion (DIC)	50.7	51.0	48.8
Between trial standard deviation (95% credible intervals)	-	0.29 (0.01, 0.93)	-
*Compared to 28 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

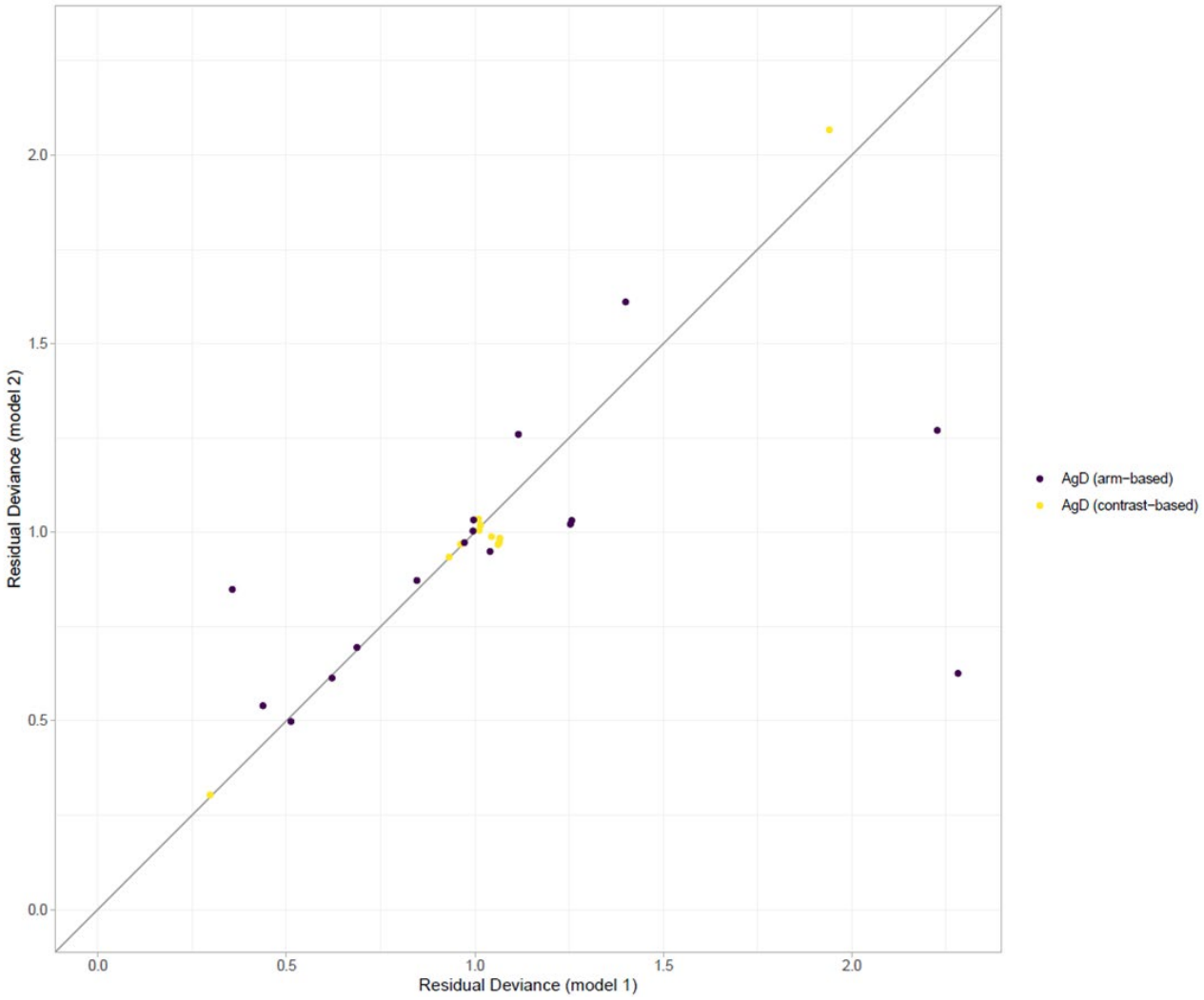
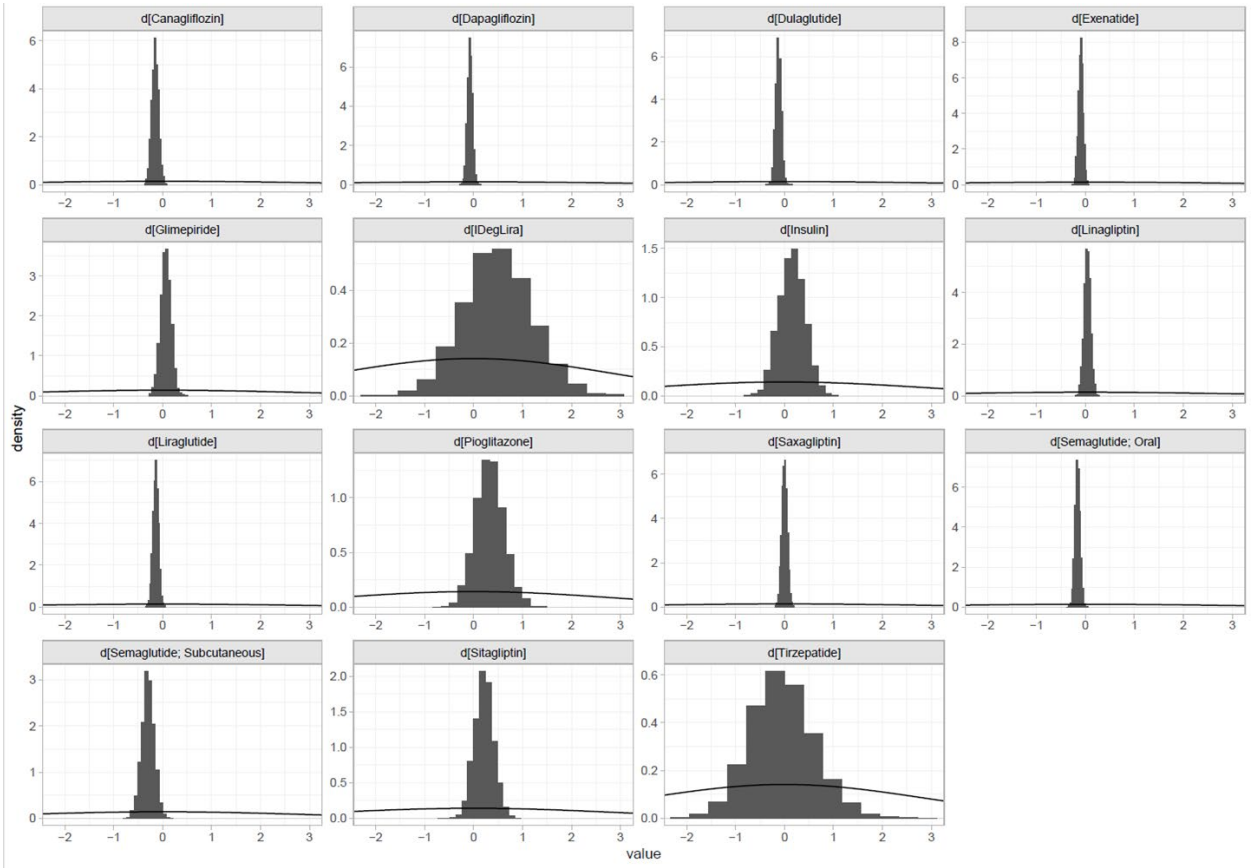


Figure 13: Prior and posterior distributions for 3-item MACE for the base case



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

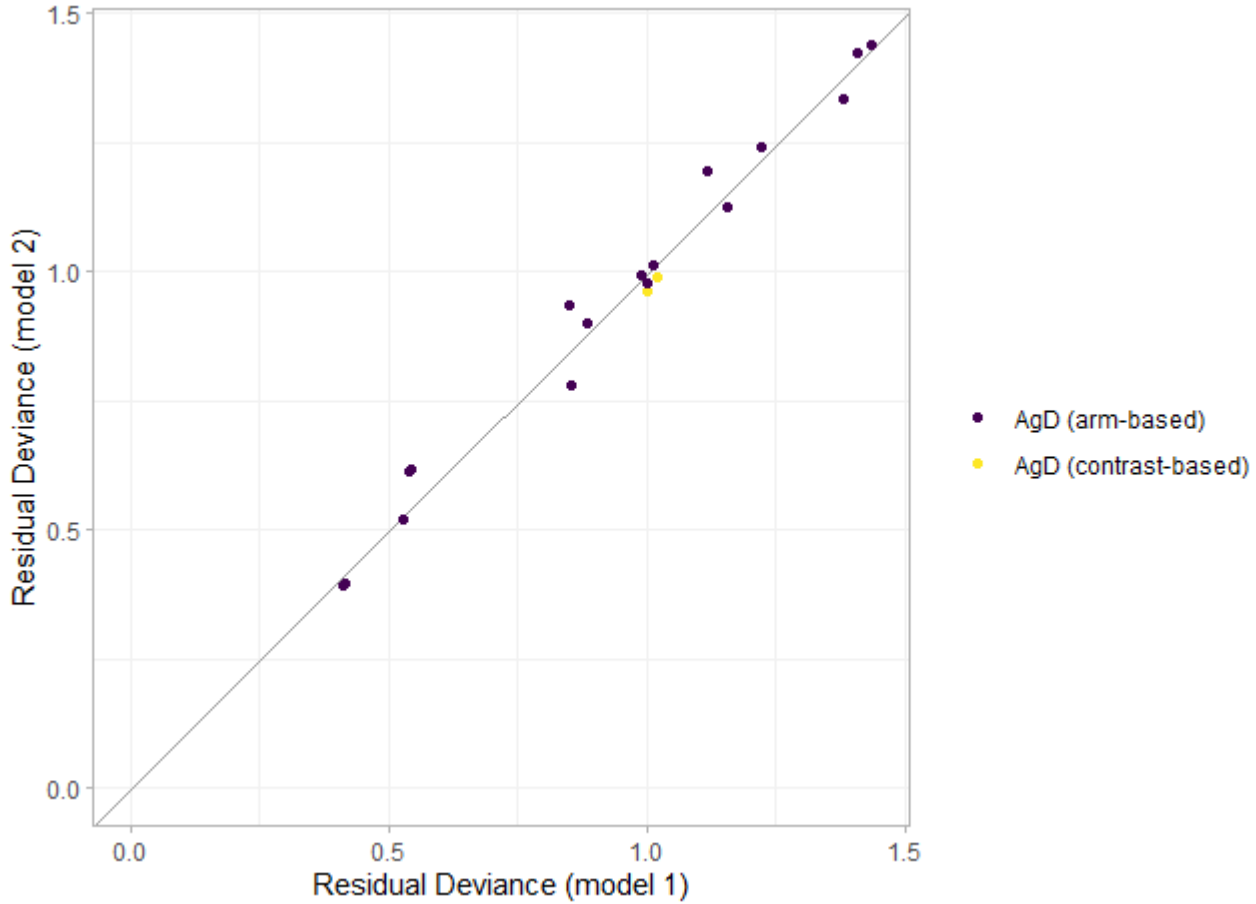
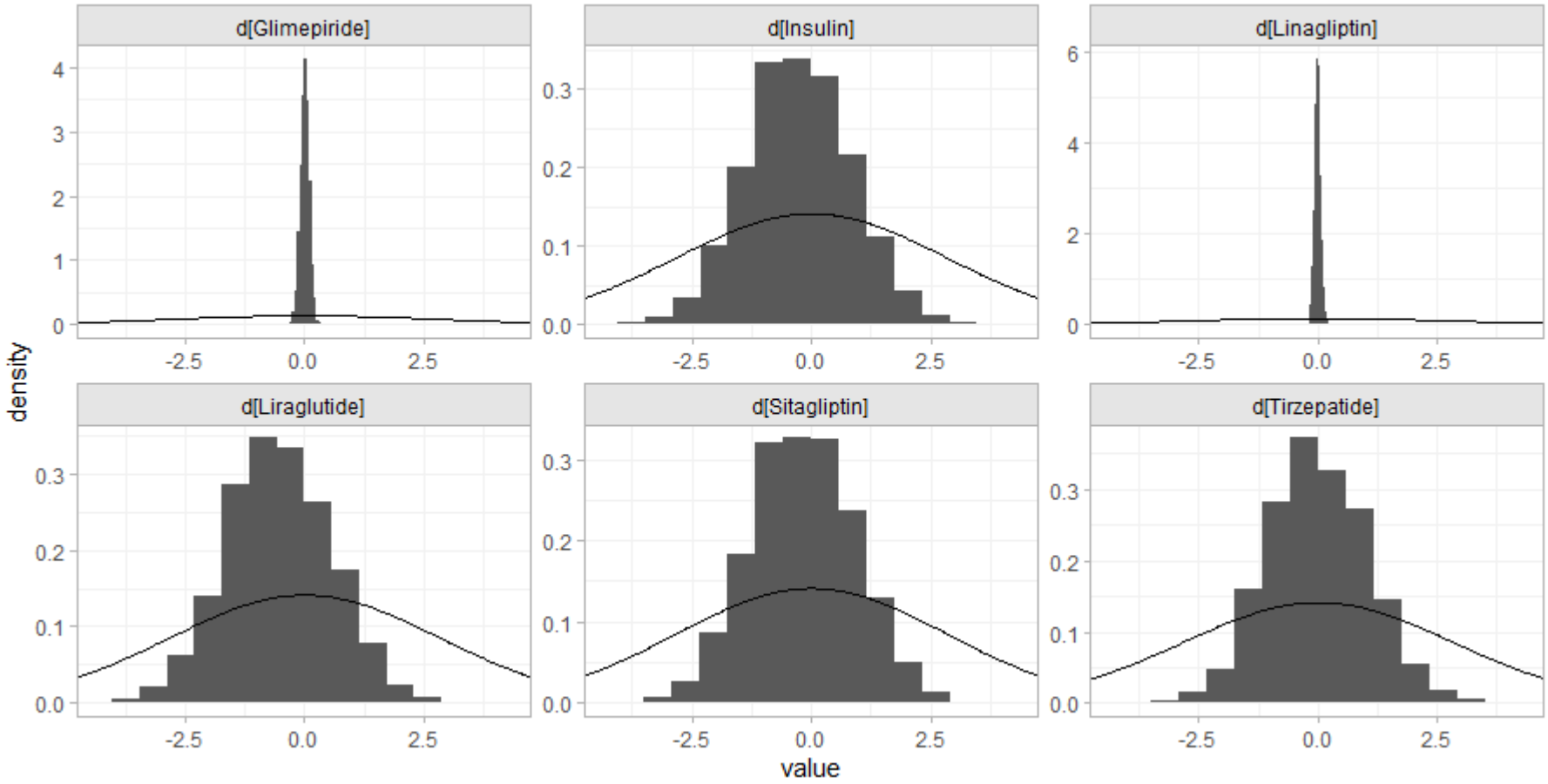


Figure 15: Prior and posterior distributions for 4-item MACE for the base case



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 MACE

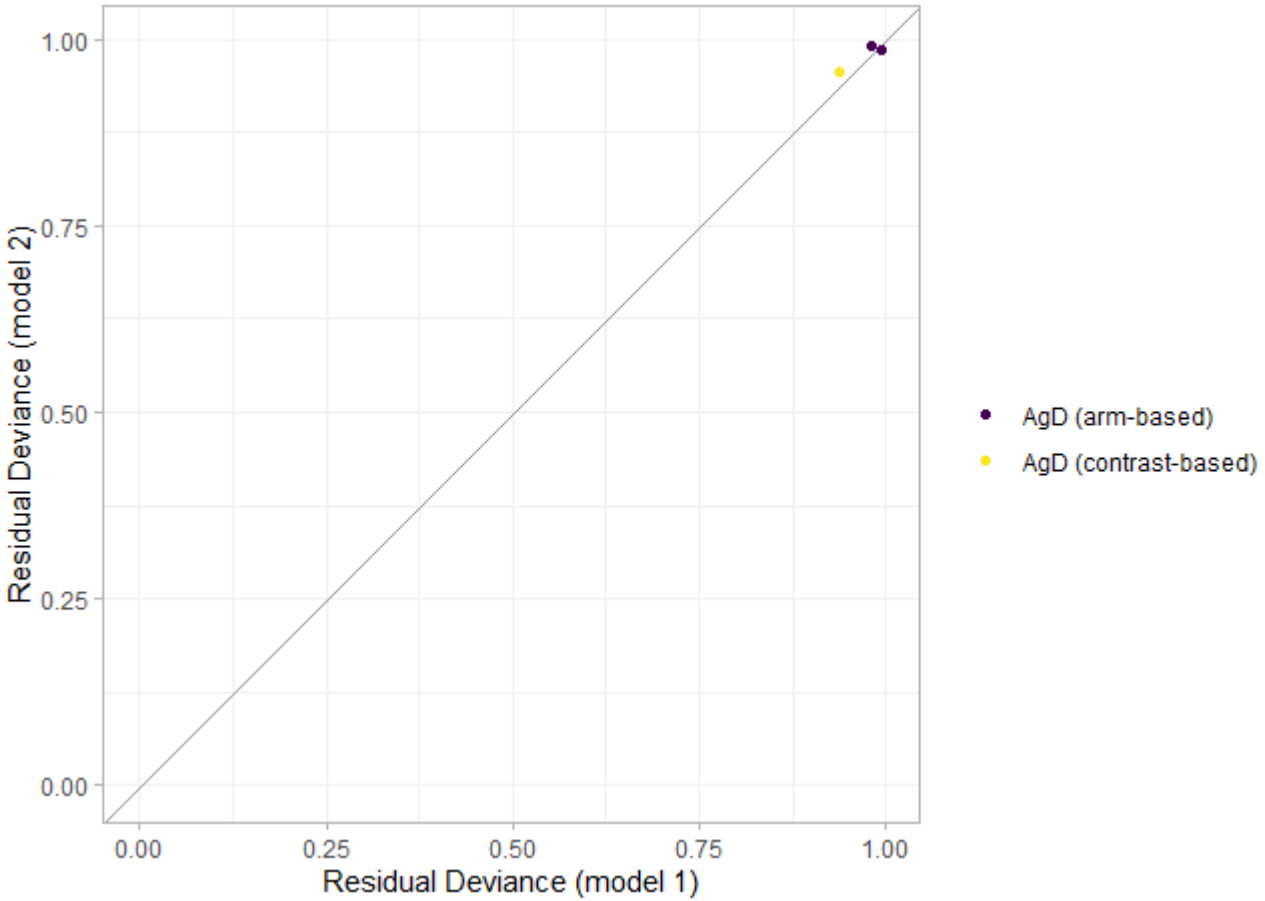
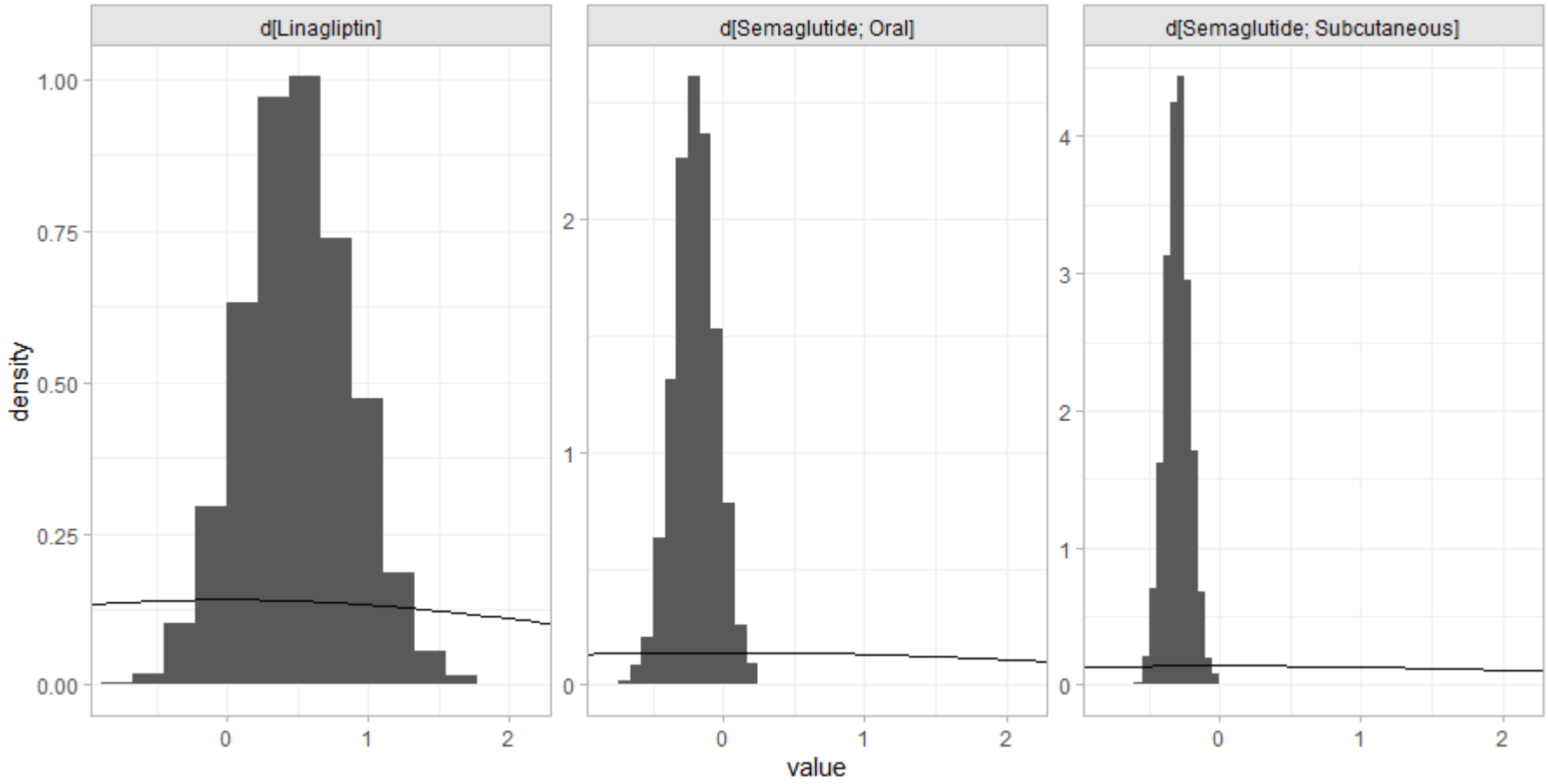


Figure 17: Prior and posterior distributions for 5-item MACE



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*	128.3	125.2	119.5
Posterior distribution (pD)	59.4	62.9	61.7
Deviance information criterion (DIC)	187.7	188.2	181.2
Between trial standard deviation (95% credible intervals)	-	0.28 (0.01, 0.79)	-
*Compared to 111 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

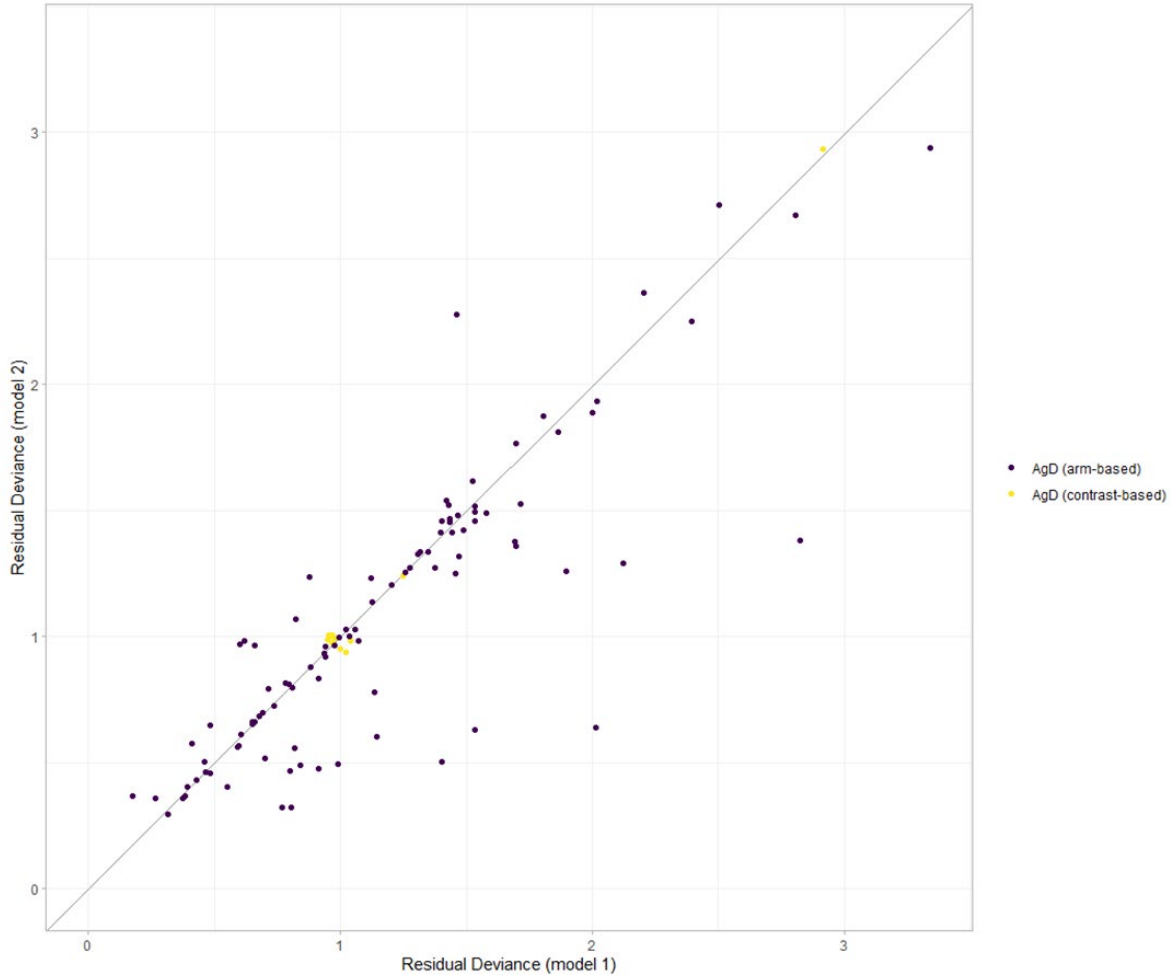
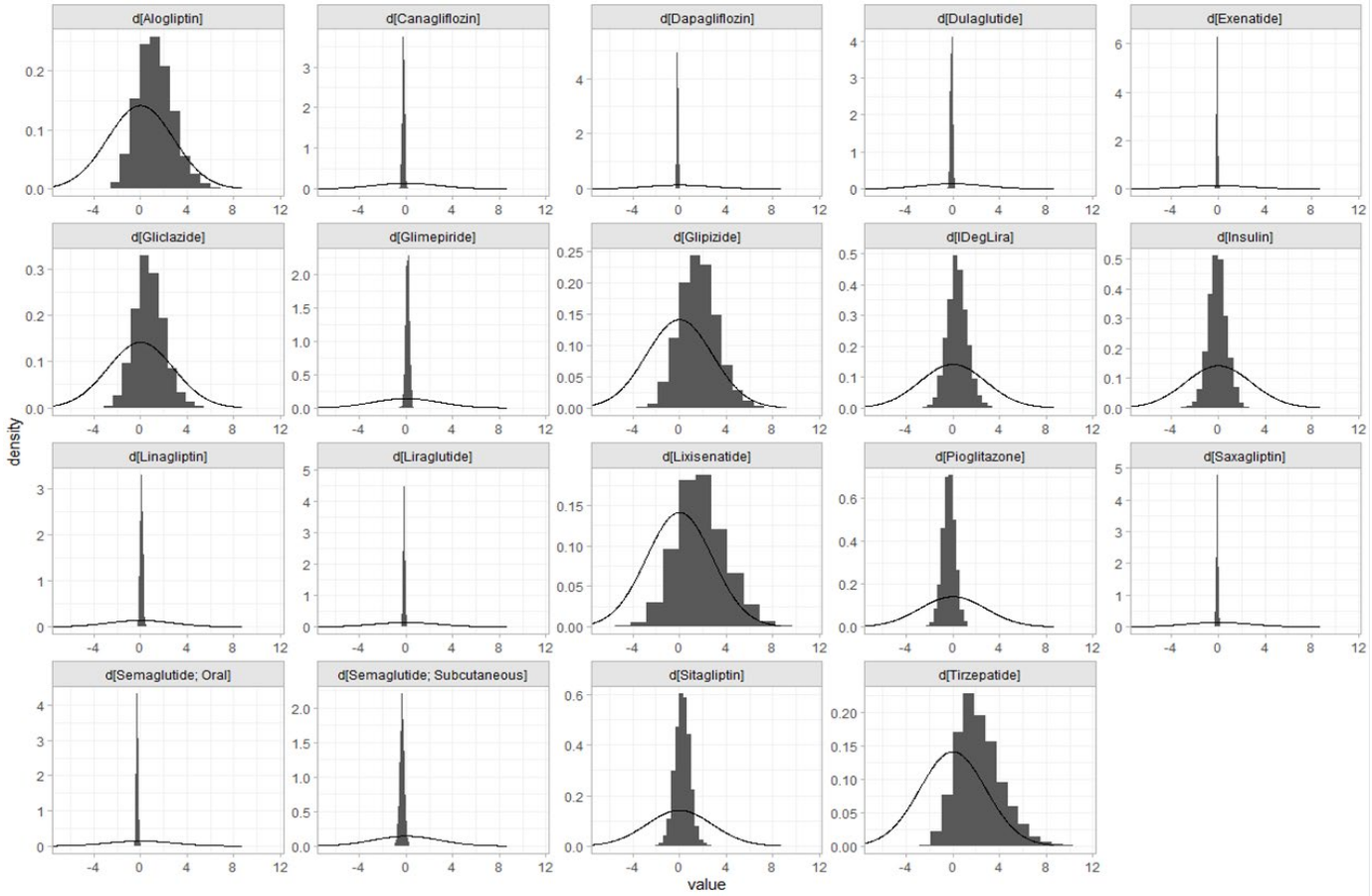


Figure 19: Prior and posterior distributions for non-fatal myocardial infarction



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*	119.4	113.3	108.5
Posterior distribution (pD)	59.1	64.1	60.9
Deviance information criterion (DIC)	178.5	177.2	169.5
Between trial standard deviation (95% credible intervals)	-	0.40 (0.02 – 1.13)	-
*Compared to 106 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

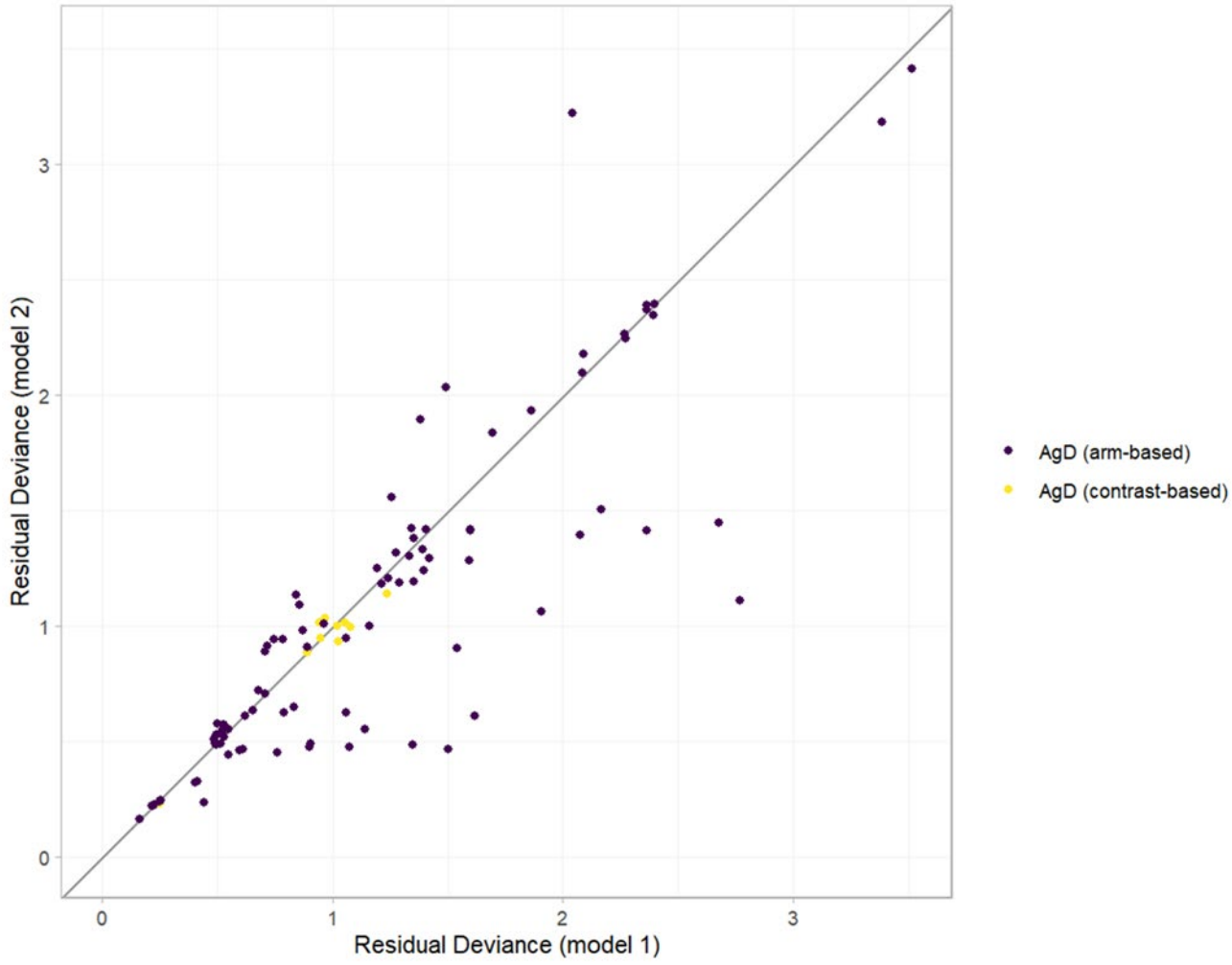
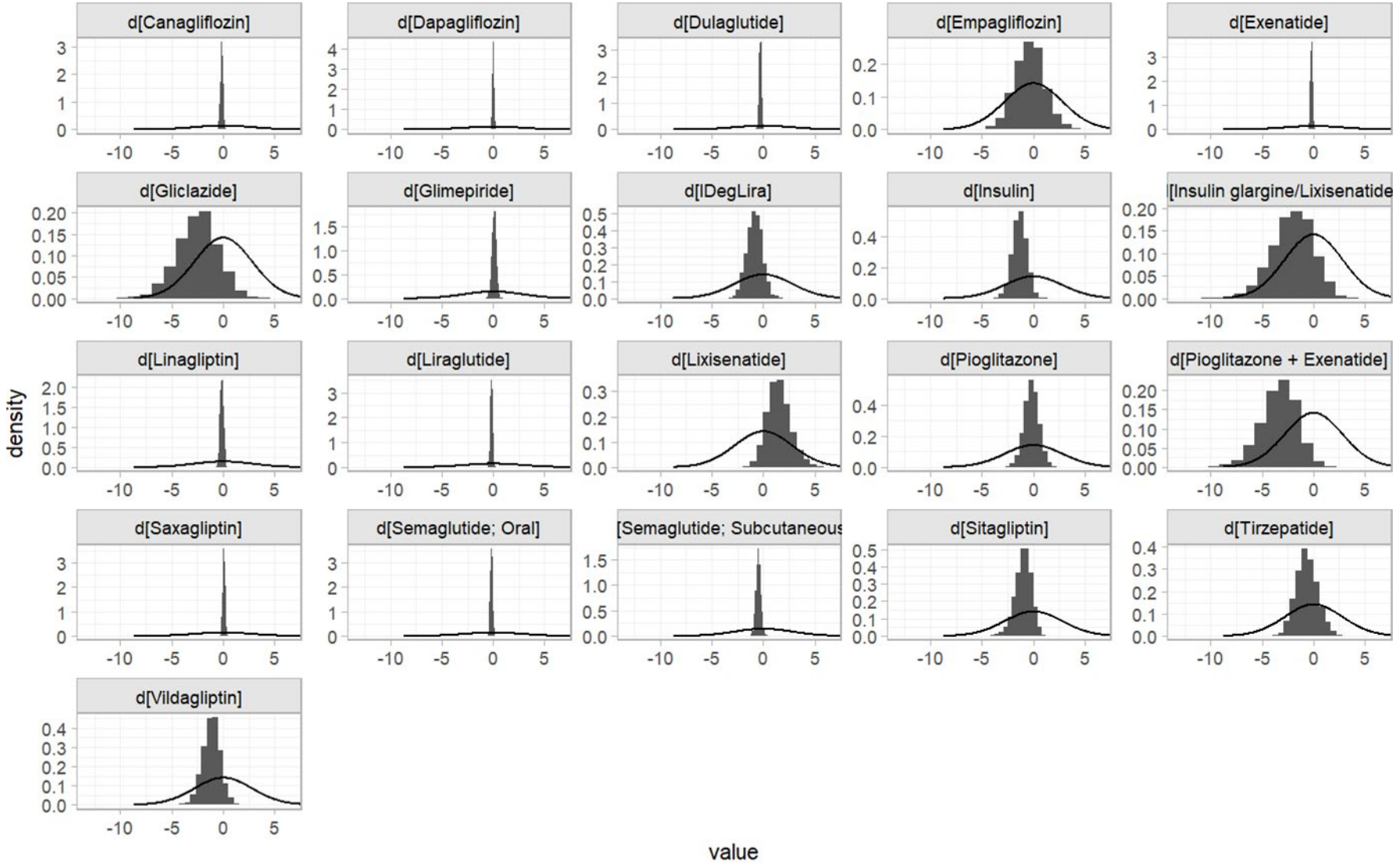


Figure 21: Prior and posterior distributions for non-fatal stroke



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*	60.9	59.0	63.8
Posterior distribution (pD)	36.4	38.7	40.5
Deviance information criterion (DIC)	97.4	97.8	104.3
Between trial standard deviation (95% credible intervals)	-	0.31 (0.02 to 1.02)	-
*Compared to 59 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. Subsequent results present data from the fixed-effects model only.

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

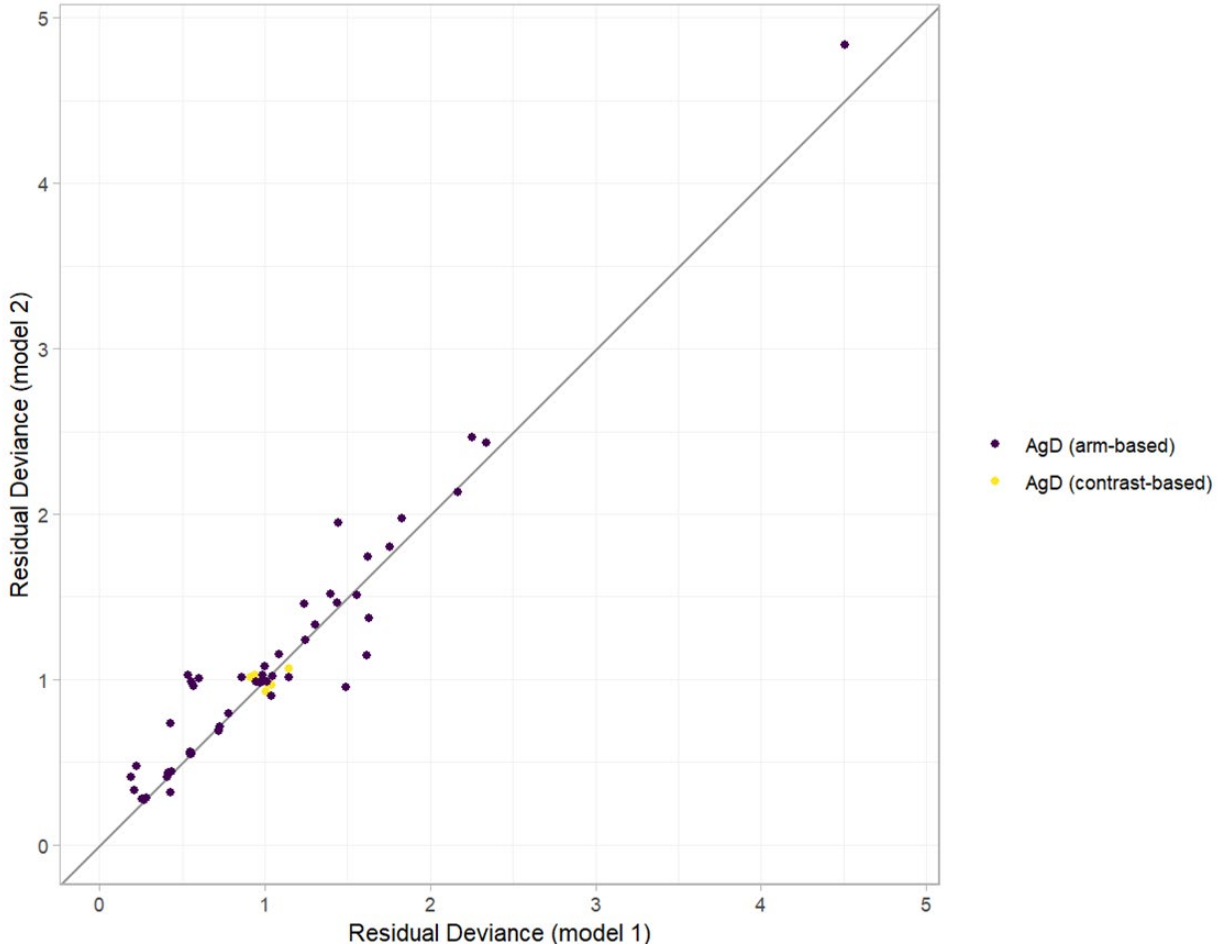
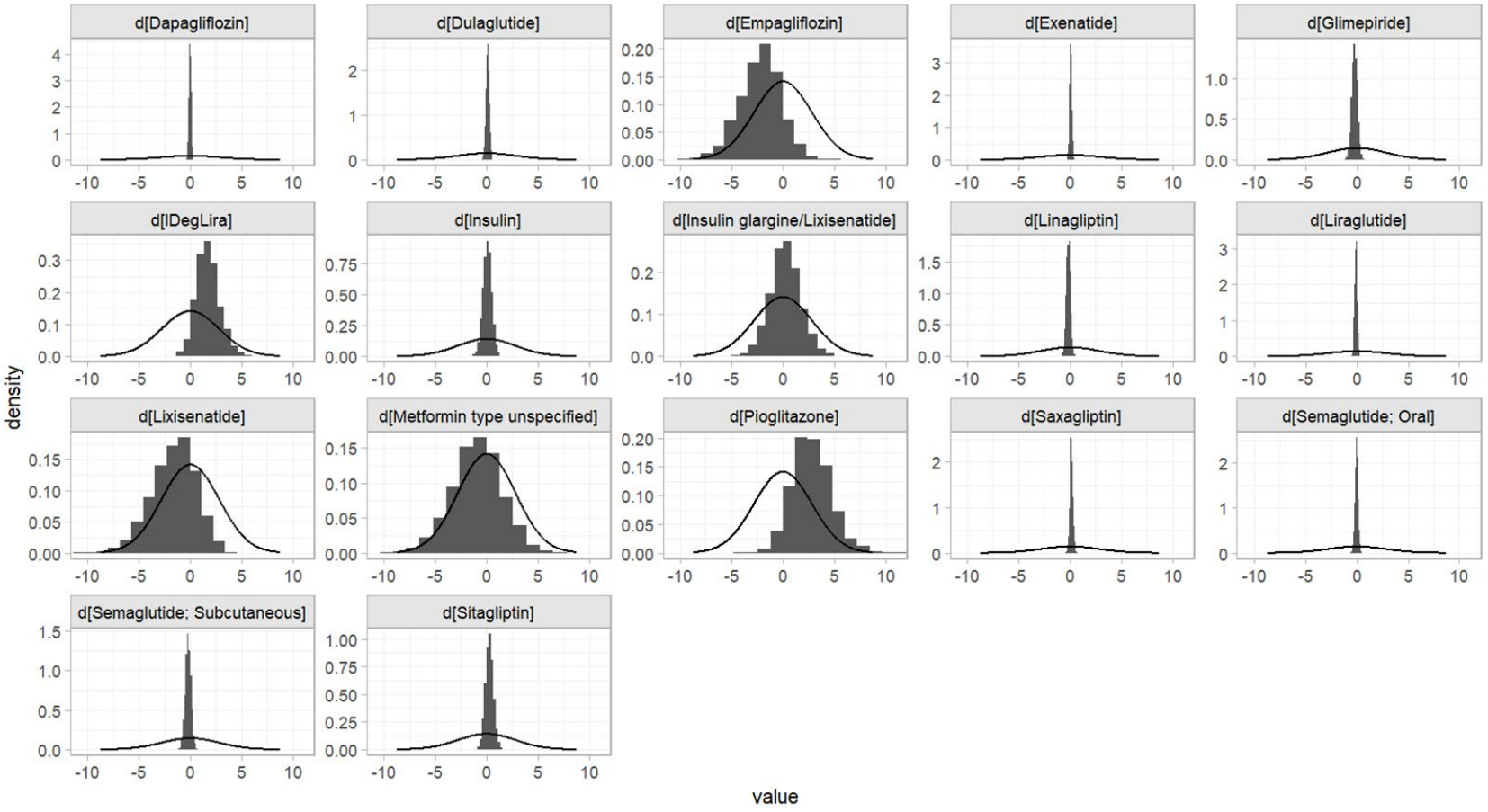


Figure 23: Prior and posterior distributions for unstable angina for the base case



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*	77.8	76.5	78.8
Posterior distribution (pD)	39.3	41.6	41.2
Deviance information criterion (DIC)	117	118.1	120
Between trial standard deviation (95% credible intervals)	-	0.23 (0.01, 1.12)	-
*Compared to 65 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

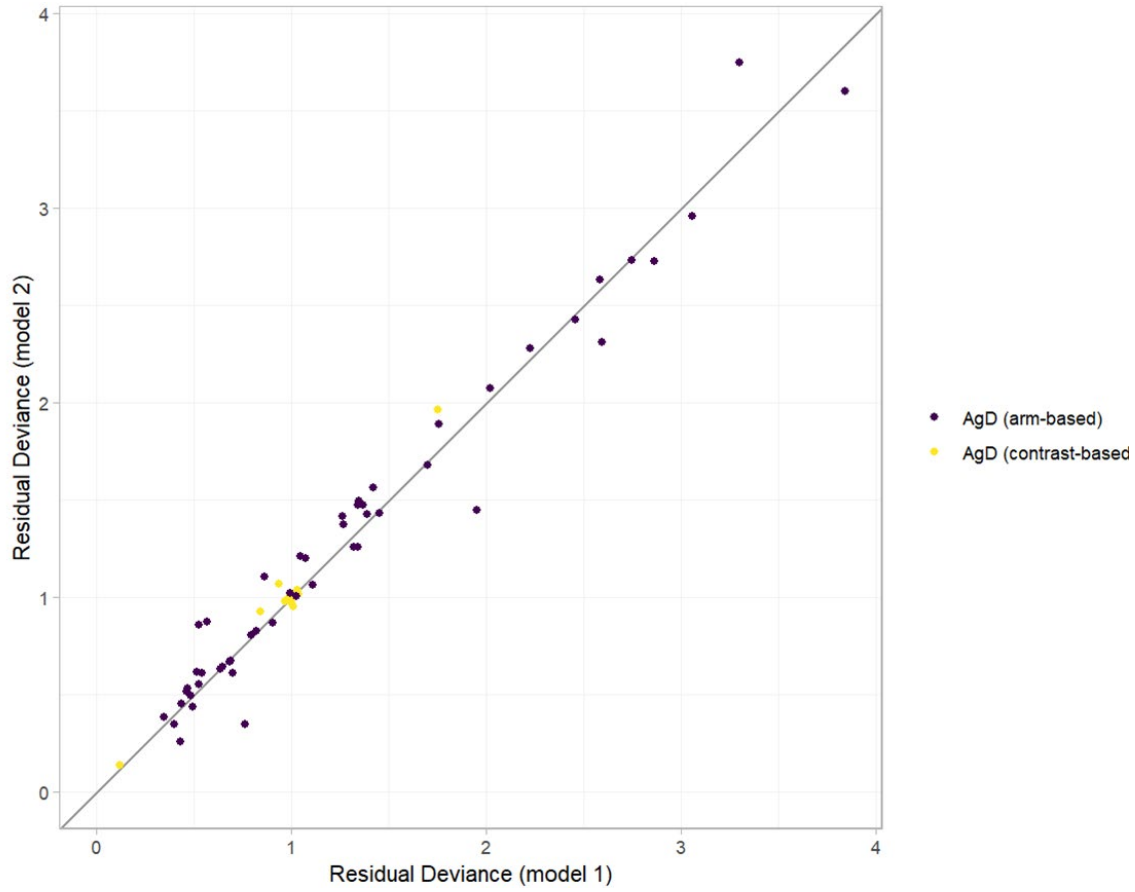
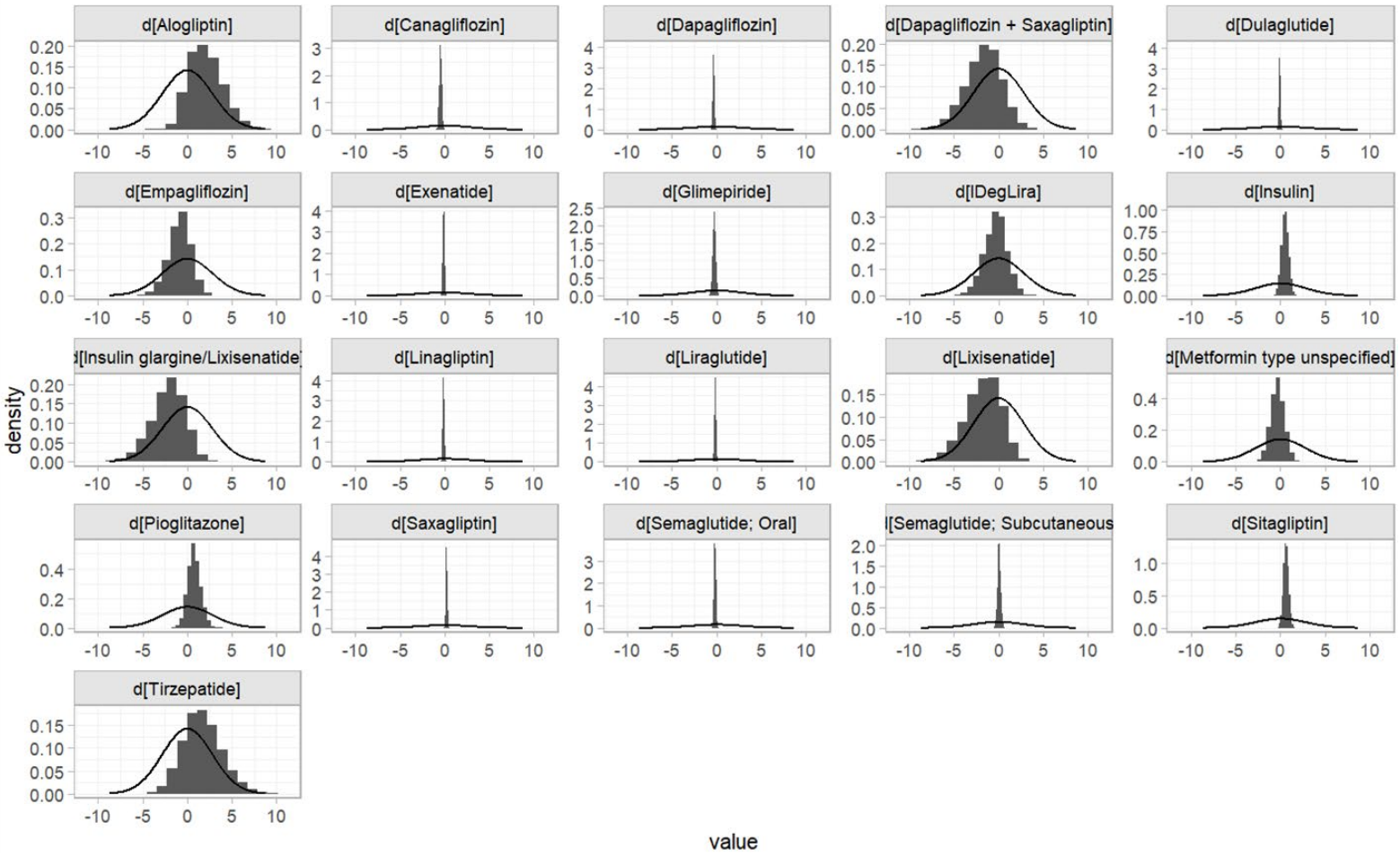


Figure 25: Prior and posterior distributions for hospitalisation for heart failure for the base case



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

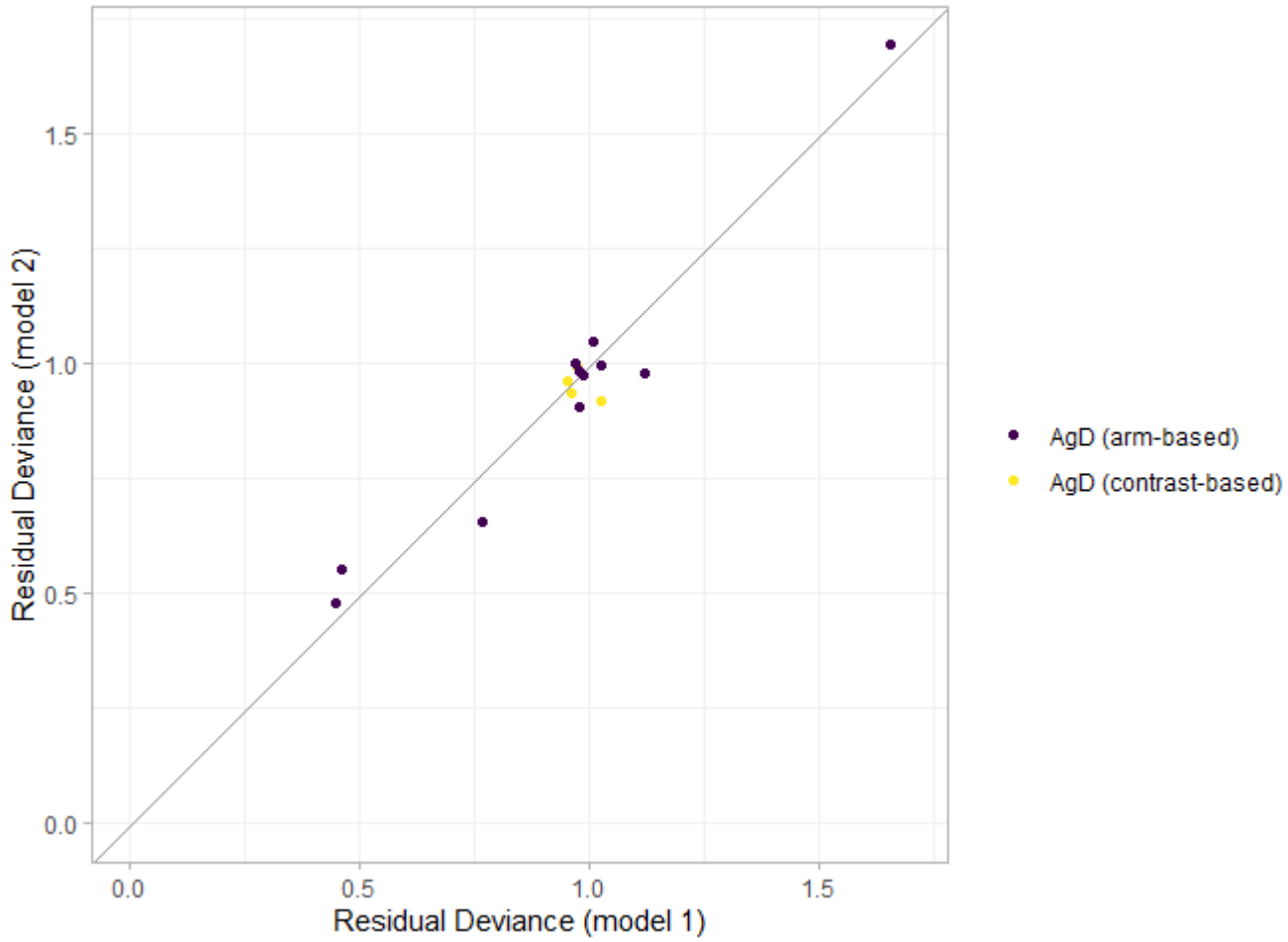
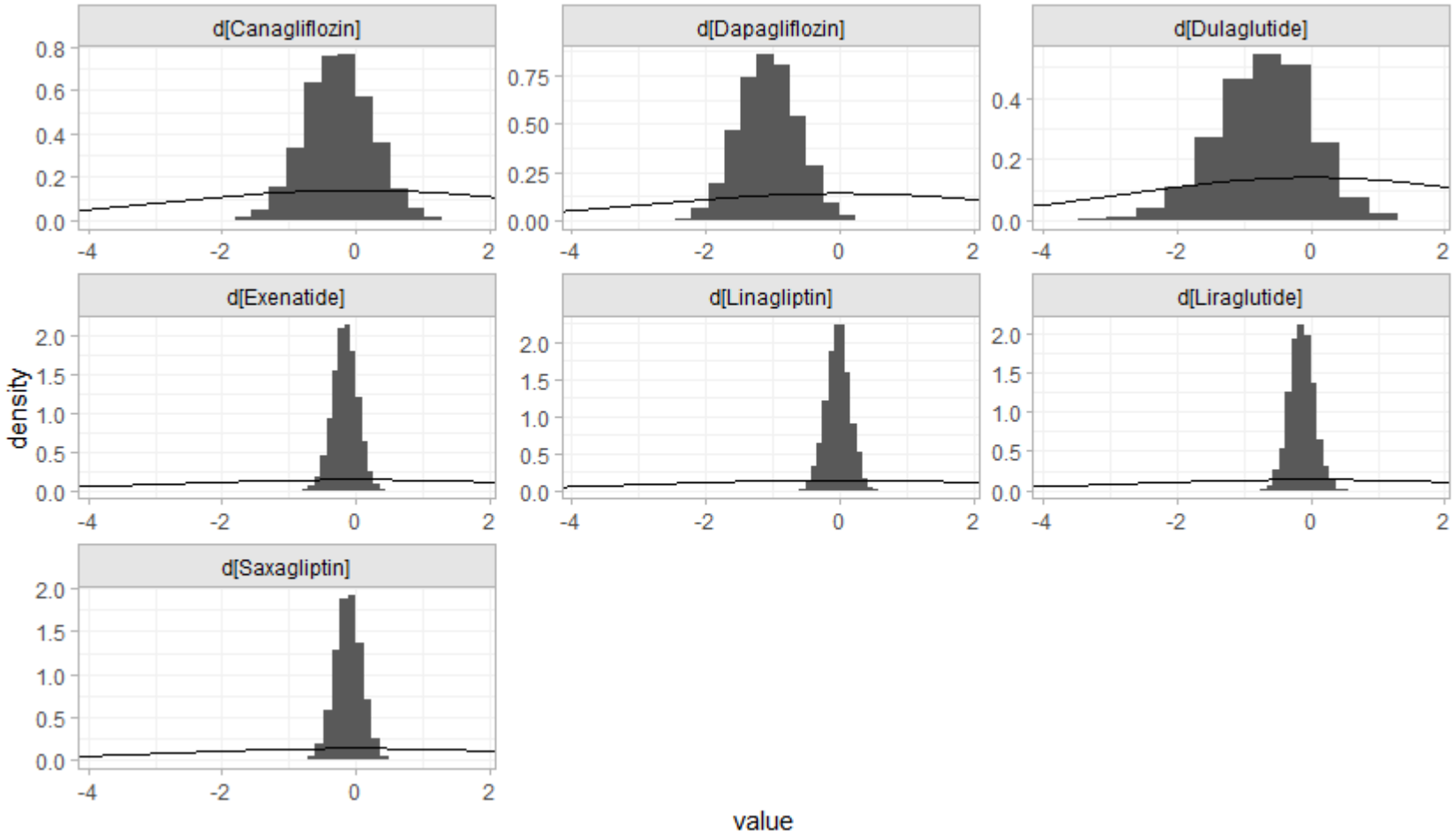


Figure 27:Prior and posterior distributions for development of end-stage renal failure



6. Results – model 5 – high cardiovascular risk

6.1. Relative effectiveness matrices

Matrices key:

FI = Favours intervention Above the dark line (indicated by NA values): Interventions are listed along the row at the top 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 Above the dark line (indicated by NA values): Comparisons are listed down the first column 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	6.25 (0.25, 581.8) NC	0.88 (0.72, 1.07) NC	0.99 (0.83, 1.19) NC	NA	NA	0.91 (0.79, 1.07) NC	6.96 (0.31, 479.07) NC	NA	NA	NA	0.87 (0.75, 1.01) NC	NA	NA	NA	NA	NA	NA	0.97 (0.83, 1.15) NC	0.79 (0.66, 0.94) FI	0.61 (0.07, 4.96) NC	2.99 (0.42, 40.36) NC	1.13 (0.06, 19.8) NC	NA	1.03 (0.87, 1.22) NC	0.89 (0.77, 1.04) NC	0.98 (0.65, 1.47) NC	0.07 (0, 1.02) NC	NA	1.03 (0.06, 17.31) NC
ALO	3.25 (0.5, 34.06) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.94 (0.45, 8.5) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CANA	0.88 (0.72, 1.06) NC	0.27 (0.03, 1.78) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	8.46 (0.26, 652.01) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5.93 (0.14, 666.72) NC	0.1 (0, 1.96) NC	NA	NA
DAPA	1 (0.84, 1.19) NC	0.31 (0.03, 2) NC	1.14 (0.89, 1.48) NC	NA	0.94 (0.06, 13.56) NC	0.1 (0, 2.46) NC	NA	NA	NA	NA	NA	0.97 (0.06, 14.22) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.11 (0, 2.43) NC	NA	NA	NA	NA	NA
DAPA/EXEN	0.82 (0.06, 8.71) NC	0.24 (0.01, 5.35) NC	0.93 (0.07, 9.34) NC	0.83 (0.06, 8.81) 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	0.14 (0, 3.2) NC	0.04 (0, 1.76) NC	0.16 (0, 3.83) NC	0.14 (0, 3.16) NC	0.18 (0, 10.06) 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	0.91 (0.78, 1.06) NC	0.29 (0.03, 1.86) NC	1.04 (0.81, 1.34) NC	0.91 (0.72, 1.16) NC	1.11 (0.11, 14.2) NC	6.4 (0.28, 547.53) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.23 (0, 8.88) NC	NA	NA	NA	NA	NA	NA	NA	NA	0.5 (0.04, 4.67) NC	8.29 (0.23, 608.71) NC	NA	NA
EMPA	4.63 (0.46, 100.79) NC	1.43 (0.06, 47.98) NC	5.25 (0.53, 116.07) NC	4.55 (0.45, 103.37) NC	5.9 (0.21, 297.97) NC	37.32 (0.65, 7315.11) NC	4.97 (0.52, 110.08) NC	NA	8.58 (0.23, 683.53) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.5 (0, 42.51) NC	NA	NA	NA	NA	NA	NA	0.16 (0, 6.93) NC	NA	NA	NA	NA
EMPA/LINA	15.93 (0.34, 873.12) NC	4.69 (0.07, 438) NC	17.81 (0.4, 1015.11) NC	15.81 (0.36, 880.28) NC	19.7 (0.27, 2328.59) NC	124.92 (0.8, 47056.21) NC	17.34 (0.38, 960.69) NC	2.9 (0.07, 246.72) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ERTU	1.99 (0.25, 33.88) NC	0.62 (0.03, 18.87) NC	2.28 (0.28, 39.77) NC	1.98 (0.25, 33.13) NC	2.61 (0.1, 92.7) NC	15.49 (0.35, 2525.71) NC	2.16 (0.27, 36) NC	0.44 (0.01, 15.61) NC	0.14 (0, 13.79) NC	NA	0.2 (0, 7.54) NC	NA	NA	0.88 (0.05, 8.08) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.27 (0, 13.08) NC	NA	NA
ERTU/SITA	0.26 (0, 13.15) NC	0.08 (0, 5.64) NC	0.3 (0, 15.09) NC	0.26 (0, 13.52) NC	0.33 (0, 34.34) NC	2.02 (0.01, 573.5) NC	0.29 (0, 14.41) NC	0.05 (0, 6.06) NC	0.02 (0, 4.25) NC	0.13 (0, 7.73) NC	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, 1.77) NC	1 (0.79, 1.28) NC	0.88 (0.71, 1.1) NC	1.07 (0.1, 13.63) NC	6.23 (0.28, 533.32) NC	0.96 (0.78, 1.19) NC	0.19 (0.01, 1.94) NC	0.06 (0, 2.65) NC	0.44 (0.03, 3.53) NC	3.39 (0.07, 391.79) NC	NA	NA	NA	NA	NA	0.1 (0, 1.96) NC	NA	NA	NA	NA	0.41 (0, 35.85) NC	NA	NA	NA	NA	NA	8.36 (0.19, 622.84) NC	NA	NA
GLIC	6.83 (0.14, 654.56) NC	1.99 (0.02, 295.98) NC	7.81 (0.16, 748.49) NC	6.77 (0.14, 685.03) NC	8.75 (0.09, 1424.45) NC	53.35 (0.3, 22909.52) NC	7.43 (0.16, 730.77) NC	1.47 (0.01, 240.41) NC	0.46 (0, 152.59) NC	3.3 (0.03, 496.97) NC	31.14 (0.1, 16003.31) NC	7.83 (0.16, 760.85) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.17 (0, 6.52) NC
GLIM	0.99 (0.75, 1.29) NC	0.31 (0.03, 2.04) NC	1.12 (0.81, 1.57) NC	0.99 (0.72, 1.35) NC	1.19 (0.11, 15.86) NC	6.94 (0.31, 577.75) NC	1.08 (0.79, 1.47) NC	0.21 (0.01, 2.15) NC	0.06 (0, 2.97) NC	0.49 (0.03, 3.97) NC	3.86 (0.07, 457.96) NC	1.12 (0.82, 1.52) NC	0.14 (0, 6.84) NC	NA	NA	NA	NA	NA	1 (0.8, 1.24) NC	NA	NA	NA	NA	NA	6.15 (0.16, 486.59) NC	NA	NA	0.16 (0, 6.08) NC	NA	1.98 (0.2, 28.74) NC
GLIP	6.05 (1.19, 44.74) FC	1.91 (0.44, 6.99) NC	6.91 (1.31, 52.41) FC	6.1 (1.17, 44.34) FC	7.88 (0.4, 208.12) NC	46.67 (1.29, 5923.17) FC	6.63 (1.3, 49.61) FC	1.28 (0.04, 29.61) NC	0.39 (0, 28.1) NC	3 (0.12, 60.06) NC	23.37 (0.34, 4281.88) NC	6.88 (1.34, 51.08) FC	0.88 (0.01, 66.71) NC	6.15 (1.18, 46.12) FC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.5 (0.03, 4.9) NC	NA	NA	0.07 (0, 1.16) NC	NA	NA
IDeglira	0.48 (0.07, 2.43) NC	0.14 (0.01, 1.67) NC	0.54 (0.08, 2.82) NC	0.48 (0.07, 2.44) NC	0.58 (0.03, 12.67) NC	3.4 (0.1, 365.34) NC	0.52 (0.08, 2.63) NC	0.1 (0, 1.79) NC	0.03 (0, 1.82) NC	0.23 (0.01, 3.39) NC	1.71 (0.02, 239.02) NC	0.54 (0.08, 2.73) NC	0.06 (0, 4.74) NC	0.49 (0.07, 2.48) NC	0.08 (0, 0.78) FI	NA	3.38 (0.69, 23.09) NC	NA	NA	0.22 (0, 7.14) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
INS	1.32 (0.7, 2.58) NC	0.42 (0.04, 2.76) NC	1.52 (0.77, 3.06) NC	1.33 (0.68, 2.67) NC	1.65 (0.15, 24.51) NC	9.24 (0.38, 905.53) NC	1.44 (0.76, 2.91) NC	0.29 (0.01, 3.3) NC	0.09 (0, 4.09) NC	0.67 (0.04, 5.91) NC	5.19 (0.09, 623.74) NC	1.51 (0.77, 2.97) NC	0.19 (0, 9.7) NC	1.34 (0.67, 2.82) NC	0.22 (0.03, 1.22) NC	2.79 (0.6, 18.67) NC	NA	0.31 (0.03, 2.24) NC	NA	NA	0.59 (0.04, 4.19) NC	0.17 (0, 5.73) NC	NA	NA	NA	NA	0.8 (0.15, 5.81) NC	1 (0.56, 1.81) NC	0.37 (0.05, 3.33) NC	NA
IGlarLixi	0.38 (0.03, 2.77) NC	0.11 (0, 1.94) NC	0.44 (0.03, 3.3) NC	0.38 (0.03, 2.78) NC	0.45 (0.01, 12.55) NC	2.74 (0.05, 357.94) NC	0.42 (0.03, 3.08) NC	0.08 (0, 1.88) NC	0.02 (0, 1.66) NC	0.17 (0, 3.22) NC	1.4 (0.01, 296.39) NC	0.44 (0.03, 3.13) NC	0.05 (0, 3.87) NC	0.39 (0.03, 2.98) NC	0.06 (0, 0.85) FI	0.8 (0.04, 12.36) NC	0.29 (0.02, 2.07) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LINA	0.98 (0.83, 1.16) NC	0.3 (0.03, 2.02) NC	1.11 (0.86, 1.45) NC	0.97 (0.77, 1.24) NC	1.19 (0.12, 15.52) NC	6.83 (0.31, 572.22) NC	1.07 (0.85, 1.34) NC	0.21 (0.01, 2.14) NC	0.06 (0, 2.82) NC	0.49 (0.03, 3.97) NC	3.78 (0.07, 458.21) NC	1.11 (0.89, 1.38) NC	0.14 (0, 6.71) NC	0.99 (0.8, 1.23) NC	0.16 (0.02, 0.84) FI	2.05 (0.39, 14.16) NC	0.74 (0.37, 1.44) NC	2.53 (0.34, 32.82) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LIRA	0.77 (0.64, 0.91) FI	0.24 (0.02, 1.56) NC	0.87 (0.67, 1.13) NC	0.76 (0.6, 0.98) FI	0.93 (0.09, 12.26) NC	5.36 (0.23, 467.98) NC	0.84 (0.67, 1.06) NC	0.17 (0.01, 1.7) NC	0.05 (0, 2.2) NC	0.39 (0.02, 3.08) NC	2.91 (0.06, 356.35) NC	0.87 (0.69, 1.09) NC	0.11 (0, 5.47) NC	0.78 (0.56, 1.06) NC	0.13 (0.02, 0.65) FI	1.62 (0.31, 10.83) NC	0.58 (0.29, 1.11) NC	1.99 (0.27, 26.12) NC	0.78 (0.62, 0.99) FI	NA	NA	NA	NA	NA	NA	NA	NA	2.61 (1.25, 5.49) FC	NA	NA
LIXI	0.7 (0.13, 3.19) NC	0.21 (0.01, 2.53) NC	0.8 (0.15, 3.64) NC	0.69 (0.13, 3.23) NC	0.84 (0.05, 15.88) NC	4.98 (0.15, 523.44) NC	0.76 (0.15, 3.55) NC	0.15 (0.01, 2.43) NC	0.04 (0, 2.95) NC	0.32 (0.01, 4.5) NC	2.62 (0.04, 397.79) NC	0.79 (0.15, 3.62) NC	0.1 (0, 5.84) NC	0.7 (0.13, 3.31) NC	0.11 (0.01, 1.08) NC	1.48 (0.16, 14.23) NC	0.52 (0.1, 2.32) NC	1.84 (0.15, 29.47) NC	0.71 (0.13, 3.3) NC	0.91 (0.17, 4.25) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MET	1.63 (0.27, 11.48) NC	0.5 (0.03, 7.61) NC	1.87 (0.31, 13.34) NC	1.64 (0.26, 11.55) NC	2.03 (0.11, 50.85) NC	11.54 (0.3, 1441.7) NC	1.77 (0.29, 12.87) NC	0.34 (0.01, 7.7) NC	0.11 (0, 7.27) NC	0.81 (0.03, 13.45) NC	6.38 (0.08, 1026.72) NC	1.84 (0.31, 13.11) NC	0.23 (0, 19.44) NC	1.64 (0.26, 11.36) NC	0.26 (0.02, 3.58) NC	3.45 (0.29, 48.37) NC	1.24 (0.18, 8.83) NC	4.41 (0.32, 92.52) NC	1.65 (0.27, 11.79) NC	2.15 (0.35, 14.93) NC	2.31 (0.23, 29.12) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA
PIO	1.02 (0.09, 10.75) NC	0.3 (0.01, 6.36) NC	1.15 (0.1, 12.39) NC	1 (0.09, 10.67) NC	1.3 (0.04, 38.65) NC	7.26 (0.13, 1124.34) NC	1.11 (0.1, 11.55) NC	0.21 (0, 5.61) NC	0.06 (0, 5.66) NC	0.48 (0.01, 11.54) NC	3.84 (0.04, 792.82) NC	1.15 (0.1, 12.47) NC	0.13 (0, 14.03) NC	1.02 (0.09, 11.25) NC	0.16 (0.01, 2.55) NC	2.17 (0.11, 41.29) NC	0.76 (0.06, 8.18) NC	2.71 (0.11, 78.45) NC	1.03 (0.09, 11.11) NC	1.32 (0.11, 13.84) NC	1.45 (0.09, 21.61) NC	0.62 (0.03, 10.35) NC	NA	0.12 (0, 3.91) NC NC	NA	NA	NA	NA	NA	NA
PIO/ALO	0.11 (0, 5.71) NC	0.03 (0, 2.19) NC	0.13 (0, 6.43) NC	0.11 (0, 5.58) NC	0.14 (0, 14.78) NC	0.79 (0, 345.89) NC	0.12 (0, 6.28) NC	0.02 (0, 2.39) NC	0.01 (0, 1.76) NC	0.05 (0, 4.88) NC	0.42 (0, 199.6) NC	0.13 (0, 6.71) NC	0.01 (0, 4.59) NC	0.11 (0, 5.74) NC	0.02 (0, 1.34) NC	0.24 (0, 16.61) NC	0.08 (0, 4.54) NC	0.3 (0, 37.19) NC	0.11 (0, 5.82) NC	0.14 (0, 7.6) NC	0.16 (0, 10.23) NC	0.07 (0, 4.91) NC	0.12 (0, 5.31) NC	NA	NA	NA	NA	NA	NA	NA
SAXA	1.03 (0.87, 1.22) NC	0.32 (0.03, 2.09) NC	1.17 (0.91, 1.52) NC	1.03 (0.81, 1.3) NC	1.27 (0.12, 15.74) NC	7.18 (0.32, 601.8) NC	1.13 (0.91, 1.41) NC	0.23 (0.01, 2.24) NC	0.06 (0, 2.81) NC	0.52 (0.03, 4.14) NC	3.98 (0.08, 495.43) NC	1.17 (0.93, 1.47) NC	0.15 (0, 7.18) NC	1.05 (0.76, 1.43) NC	0.17 (0.02, 0.85) FI	2.17 (0.43, 14.84) NC	0.78 (0.39, 1.51) NC	2.7 (0.37, 33.92) NC	1.06 (0.84, 1.33) NC	1.35 (1.05, 1.72) FC	1.48 (0.32, 7.71) NC	0.64 (0.09, 3.9) NC	1.03 (0.1, 11.74) NC	9.42 (0.18, 811.98) NC	NA	NA	NA	NA	NA
SEMA-O	0.89 (0.77, 1.03) NC	0.27 (0.03, 1.74) NC	1.02 (0.79, 1.31) NC	0.89 (0.7, 1.12) NC	1.09 (0.1, 14.43) NC	6.14 (0.28, 524.47) NC	0.97 (0.79, 1.22) NC	0.19 (0.01, 1.93) NC	0.06 (0, 2.69) NC	0.46 (0.03, 3.57) NC	3.41 (0.07, 411.32) NC	1.01 (0.83, 1.24) NC	0.13 (0, 6.28) NC	0.9 (0.66, 1.23) NC	0.15 (0.02, 0.75) FI	1.87 (0.36, 12.33) NC	0.67 (0.34, 1.31) NC	2.29 (0.32, 28.37) NC	0.91 (0.73, 1.14) NC	1.17 (0.93, 1.46) NC	1.29 (0.28, 6.63) NC	0.55 (0.08, 3.38) NC	0.88 (0.08, 10.36) NC	8.04 (0.16, 718.29) NC	0.87 (0.69, 1.09) NC	NA	NA	1.15 (0.15, 7.36) NC	NA	NA
SEMA-S	0.95 (0.66, 1.4) NC	0.3 (0.03, 1.96) NC	1.09 (0.71, 1.68) NC	0.95 (0.63, 1.45) NC	1.16 (0.11, 15.84) NC	6.45 (0.29, 583.99) NC	1.04 (0.7, 1.57) NC	0.21 (0.01, 2.15) NC	0.06 (0, 2.8) NC	0.48 (0.03, 4) NC	3.71 (0.07, 439.97) NC	1.09 (0.73, 1.63) NC	0.14 (0, 6.62) NC	0.97 (0.61, 1.54) NC	0.16 (0.02, 0.82) FI	2.01 (0.4, 13.21) NC	0.72 (0.35, 1.45) NC	2.48 (0.33, 32.48) NC	0.97 (0.64, 1.5) NC	1.25 (0.83, 1.87) NC	1.38 (0.29, 7.3) NC	0.58 (0.08, 3.62) NC	0.94 (0.08, 11.13) NC	8.46 (0.16, 782.18) NC	0.92 (0.61, 1.41) NC	1.07 (0.72, 1.6) NC	NA	0.94 (0.13, 4.69) NC	10.57 (0.72, 831.93) NC	NA
SITA	1.28 (0.75, 2.12) NC	0.4 (0.04, 2.59) NC	1.46 (0.82, 2.54) NC	1.28 (0.73, 2.2) NC	1.56 (0.14, 21.66) NC	8.93 (0.38, 860.32) NC	1.4 (0.8, 2.4) NC	0.28 (0.01, 2.99) NC	0.08 (0, 3.88) NC	0.64 (0.04, 5.04) NC	4.87 (0.09, 558) NC	1.45 (0.84, 2.45) NC	0.19 (0, 9.28) NC	1.29 (0.71, 2.31) NC	0.21 (0.03, 1.08) NC	2.66 (0.55, 17.96) NC	0.96 (0.55, 1.64) NC	3.37 (0.45, 42.73) NC	1.31 (0.76, 2.27) NC	1.67 (0.98, 2.8) NC	1.83 (0.39, 9.74) NC	0.79 (0.1, 5.07) NC	1.28 (0.12, 14.3) NC	11.26 (0.22, 976.92) NC	1.24 (0.71, 2.14) NC	1.43 (0.83, 2.45) NC	1.34 (0.72, 2.46) NC	NA	NA	NA
TIRZE	1.39 (0.31, 9.26) NC	0.44 (0.03, 5.65) NC	1.58 (0.34, 10.44) NC	1.39 (0.3, 9.26) NC	1.75 (0.1, 40.52) NC	10.03 (0.3, 1124.47) NC	1.52 (0.33, 10.23) NC	0.31 (0.01, 6.12) NC	0.09 (0, 7.16) NC	0.71 (0.03, 11.81) NC	5.58 (0.08, 933.06) NC	1.59 (0.34, 10.36) NC	0.2 (0, 15.86) NC	1.42 (0.3, 9.51) NC	0.23 (0.02, 2.62) NC	3 (0.37, 40.81) NC	1.04 (0.23, 6.85) NC	3.84 (0.29, 82.03) NC	1.43 (0.31, 9.63) NC	1.82 (0.4, 11.98) NC	2.06 (0.23, 24.23) NC	0.87 (0.08, 10.99) NC	1.43 (0.09, 27.94) NC	12.97 (0.17, 1478.78) NC	1.34 (0.3, 8.97) NC	1.56 (0.34, 10.38) NC	1.44 (0.34, 9.57) NC	1.1 (0.24, 7.53) NC	NA	NA
VILDA	1.19 (0.19, 8) NC	0.37 (0.02, 5.07) NC	1.37 (0.21, 8.95) NC	1.19 (0.18, 7.97) NC	1.48 (0.08, 34.58) NC	9.08 (0.23, 1084.79) NC	1.31 (0.2, 8.61) NC	0.25 (0.01, 4.87) NC	0.08 (0, 5.6) NC	0.61 (0.02, 9.5) NC	4.69 (0.06, 845.2) NC	1.36 (0.21, 8.91) NC	0.18 (0, 8.23) NC	1.21 (0.19, 7.96) NC	0.2 (0.01, 2.41) NC	2.57 (0.2, 37.69) NC	0.91 (0.12, 6.58) NC	3.28 (0.19, 71.51) NC	1.23 (0.19, 8.23) NC	1.57 (0.24, 10.43) NC	1.79 (0.17, 22.93) NC	0.75 (0.05, 9.39) NC	1.25 (0.06, 25.09) NC	11.4 (0.13, 1295.73) NC	1.16 (0.18, 7.78) NC	1.34 (0.21, 9) NC	1.26 (0.18, 8.65) NC	0.95 (0.13, 6.29) NC	0.85 (0.06, 10.41) 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	6.25 (0.25, 581.8) NC	0.88 (0.72, 1.07) NC	0.99 (0.83, 1.19) NC	NA	NA	0.91 (0.79, 1.07) NC	6.96 (0.31, 479.07) NC	NA	NA	NA	0.87 (0.75, 1.01) NC	NA	NA
ALO	3.25 (0.5, 34.06) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CANA	0.88 (0.72, 1.06) NC	0.27 (0.03, 1.78) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	8.46 (0.26, 652.01) NC
DAPA	1 (0.84, 1.19) NC	0.31 (0.03, 2) NC	1.14 (0.89, 1.48) NC	Line	0.94 (0.06, 13.56) NC	0.1 (0, 2.46) NC	NA	NA	NA	NA	NA	0.97 (0.06, 14.22) NC	0.94 (0.06, 13.56) NC	0.1 (0, 2.46) NC
DAPA/EXEN	0.82 (0.06, 8.71) NC	0.24 (0.01, 5.35) NC	0.93 (0.07, 9.34) NC	0.83 (0.06, 8.81) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA
DAPA/SAXA	0.14 (0, 3.2) NC	0.04 (0, 1.76) NC	0.16 (0, 3.83) NC	0.14 (0, 3.16) NC	0.18 (0, 10.06) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA
DULA	0.91 (0.78, 1.06) NC	0.29 (0.03, 1.86) NC	1.04 (0.81, 1.34) NC	0.91 (0.72, 1.16) NC	1.11 (0.11, 14.2) NC	6.4 (0.28, 547.53) NC	Line	NA	NA	NA	NA	NA	NA	NA

EMPA	4.63 (0.46, 100.79) NC	1.43 (0.06, 47.98) NC	5.25 (0.53, 116.07) NC	4.55 (0.45, 103.37) NC	5.9 (0.21, 297.97) NC	37.32 (0.65, 7315.11) NC	4.97 (0.52, 110.08) NC	Line8.58 (0.23, 683.53) NC	NA	NA	NA	NA	NA
EMPA/LINA	15.93 (0.34, 873.12) NC	4.69 (0.07, 438) NC	17.81 (0.4, 1015.11) NC	15.81 (0.36, 880.28) NC	19.7 (0.27, 2328.59) NC	124.92 (0.8, 47056.21) NC	17.34 (0.38, 960.69) NC	2.9 (0.07, 246.72) NC	LineNA	NA	NA	NA	NA
ERTU	1.99 (0.25, 33.88) NC	0.62 (0.03, 18.87) NC	2.28 (0.28, 39.77) NC	1.98 (0.25, 33.13) NC	2.61 (0.1, 92.7) NC	15.49 (0.35, 2525.71) NC	2.16 (0.27, 36) NC	0.44 (0.01, 15.61) NC	0.14 (0, 13.79) NC	Line	0.2 (0, 7.54) NC	NA	NA	0.88 (0.05, 8.08) NC
ERTU/SITA	0.26 (0, 13.15) NC	0.08 (0, 5.64) NC	0.3 (0, 15.09) NC	0.26 (0, 13.52) NC	0.33 (0, 34.34) NC	2.02 (0.01, 573.5) NC	0.29 (0, 14.41) NC	0.05 (0, 6.06) NC	0.02 (0, 4.25) NC	0.13 (0, 7.73) NC	Line	NA	NA	NA
EXEN	0.88 (0.76, 1.02) NC	0.27 (0.03, 1.77) NC	1 (0.79, 1.28) NC	0.88 (0.71, 1.1) NC	1.07 (0.1, 13.63) NC	6.23 (0.28, 533.32) NC	0.96 (0.78, 1.19) NC	0.19 (0.01, 1.94) NC	0.06 (0, 2.65) NC	0.44 (0.03, 3.53) NC	3.39 (0.07, 391.79) NC	Line	NA	NA
GLIC	6.83 (0.14, 654.56) NC	1.99 (0.02, 295.98) NC	7.81 (0.16, 748.49) NC	6.77 (0.14, 685.03) NC	8.75 (0.09, 1424.45) NC	53.35 (0.3, 22909.52) NC	7.43 (0.16, 730.77) NC	1.47 (0.01, 240.41) NC	0.46 (0, 152.59) NC	3.3 (0.03, 496.97) NC	31.14 (0.1, 16003.31) NC	7.83 (0.16, 760.85) NC	Line	NA
GLIM	0.99 (0.75, 1.29) NC	0.31 (0.03, 2.04) NC	1.12 (0.81, 1.57) NC	0.99 (0.72, 1.35) NC	1.19 (0.11, 15.86) NC	6.94 (0.31, 577.75) NC	1.08 (0.79, 1.47) NC	0.21 (0.01, 2.15) NC	0.06 (0, 2.97) NC	0.49 (0.03, 3.97) NC	3.86 (0.07, 457.96) NC	1.12 (0.82, 1.52) NC	0.14 (0, 6.84) NC	Line

GLIP	6.05 (1.19, 44.74) FC	1.91 (0.44, 6.99) NC	6.91 (1.31, 52.41) FC	6.1 (1.17, 44.34) FC	7.88 (0.4, 208.12) NC	46.67 (1.29, 5923.17) FC	6.63 (1.3, 49.61) FC	1.28 (0.04, 29.61) NC	0.39 (0, 28.1) NC	3 (0.12, 60.06) NC	23.37 (0.34, 4281.88) NC	6.88 (1.34, 51.08) FC	0.88 (0.01, 66.71) NC	6.15 (1.18, 46.12) FC
IDegLira	0.48 (0.07, 2.43) NC	0.14 (0.01, 1.67) NC	0.54 (0.08, 2.82) NC	0.48 (0.07, 2.44) NC	0.58 (0.03, 12.67) NC	3.4 (0.1, 365.34) NC	0.52 (0.08, 2.63) NC	0.1 (0, 1.79) NC	0.03 (0, 1.82) NC	0.23 (0.01, 3.39) NC	1.71 (0.02, 239.02) NC	0.54 (0.08, 2.73) NC	0.06 (0, 4.74) NC	0.49 (0.07, 2.48) NC
INS	1.32 (0.7, 2.58) NC	0.42 (0.04, 2.76) NC	1.52 (0.77, 3.06) NC	1.33 (0.68, 2.67) NC	1.65 (0.15, 24.51) NC	9.24 (0.38, 905.53) NC	1.44 (0.76, 2.91) NC	0.29 (0.01, 3.3) NC	0.09 (0, 4.09) NC	0.67 (0.04, 5.91) NC	5.19 (0.09, 623.74) NC	1.51 (0.77, 2.97) NC	0.19 (0, 9.7) NC	1.34 (0.67, 2.82) NC
IGlarLixi	0.38 (0.03, 2.77) NC	0.11 (0, 1.94) NC	0.44 (0.03, 3.3) NC	0.38 (0.03, 2.78) NC	0.45 (0.01, 12.55) NC	2.74 (0.05, 357.94) NC	0.42 (0.03, 3.08) NC	0.08 (0, 1.88) NC	0.02 (0, 1.66) NC	0.17 (0, 3.22) NC	1.4 (0.01, 296.39) NC	0.44 (0.03, 3.13) NC	0.05 (0, 3.87) NC	0.39 (0.03, 2.98) NC
LINA	0.98 (0.83, 1.16) NC	0.3 (0.03, 2.02) NC	1.11 (0.86, 1.45) NC	0.97 (0.77, 1.24) NC	1.19 (0.12, 15.52) NC	6.83 (0.31, 572.22) NC	1.07 (0.85, 1.34) NC	0.21 (0.01, 2.14) NC	0.06 (0, 2.82) NC	0.49 (0.03, 3.97) NC	3.78 (0.07, 458.21) NC	1.11 (0.89, 1.38) NC	0.14 (0, 6.71) NC	0.99 (0.8, 1.23) NC
LIRA	0.77 (0.64, 0.91) FI	0.24 (0.02, 1.56) NC	0.87 (0.67, 1.13) NC	0.76 (0.6, 0.98) FI	0.93 (0.09, 12.26) NC	5.36 (0.23, 467.98) NC	0.84 (0.67, 1.06) NC	0.17 (0.01, 1.7) NC	0.05 (0, 2.2) NC	0.39 (0.02, 3.08) NC	2.91 (0.06, 356.35) NC	0.87 (0.69, 1.09) NC	0.11 (0, 5.47) NC	0.78 (0.56, 1.06) NC
LIXI	0.7 (0.13, 3.19) NC	0.21 (0.01, 2.53) NC	0.8 (0.15, 3.64) NC	0.69 (0.13, 3.23) NC	0.84 (0.05, 15.88) NC	4.98 (0.15, 523.44) NC	0.76 (0.15, 3.55) NC	0.15 (0.01, 2.43) NC	0.04 (0, 2.95) NC	0.32 (0.01, 4.5) NC	2.62 (0.04, 397.79) NC	0.79 (0.15, 3.62) NC	0.1 (0, 5.84) NC	0.7 (0.13, 3.31) NC

MET	1.63 (0.27, 11.48) NC	0.5 (0.03, 7.61) NC	1.87 (0.31, 13.34) NC	1.64 (0.26, 11.55) NC	2.03 (0.11, 50.85) NC	11.54 (0.3, 1441.7) NC	1.77 (0.29, 12.87) NC	0.34 (0.01, 7.7) NC	0.11 (0, 7.27) NC	0.81 (0.03, 13.45) NC	6.38 (0.08, 1026.72) NC	1.84 (0.31, 13.11) NC	0.23 (0, 19.44) NC	1.64 (0.26, 11.36) NC
PIO	1.02 (0.09, 10.75) NC	0.3 (0.01, 6.36) NC	1.15 (0.1, 12.39) NC	1 (0.09, 10.67) NC	1.3 (0.04, 38.65) NC	7.26 (0.13, 1124.34) NC	1.11 (0.1, 11.55) NC	0.21 (0, 5.61) NC	0.06 (0, 5.66) NC	0.48 (0.01, 11.54) NC	3.84 (0.04, 792.82) NC	1.15 (0.1, 12.47) NC	0.13 (0, 14.03) NC	1.02 (0.09, 11.25) NC
PIO/ALO	0.11 (0, 5.71) NC	0.03 (0, 2.19) NC	0.13 (0, 6.43) NC	0.11 (0, 5.58) NC	0.14 (0, 14.78) NC	0.79 (0, 345.89) NC	0.12 (0, 6.28) NC	0.02 (0, 2.39) NC	0.01 (0, 1.76) NC	0.05 (0, 4.88) NC	0.42 (0, 199.6) NC	0.13 (0, 6.71) NC	0.01 (0, 4.59) NC	0.11 (0, 5.74) NC
SAXA	1.03 (0.87, 1.22) NC	0.32 (0.03, 2.09) NC	1.17 (0.91, 1.52) NC	1.03 (0.81, 1.3) NC	1.27 (0.12, 15.74) NC	7.18 (0.32, 601.8) NC	1.13 (0.91, 1.41) NC	0.23 (0.01, 2.24) NC	0.06 (0, 2.81) NC	0.52 (0.03, 4.14) NC	3.98 (0.08, 495.43) NC	1.17 (0.93, 1.47) NC	0.15 (0, 7.18) NC	1.05 (0.76, 1.43) NC
SEMA-O	0.89 (0.77, 1.03) NC	0.27 (0.03, 1.74) NC	1.02 (0.79, 1.31) NC	0.89 (0.7, 1.12) NC	1.09 (0.1, 14.43) NC	6.14 (0.28, 524.47) NC	0.97 (0.79, 1.22) NC	0.19 (0.01, 1.93) NC	0.06 (0, 2.69) NC	0.46 (0.03, 3.57) NC	3.41 (0.07, 411.32) NC	1.01 (0.83, 1.24) NC	0.13 (0, 6.28) NC	0.9 (0.66, 1.23) NC
SEMA-S	0.95 (0.66, 1.4) NC	0.3 (0.03, 1.96) NC	1.09 (0.71, 1.68) NC	0.95 (0.63, 1.45) NC	1.16 (0.11, 15.84) NC	6.45 (0.29, 583.99) NC	1.04 (0.7, 1.57) NC	0.21 (0.01, 2.15) NC	0.06 (0, 2.8) NC	0.48 (0.03, 4) NC	3.71 (0.07, 439.97) NC	1.09 (0.73, 1.63) NC	0.14 (0, 6.62) NC	0.97 (0.61, 1.54) NC
SITA	1.28 (0.75, 2.12) NC	0.4 (0.04, 2.59) NC	1.46 (0.82, 2.54) NC	1.28 (0.73, 2.2) NC	1.56 (0.14, 21.66) NC	8.93 (0.38, 860.32) NC	1.4 (0.8, 2.4) NC	0.28 (0.01, 2.99) NC	0.08 (0, 3.88) NC	0.64 (0.04, 5.04) NC	4.87 (0.09, 558) NC	1.45 (0.84, 2.45) NC	0.19 (0, 9.28) NC	1.29 (0.71, 2.31) NC

TIRZE	1.39 (0.31, 9.26) NC	0.44 (0.03, 5.65) NC	1.58 (0.34, 10.44) NC	1.39 (0.3, 9.26) NC	1.75 (0.1, 40.52) NC	10.03 (0.3, 1124.47) NC	1.52 (0.33, 10.23) NC	0.31 (0.01, 6.12) NC	0.09 (0, 7.16) NC	0.71 (0.03, 11.81) NC	5.58 (0.08, 933.06) NC	1.59 (0.34, 10.36) NC	0.2 (0, 15.86) NC	1.42 (0.3, 9.51) NC
VILDA	1.19 (0.19, 8) NC	0.37 (0.02, 5.07) NC	1.37 (0.21, 8.95) NC	1.19 (0.18, 7.97) NC	1.48 (0.08, 34.58) NC	9.08 (0.23, 1084.79) NC	1.31 (0.2, 8.61) NC	0.25 (0.01, 4.87) NC	0.08 (0, 5.6) NC	0.61 (0.02, 9.5) NC	4.69 (0.06, 845.2) NC	1.36 (0.21, 8.91) NC	0.18 (0, 8.23) NC	1.21 (0.19, 7.96) NC

Table 13: Relative effectiveness (hazard ratios) showing pairwise comparisons for cardiovascular mortality for the base case (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 (0.83, 1.15) NC	0.79 (0.66, 0.94) FI	0.61 (0.07, 4.96) NC	2.99 (0.42, 40.36) NC	1.13 (0.06, 19.8) NC	NA	1.03 (0.87, 1.22) NC	0.89 (0.77, 1.04) NC	0.98 (0.65, 1.47) NC	0.07 (0, 1.02) NC	NA	1.03 (0.06, 17.31) NC
ALO	1.94 (0.45, 8.5) 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	5.93 (0.14, 666.72) NC	0.1 (0, 1.96) NC	NA	NA
DAPA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.11 (0, 2.43) 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	0.23 (0, 8.88) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.5 (0.04, 4.67) NC	8.29 (0.23, 608.71) NC	NA	NA
EMPA	NA	NA	NA	NA	0.5 (0, 42.51) NC	NA	NA	NA	NA	NA	NA	0.16 (0, 6.93) 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	0.27 (0, 13.08) 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, 1.96) NC	NA	NA	NA	NA	NA	0.41 (0, 35.85) NC	NA	NA	NA	NA	8.36 (0.19, 622.84) NC	NA	NA

GLIC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.17 (0, 6.52) NC
GLIM	NA	NA	NA	NA	1 (0.8, 1.24) NC	NA	NA	NA	NA	NA	6.15 (0.16, 486.59) NC	NA	NA	0.16 (0, 6.08) NC	NA	1.98 (0.2, 28.74) NC
GLIP	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.5 (0.03, 4.9) NC	NA	NA	0.07 (0, 1.16) NC	NA	NA
IDegLira	0.08 (0, 0.78) FI	Line	3.38 (0.69, 23.09) NC	NA	NA	0.22 (0, 7.14) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
INS	0.22 (0.03 , 1.22) NC	2.79 (0.6, 18.67) NC	Line	0.31 (0.03, 2.24) NC	NA	NA	0.59 (0.04, 4.19) NC	0.17 (0, 5.73) NC	NA	NA	NA	NA	0.8 (0.15, 5.81) NC	1 (0.56, 1.81) NC	0.37 (0.05, 3.33) NC	NA
IGlarLixi	0.06 (0, 0.85) FI	0.8 (0.04, 12.36) NC	0.29 (0.02, 2.07) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LINA	0.16 (0.02 , 0.84) FI	2.05 (0.39, 14.16) NC	0.74 (0.37, 1.44) NC	2.53 (0.34, 32.82) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

LIRA	0.13 (0.02, 0.65) FI	1.62 (0.31, 10.83) NC	0.58 (0.29, 1.11) NC	1.99 (0.27, 26.12) NC	0.78 (0.62, 0.99) FI	Line	NA	NA	NA	NA	NA	NA	NA	2.61 (1.25, 5.49) FC	NA	NA
LIXI	0.11 (0.01, 1.08) NC	1.48 (0.16, 14.23) NC	0.52 (0.1, 2.32) NC	1.84 (0.15, 29.47) NC	0.71 (0.13, 3.3) NC	0.91 (0.17, 4.25) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA
MET	0.26 (0.02, 3.58) NC	3.45 (0.29, 48.37) NC	1.24 (0.18, 8.83) NC	4.41 (0.32, 92.52) NC	1.65 (0.27, 11.79) NC	2.15 (0.35, 14.93) NC	2.31 (0.23, 29.12) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA
PIO	0.16 (0.01, 2.55) NC	2.17 (0.11, 41.29) NC	0.76 (0.06, 8.18) NC	2.71 (0.11, 78.45) NC	1.03 (0.09, 11.11) NC	1.32 (0.11, 13.84) NC	1.45 (0.09, 21.61) NC	0.62 (0.03, 10.35) NC	Line	0.12 (0, 3.91) NC NC	NA	NA	NA	NA	NA	NA
PIO/ALO	0.02 (0, 1.34) NC	0.24 (0, 16.61) NC	0.08 (0, 4.54) NC	0.3 (0, 37.19) NC	0.11 (0, 5.82) NC	0.14 (0, 7.6) NC	0.16 (0, 10.23) NC	0.07 (0, 4.91) NC	0.12 (0, 5.31) NC	Line	NA	NA	NA	NA	NA	NA
SAXA	0.17 (0.02, 0.85) FI	2.17 (0.43, 14.84) NC	0.78 (0.39, 1.51) NC	2.7 (0.37, 33.92) NC	1.06 (0.84, 1.33) NC	1.35 (1.05, 1.72) FC	1.48 (0.32, 7.71) NC	0.64 (0.09, 3.9) NC	1.03 (0.1, 11.74) NC	9.42 (0.18, 811.98) NC	Line	NA	NA	NA	NA	NA
SEMA-O	0.15 (0.02, 0.75) FI	1.87 (0.36, 12.33) NC	0.67 (0.34, 1.31) NC	2.29 (0.32, 28.37) NC	0.91 (0.73, 1.14) NC	1.17 (0.93, 1.46) NC	1.29 (0.28, 6.63) NC	0.55 (0.08, 3.38) NC	0.88 (0.08, 10.36) NC	8.04 (0.16, 718.29) NC	0.87 (0.69, 1.09) NC	Line	NA	1.15 (0.15, 7.36) NC	NA	NA

SEMA-S	0.16 (0.02, 0.82) FI	2.01 (0.4, 13.21) NC	0.72 (0.35, 1.45) NC	2.48 (0.33, 32.48) NC	0.97 (0.64, 1.5) NC	1.25 (0.83, 1.87) NC	1.38 (0.29, 7.3) NC	0.58 (0.08, 3.62) NC	0.94 (0.08, 11.13) NC	8.46 (0.16, 782.18) NC	0.92 (0.61, 1.41) NC	1.07 (0.72, 1.6) NC	Line	0.94 (0.13, 4.69) NC	10.57 (0.72, 831.93) NC	NA
SITA	0.21 (0.03, 1.08) NC	2.66 (0.55, 17.96) NC	0.96 (0.55, 1.64) NC	3.37 (0.45, 42.73) NC	1.31 (0.76, 2.27) NC	1.67 (0.98, 2.8) NC	1.83 (0.39, 9.74) NC	0.79 (0.1, 5.07) NC	1.28 (0.12, 14.3) NC	11.26 (0.22, 976.92) NC	1.24 (0.71, 2.14) NC	1.43 (0.83, 2.45) NC	1.34 (0.72, 2.46) NC	Line	NA	NA
TIRZE	0.23 (0.02, 2.62) NC	3 (0.37, 40.81) NC	1.04 (0.23, 6.85) NC	3.84 (0.29, 82.03) NC	1.43 (0.31, 9.63) NC	1.82 (0.4, 11.98) NC	2.06 (0.23, 24.23) NC	0.87 (0.08, 10.99) NC	1.43 (0.09, 27.94) NC	12.97 (0.17, 1478.78) NC	1.34 (0.3, 8.97) NC	1.56 (0.34, 10.38) NC	1.44 (0.34, 9.57) NC	1.1 (0.24, 7.53) NC	NA	
VILDA	0.2 (0.01, 2.41) NC	2.57 (0.2, 37.69) NC	0.91 (0.12, 6.58) NC	3.28 (0.19, 71.51) NC	1.23 (0.19, 8.23) NC	1.57 (0.24, 10.43) NC	1.79 (0.17, 22.93) NC	0.75 (0.05, 9.39) NC	1.25 (0.06, 25.09) NC	11.4 (0.13, 1295.73) NC	1.16 (0.18, 7.78) NC	1.34 (0.21, 9) NC	1.26 (0.18, 8.65) NC	0.95 (0.13, 6.29) NC	0.85 (0.06, 10.41) NC	Line

1
2

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	NA	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, 0.97) FI	1.53 (0.89, 2.89) NC	1 (0.9, 1.12) NC	0.85 (0.77, 0.95) FI	0.74 (0.58, 0.94) FI	NA	0.91 (0.3, 3.26) NC
CANA	0.86 (0.75, 0.98) FI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DAPA	0.93 (0.84, 1.03) NC	1.08 (0.92, 1.27) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DULA	0.88 (0.79, 0.98) FI	1.02 (0.85, 1.22) NC	0.95 (0.81, 1.11) NC	NA	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 (0.85, 1.13) NC	1.03 (0.89, 1.2) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GLIM	1.07 (0.87, 1.31) NC	1.24 (0.97, 1.57) NC	1.15 (0.91, 1.45) NC	1.21 (0.96, 1.54) NC	1.17 (0.94, 1.47) NC	NA	NA	NA	0.98 (0.85, 1.14) NC	NA	0.09 (0, 1.91) NC	NA	NA	NA	NA	NA
IDegLira	1.61 (0.43, 6.63) NC	1.87 (0.49, 7.57) NC	1.73 (0.46, 7.17) NC	1.83 (0.48, 7.65) NC	1.77 (0.47, 7.24) NC	1.5 (0.4, 6.21) NC	NA	0.72 (0.16, 2.64) NC	NA	0.51 (0.04, 3.22) NC	NA	NA	NA	NA	NA	NA
INS	1.17 (0.72, 1.94) NC	1.36 (0.81, 2.27) NC	1.26 (0.76, 2.1) NC	1.33 (0.79, 2.23) NC	1.28 (0.77, 2.15) NC	1.09 (0.63, 1.88) NC	0.72 (0.18, 2.47) NC	NA	NA	NA	NA	NA	NA	NA	1.07 (0.75, 1.51) NC	NA

LINE	PCO	CANA	DAPA	DULA	EXEN	GLIM	IDegLira	INS	LINA	LIRA	PIO	SAXA	SEMA-O	SEMA-S	SITA	TIRZE
LINA	1.04 (0.91, 1.18) NC	1.21 (0.99, 1.46) NC	1.11 (0.95, 1.31) NC	1.18 (0.98, 1.4) NC	1.14 (0.97, 1.34) NC	0.97 (0.83, 1.14) NC	0.64 (0.16, 2.43) NC	0.89 (0.53, 1.49) NC	NA	NA	NA	NA	NA	NA	NA	NA
LIRA	0.87 (0.78, 0.97) FI	1.01 (0.85, 1.2) NC	0.94 (0.8, 1.08) NC	0.99 (0.85, 1.15) NC	0.96 (0.83, 1.11) NC	0.82 (0.65, 1.03) NC	0.54 (0.13, 2.05) NC	0.74 (0.45, 1.21) NC	0.84 (0.7, 1) NC	NA	NA	NA	NA	NA	1.42 (0.99, 2.08) NC	NA
PIO	1.39 (0.8, 2.49) NC	1.61 (0.92, 2.95) NC	1.49 (0.86, 2.68) NC	1.58 (0.91, 2.88) NC	1.52 (0.88, 2.75) NC	1.29 (0.73, 2.39) NC	0.86 (0.19, 3.74) NC	1.2 (0.57, 2.55) NC	1.34 (0.76, 2.41) NC	1.59 (0.91, 2.91) NC	NA	NA	NA	NA	NA	NA
SAXA	1 (0.9, 1.12) NC	1.16 (0.98, 1.38) NC	1.07 (0.92, 1.25) NC	1.13 (0.97, 1.34) NC	1.1 (0.95, 1.28) NC	0.94 (0.74, 1.19) NC	0.62 (0.15, 2.38) NC	0.85 (0.51, 1.42) NC	0.96 (0.81, 1.14) NC	1.15 (0.98, 1.35) NC	0.72 (0.4, 1.25) NC	NA	NA	NA	NA	NA
SEMA-O	0.85 (0.77, 0.95) FI	0.99 (0.84, 1.17) NC	0.92 (0.79, 1.06) NC	0.97 (0.83, 1.13) NC	0.94 (0.81, 1.09) NC	0.8 (0.64, 1) NC	0.53 (0.13, 2.03) NC	0.73 (0.44, 1.21) NC	0.82 (0.69, 0.97) FI	0.98 (0.84, 1.15) NC	0.61 (0.34, 1.07) NC	0.85 (0.73, 1) NC	NA	NA	NA	NA
SEMA-S	0.74 (0.58, 0.95) FI	0.86 (0.65, 1.14) NC	0.8 (0.61, 1.03) NC	0.84 (0.64, 1.09) NC	0.81 (0.62, 1.05) NC	0.69 (0.5, 0.96) FI	0.46 (0.11, 1.8) NC	0.63 (0.36, 1.11) NC	0.71 (0.54, 0.94) FI	0.85 (0.65, 1.11) NC	0.53 (0.29, 0.96) FI	0.74 (0.56, 0.97) FI	0.87 (0.66, 1.13) NC	NA	NA	NA
SITA	1.24 (0.86, 1.81) NC	1.45 (0.96, 2.15) NC	1.33 (0.91, 1.97) NC	1.42 (0.95, 2.11) NC	1.36 (0.93, 2) NC	1.16 (0.76, 1.81) NC	0.77 (0.2, 2.73) NC	1.06 (0.76, 1.5) NC	1.19 (0.81, 1.79) NC	1.43 (0.99, 2.05) NC	0.9 (0.45, 1.73) NC	1.24 (0.84, 1.85) NC	1.46 (0.98, 2.18) NC	1.67 (1.07, 2.67) FC	NA	NA
TIRZE	0.93 (0.29, 3.59) NC	1.08 (0.33, 4.21) NC	1 (0.31, 3.95) NC	1.06 (0.32, 4.11) NC	1.03 (0.32, 3.96) NC	0.87 (0.26, 3.45) NC	0.58 (0.09, 3.74) NC	0.81 (0.21, 3.54) NC	0.9 (0.28, 3.56) NC	1.07 (0.33, 4.23) NC	0.67 (0.18, 2.86) NC	0.93 (0.28, 3.59) NC	1.1 (0.33, 4.24) NC	1.26 (0.37, 4.92) NC	0.76 (0.21, 3.18) NC	NA

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	6.08 (0.3, 641.64) NC	0.85 (0.69, 1.05) NC	0.89 (0.78, 1.02) NC	0.95 (0.79, 1.14) NC	0.95 (0.84, 1.08) NC	NA	0.32 (0.02, 2.37) NC	NA	4.6 (0.1, 575.91) NC	NA	1.17 (0.92, 1.47) NC	0.88 (0.76, 1.03) NC	5.78 (0.17, 468.19) NC	0.77 (0.23, 2.37) NC	0.95 (0.81, 1.12) NC	0.78 (0.65, 0.94) FI	0.73 (0.51, 1.05) NC	0.57 (0.04, 6.38) NC	NA
ALO	3.39 (0.26, 93.03) NC	Line	NA	NA	NA	NA	NA	NA	1.51 (0.38, 5.48) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CANA	0.85 (0.69, 1.04) NC	0.25 (0.01, 3.28) 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	0.26 (0.01, 3.41) NC	1.05 (0.82, 1.34) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DULA	0.96 (0.79, 1.16) NC	0.28 (0.01, 3.71) NC	1.13 (0.85, 1.49) NC	1.08 (0.85, 1.37) NC	Line	NA	NA	NA	NA	NA	0.16 (0, 5.98) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA
EXEN	0.95 (0.83, 1.07) NC	0.28 (0.01, 3.68) NC	1.11 (0.88, 1.4) NC	1.06 (0.89, 1.28) NC	0.99 (0.78, 1.24) NC	Line	NA	NA	NA	NA	11.42 (0.55, 1008.22) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA

GLIC	2.05 (0.21, 29.31) NC	0.6 (0.01, 25.43) NC	2.4 (0.24, 33.72) NC	2.3 (0.23, 32.66) NC	2.13 (0.21, 30.61) NC	2.17 (0.22, 31.43) NC	Line	0.09 (0, 1.94) NC	NA	NA	NA	NA	NA	NA	5.9 (0.16, 675.17) NC	NA	NA	NA	NA	NA
GLIM	1.16 (0.84, 1.61) NC	0.34 (0.01, 4.71) NC	1.36 (0.93, 1.99) NC	1.31 (0.93, 1.86) NC	1.21 (0.84, 1.74) NC	1.22 (0.88, 1.74) NC	0.56 (0.04, 5.6) NC	Line	NA	NA	NA	0.98 (0.78, 1.24) NC	NA	NA	0.09 (0, 2) NC	0.16 (0, 6.28) NC	NA	NA	NA	NA
GLIP	5.04 (0.31, 137.22) NC	1.44 (0.34, 5.56) NC	5.95 (0.36, 164.96) NC	5.64 (0.35, 154.84) NC	5.2 (0.33, 145.13) NC	5.26 (0.32, 144.78) NC	2.39 (0.05, 143.2) NC	4.36 (0.26, 121.57) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
IDegLira	1.47 (0.31, 8.52) NC	0.43 (0.01, 9.4) NC	1.75 (0.36, 10.06) NC	1.68 (0.34, 9.62) NC	1.52 (0.31, 8.84) NC	1.56 (0.33, 8.93) NC	0.72 (0.03, 13.12) NC	1.27 (0.26, 7.43) NC	0.3 (0.01, 8.03) NC	Line	0.68 (0.18, 2.11) NC	NA	0.79 (0.05, 6.62) NC	NA	NA	NA	NA	NA	NA	NA
INS	0.96 (0.22, 4.47) NC	0.27 (0.01, 5.55) NC	1.13 (0.26, 5.37) NC	1.08 (0.25, 5.32) NC	1 (0.23, 4.77) NC	1.02 (0.23, 4.79) NC	0.46 (0.02, 7.82) NC	0.82 (0.19, 3.97) NC	0.19 (0.01, 5.04) NC	0.65 (0.19, 2.08) NC	Line	NA	NA	NA	NA	NA	NA	NA	5.39 (0.17, 425.81) NC	3.6 (0.09, 385.81) NC
LINA	1.15 (0.91, 1.45) NC	0.34 (0.01, 4.47) NC	1.35 (1, 1.83) NC	1.29 (0.99, 1.71) NC	1.2 (0.9, 1.61) NC	1.22 (0.94, 1.59) NC	0.56 (0.04, 5.43) NC	0.99 (0.79, 1.25) NC	0.23 (0.01, 3.67) NC	0.78 (0.14, 3.77) NC	1.21 (0.25, 5.25) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA
LIRA	0.88 (0.76,	0.26 (0.01,	1.04 (0.8,	1 (0.81,	0.92 (0.72,	0.94 (0.76,	0.43 (0.03,	0.76 (0.53,	0.18 (0.01,	0.6 (0.11,	0.92 (0.2,	0.77 (0.57,	Line	NA	NA	NA	NA	NA	5.73 (0.15,	NA

	1.03) NC	3.39) NC	1.33) NC	1.23) NC	1.18) NC	1.14) NC	4.26) NC	1.08) NC	2.89) NC	2.82) NC	3.9) NC	1.01) NC						439.33) NC	
LIXI	5.47 (0.14, 526.71) NC	1.6 (0.01, 283.37) NC	6.52 (0.16, 634.89) NC	6.25 (0.16, 605.8) NC	5.77 (0.15, 558.34) NC	5.87 (0.14, 559.96) NC	2.8 (0.03, 338.76) NC	4.78 (0.12, 453.09) NC	1.15 (0.01, 200.76) NC	3.88 (0.07, 434.84) NC	5.83 (0.11, 643.98) NC	4.81 (0.12, 470.14) NC	6.23 (0.16, 593.45) NC	Line	NA	NA	NA	NA	NA	NA
PIO	0.74 (0.25, 2.07) NC	0.21 (0.01, 3.67) NC	0.88 (0.29, 2.47) NC	0.83 (0.28, 2.38) NC	0.77 (0.26, 2.18) NC	0.78 (0.27, 2.23) NC	0.35 (0.02, 3.87) NC	0.64 (0.21, 1.85) NC	0.15 (0, 3.21) NC	0.5 (0.07, 3.37) NC	0.77 (0.12, 4.77) NC	0.65 (0.21, 1.85) NC	0.84 (0.28, 2.32) NC	0.13 (0, 6.26) NC	Line	NA	NA	NA	NA	NA
SAXA	0.95 (0.8, 1.12) NC	0.28 (0.01, 3.67) NC	1.11 (0.86, 1.45) NC	1.07 (0.87, 1.32) NC	0.99 (0.77, 1.28) NC	1.01 (0.81, 1.24) NC	0.47 (0.03, 4.61) NC	0.82 (0.57, 1.17) NC	0.19 (0.01, 3.08) NC	0.64 (0.11, 3.06) NC	0.99 (0.21, 4.23) NC	0.83 (0.62, 1.09) NC	1.08 (0.86, 1.34) NC	0.17 (0, 7) NC	1.28 (0.45, 3.86) NC	Line	NA	NA	NA	NA
SEMA-O	0.79 (0.66, 0.93) FI	0.23 (0.01, 3.13) NC	0.92 (0.7, 1.2) NC	0.89 (0.71, 1.11) NC	0.82 (0.63, 1.07) NC	0.83 (0.66, 1.04) NC	0.38 (0.03, 3.88) NC	0.68 (0.47, 0.98) FI	0.16 (0.01, 2.58) NC	0.53 (0.09, 2.51) NC	0.82 (0.17, 3.49) NC	0.68 (0.51, 0.91) FI	0.89 (0.71, 1.12) NC	0.14 (0, 5.6) NC	1.06 (0.37, 3.27) NC	0.83 (0.65, 1.06) NC	Line	NA	1.31 (0.19, 6.68) NC	NA
SEMA-S	0.73 (0.49, 1.07) NC	0.21 (0.01, 2.92) NC	0.86 (0.56, 1.32) NC	0.82 (0.54, 1.23) NC	0.76 (0.5, 1.14) NC	0.77 (0.51, 1.15) NC	0.35 (0.02, 3.48) NC	0.63 (0.38, 1.03) NC	0.14 (0.01, 2.46) NC	0.49 (0.08, 2.49) NC	0.75 (0.15, 3.51) NC	0.63 (0.4, 0.98) FI	0.82 (0.55, 1.22) NC	0.13 (0, 5.3) NC	0.98 (0.32, 3.2) NC	0.77 (0.51, 1.15) NC	0.93 (0.61, 1.4) NC	Line	NA	7.61 (0.38, 770.5) NC
SITA	1.35 (0.39, 4.71) NC	0.39 (0.01, 7.07) NC	1.59 (0.45, 5.49) NC	1.51 (0.43, 5.18) NC	1.4 (0.4, 4.91) NC	1.43 (0.41, 4.95) NC	0.64 (0.04, 9.07) NC	1.16 (0.32, 4.11) NC	0.26 (0.01, 5.64) NC	0.89 (0.11, 6.63) NC	1.39 (0.21, 8.94) NC	1.17 (0.33, 4.11) NC	1.52 (0.44, 5.22) NC	0.24 (0, 12.11) NC	1.83 (0.36, 9.13) NC	1.41 (0.42, 4.83) NC	1.71 (0.5, 5.83) NC	1.84 (0.53, 6.73) NC	Line	NA
TIR	7.67 (0.44	2.27 (0.03	9 (0.49	8.58 (0.48	7.88 (0.45	8.03 (0.45	3.84 (0.07	6.54 (0.36	1.65 (0.02	5.36 (0.2,	7.88 (0.36,	6.66 (0.36	8.65 (0.48	1.5 (0.01	10.8 (0.4	8.23 (0.44	9.66 (0.54	10.38 (0.59	5.93 (0.24	Line

ZE	, 607.16) NC	, 439.63) NC	, 712.35) NC	, 688.27) NC	, 620.86) NC	, 637.52) NC	, 524.56) NC	, 546.14) NC	, 326.98) NC	541.58) NC	728.25) NC	, 525.51) NC	, 712.08) NC	, 522.46) NC	9, 1011) NC	, 661.35) NC	, 806.38) NC	, 880.35) NC	, 615.55) NC	

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	IDegLira	INS	IGlarLixi	LINA	LIRA	LIXI	PIO	PIO + EXEN	SAXA	SEMA-O	SEMA-S	SITA	TIRZE	VILDA
PCO	Line	0.9 (0.71, 1.16) NC	1.01 (0.84, 1.22) NC	0.77 (0.62, 0.96) FI	0.12 (0, 4.22) NC	0.86 (0.69, 1.06) NC	NA	5.23 (0.16, 638.44) NC	NA	NA	NA	0.89 (0.64, 1.23) NC	0.88 (0.71, 1.09) NC	14.41 (0.87, 775.25) NC	1.32 (0.18, 9.7) NC	NA	1.11 (0.89, 1.38) NC	0.86 (0.7, 1.06) NC	0.62 (0.39, 1.01) NC	0.17 (0, 5.91) NC	NA	0.21 (0.02, 1.56) NC
CANA	0.9 (0.7, 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 (0.83, 1.51) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DULA	0.78 (0.62, 0.97) FI	0.87 (0.62, 1.2) NC	0.77 (0.58, 1.02) NC	Line	NA	NA	NA	NA	NA	0.09 (0, 1.79) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EMPA	0.7 (0.04, 13.73) NC	0.79 (0.04, 15.33) NC	0.7 (0.04, 13.05) NC	0.92 (0.05, 18.67) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.16 (0, 5.28) NC	NA	NA	NA	NA	NA	NA	NA

EXEN	0.87 (0.71, 1.06) NC	0.96 (0.7, 1.33) NC	0.85 (0.65, 1.11) NC	1.11 (0.81, 1.51) NC	1.21 (0.06, 21.13) NC	Line	NA	NA	NA	0.18 (0, 6.79) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
GLIC	0.09 (0, 3.65) NC	0.1 (0, 3.98) NC	0.09 (0, 3.56) NC	0.11 (0, 4.46) NC	0.12 (0, 12.06) NC	0.1 (0, 4.19) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6.59 (0.17, 404.6) NC
GLIM	1.11 (0.72, 1.69) NC	1.23 (0.74, 2.03) NC	1.09 (0.67, 1.73) NC	1.42 (0.88, 2.31) NC	1.54 (0.08, 27.87) NC	1.28 (0.8, 2.03) NC	12.29 (0.3, 791.75) NC	Line	NA	NA	NA	0.81 (0.62, 1.06) NC	NA	NA	1.04 (0.06, 19.02) NC	NA	NA	NA	NA	NA	NA	NA
IDegLira	0.44 (0.1, 1.89) NC	0.49 (0.11, 2.12) NC	0.44 (0.1, 1.87) NC	0.57 (0.13, 2.42) NC	0.64 (0.02, 16.38) NC	0.51 (0.12, 2.2) NC	4.74 (0.09, 402.82) NC	0.4 (0.09, 1.81) NC	Line	0.25 (0.02, 1.48) NC	NA	NA	4.34 (0.9, 31.1) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA
INS	0.26 (0.06, 0.95) FI	0.29 (0.07, 1.06) NC	0.26 (0.06, 0.94) FI	0.34 (0.08, 1.27) NC	0.36 (0.01, 8.84) NC	0.3 (0.07, 1.12) NC	2.94 (0.06, 239.62) NC	0.24 (0.05, 0.96) FI	0.6 (0.13, 2.41) NC	Line	0.15 (0, 4.91) NC	NA	0.16 (0, 6.38) NC	2.13 (0.1, 44.89) NC	NA	0.09 (0, 1.92) NC	NA	NA	NA	NA	1.74 (0.46, 10.39) NC	NA
IGlarLixi	0.15 (0, 4.5	0.16 (0, 5.0	0.14 (0, 4.5	0.19 (0, 5.8	0.2 (0, 18.8	0.17 (0, 5.2	1.61 (0.01, 443.	0.14 (0, 4.55) NC	0.33 (0, 14.25) NC	0.58 (0.01, 22.1	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	9) NC	7) NC	3) NC	2) NC	2) NC	8) NC	82) NC			7) NC											
LINA	0.9 (0.64, 1.25) NC	0.99 (0.65, 1.51) NC	0.89 (0.6, 1.29) NC	1.15 (0.77, 1.71) NC	1.24 (0.06, 23) NC	1.04 (0.71, 1.52) NC	9.79 (0.25, 614.76) NC	0.81 (0.61, 1.07) NC	2.03 (0.47, 8.89) NC	3.44 (0.89, 14.61) NC	5.98 (0.19, 433.43) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LIRA	0.88 (0.71, 1.09) NC	0.97 (0.7, 1.37) NC	0.87 (0.65, 1.15) NC	1.12 (0.83, 1.54) NC	1.23 (0.06, 22.56) NC	1.01 (0.75, 1.37) NC	9.91 (0.24, 621) NC	0.79 (0.5, 1.29) NC	1.96 (0.48, 8.49) NC	3.35 (0.94, 13.95) NC	5.92 (0.19, 456.24) NC	0.98 (0.66, 1.47) NC	Line	NA	NA	NA	NA	NA	NA	5.79 (0.16, 582.47) NC	NA	NA
LIXI	4.31 (0.59, 61.59) NC	4.81 (0.65, 67.12) NC	4.22 (0.58, 60.17) NC	5.53 (0.73, 79.79) NC	6.4 (0.2, 260.93) NC	5.03 (0.68, 71.1) NC	51.13 (0.81, 7106) NC	3.9 (0.5, 59.41) NC	9.96 (0.95, 178.51) NC	16.54 (1.96, 281.06) FC	28.45 (1, 3796.97) FC	4.8 (0.65, 72.53) NC	4.94 (0.66, 70.73) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA
PIO	0.84 (0.2, 3.36) NC	0.94 (0.23, 3.95) NC	0.83 (0.2, 3.41) NC	1.1 (0.25, 4.38) NC	1.17 (0.06, 23.73) NC	0.98 (0.23, 4) NC	9.42 (0.21, 690.28) NC	0.76 (0.17, 3.21) NC	1.9 (0.26, 13.81) NC	3.33 (0.46, 21.63) NC	5.94 (0.12, 532.73) NC	0.94 (0.22, 3.81) NC	0.97 (0.23, 3.78) NC	0.19 (0.01, 2.26) NC	Line	NA	NA	NA	NA	NA	NA	0.49 (0.03, 4.91) NC
PIO + EXEN	0.04 (0, 0.81) FI	0.04 (0, 0.89) FI	0.04 (0, 0.82) FI	0.05 (0, 1.07) NC	0.06 (0, 3.68) NC	0.05 (0, 0.95) FI	0.43 (0, 84.36) NC	0.04 (0, 0.77) FI	0.09 (0, 1.97) NC	0.16 (0, 2.52) NC	0.26 (0, 48.38) NC	0.04 (0, 0.95) FI	0.05 (0, 0.95) FI	0.01 (0, 0.32) FI	0.05 (0, 1.28) NC	Line	NA	NA	NA	NA	NA	NA
SAXA	1.11	1.23	1.09	1.42	1.57 (0.0	1.29	12.39	1.01 (0.6	2.51 (0.58	4.31 (1.1	7.54 (0.24	1.24	1.27	0.25 (0.0	1.32	27.6 (1.34	Line	NA	NA	NA	NA	NA

	(0.88, 1.39) NC	(0.89, 1.72) NC	(0.82, 1.45) NC	(1.04, 1.96) FC	8, 28.39) NC	(0.94, 1.72) NC	(0.31, 830.47) NC	2, 1.65) NC	, 10.82) NC	7, 17.92) FC	, 544.49) NC	(0.83, 1.87) NC	(0.92, 1.7) NC	2, 1.9) NC	(0.32, 5.52) NC	, 1511.6) FC					
SEMA-O	0.87 (0.7, 1.07) NC	0.96 (0.69, 1.36) NC	0.85 (0.64, 1.15) NC	1.11 (0.82, 1.51) NC	1.22 (0.06, 21.59) NC	1 (0.74, 1.35) NC	9.71 (0.25, 602.91) NC	0.79 (0.48, 1.26) NC	1.94 (0.46, 8.42) NC	3.32 (0.92, 13.7) NC	5.82 (0.19, 421.92) NC	0.97 (0.65, 1.44) NC	0.99 (0.73, 1.32) NC	0.2 (0.01, 1.47) NC	1.02 (0.25, 4.39) NC	21.71 (1.01, 1108.38) FC	0.78 (0.58, 1.07) NC	Line	NA	0.29 (0.02, 1.66) NC	NA	NA
SEMA-S	0.63 (0.4, 1) NC	0.7 (0.41, 1.2) NC	0.62 (0.38, 1.04) NC	0.8 (0.49, 1.36) NC	0.89 (0.05, 16.7) NC	0.73 (0.45, 1.21) NC	7.17 (0.18, 467.46) NC	0.57 (0.3, 1.11) NC	1.42 (0.31, 6.4) NC	2.39 (0.62, 10.73) NC	4.34 (0.13, 340.64) NC	0.7 (0.4, 1.28) NC	0.71 (0.44, 1.19) NC	0.14 (0.01, 1.1) NC	0.75 (0.16, 3.39) NC	15.96 (0.76, 863.66) NC	0.56 (0.34, 0.94) FI	0.72 (0.44, 1.23) NC	Line	NA	NA	NA
SITA	0.4 (0.06, 1.53) NC	0.44 (0.07, 1.73) NC	0.4 (0.06, 1.53) NC	0.51 (0.08, 2.05) NC	0.55 (0.02, 13.33) NC	0.46 (0.07, 1.79) NC	4.13 (0.08, 340.95) NC	0.36 (0.06, 1.49) NC	0.9 (0.1, 6.84) NC	1.48 (0.17, 10.89) NC	2.57 (0.05, 249.43) NC	0.44 (0.07, 1.83) NC	0.45 (0.07, 1.81) NC	0.09 (0, 0.99) FI	0.47 (0.05, 3.28) NC	9.76 (0.3, 599.05) NC	0.36 (0.06, 1.42) NC	0.46 (0.08, 1.79) NC	0.63 (0.1, 2.77) NC	Line	NA	NA
TIRZE	0.51 (0.08, 4.6) NC	0.57 (0.08, 5.21) NC	0.51 (0.07, 4.6) NC	0.66 (0.1, 6.03) NC	0.72 (0.02, 29.72) NC	0.59 (0.09, 5.37) NC	5.95 (0.09, 758.97) NC	0.46 (0.06, 4.48) NC	1.19 (0.15, 11.18) NC	1.96 (0.5, 13.02) NC	3.69 (0.07, 379.62) NC	0.57 (0.08, 5.35) NC	0.59 (0.09, 5.23) NC	0.12 (0.01, 1.87) NC	0.62 (0.06, 7.93) NC	13.41 (0.53, 922.85) NC	0.47 (0.07, 4.19) NC	0.59 (0.09, 5.34) NC	0.83 (0.12, 8.02) NC	1.37 (0.11, 21.82) NC	Line	NA
VILDA	0.33 (0.06, 1.6	0.37 (0.06,	0.33 (0.06, 1.6	0.43 (0.07, 2.1	0.47 (0.02, 11.5	0.38 (0.06, 1.9	3.37 (0.1, 269.14) NC	0.3 (0.05, 1.6) NC	0.74 (0.07, 6.65) NC	1.27 (0.14, 10.3	2.26 (0.05, 220.2	0.37 (0.06, 1.9	0.38 (0.06, 1.9	0.07 (0, 0.92) FI	0.4 (0.05, 2.2	8.13 (0.28, 590.	0.3 (0.05, 1.5	0.38 (0.06, 1.98	0.52 (0.09, 2.95	0.85 (0.09, 8.43) NC	0.63 (0.04, 8.0	Line

	9) NC	1.9) NC	5) NC	4) NC	6) NC	6) NC				7) NC	1) NC	7) NC	6) NC		4) NC	36) NC	4) NC	) NC	) NC		1) NC	

1
2

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, 1.51) NC	0.11 (0, 4.32) NC	1.14 (0.92, 1.44) NC	NA	NA	NA	NA	0.88 (0.59, 1.34) NC	0.97 (0.76, 1.24) NC	NA	NA	NA	1.19 (0.9, 1.58) NC	0.98 (0.73, 1.32) NC	0.82 (0.46, 1.46) NC	0.98 (0.05, 18.32) NC
DAPA	1.02 (0.85, 1.21) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	1.16 (0.14, 9.19) NC	NA	NA	NA	NA	NA	NA	NA
DULA	1.12 (0.83, 1.52) NC	1.1 (0.77, 1.55) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EMPA	0.12 (0, 5.2) NC	0.12 (0, 5.04) NC	0.11 (0, 4.73) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EXEN	1.14 (0.91, 1.43) NC	1.12 (0.86, 1.49) NC	1.02 (0.7, 1.49) NC	9.18 (0.22, 719.1) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	8.59 (0.2, 990.75) NC	NA	NA	NA	0.41 (0, 31.18) NC
GLIM	0.82 (0.48, 1.41) NC	0.81 (0.46, 1.44) NC	0.74 (0.4, 1.36) NC	6.65 (0.16, 576.6) NC	0.72 (0.4, 1.28) NC	Line	NA	NA	NA	1.07 (0.76, 1.54) NC	NA	NA	NA	NA	NA	NA	NA	NA
IDeg Lira	5.3 (0.76, 64.45) NC	5.23 (0.73, 63.11) NC	4.76 (0.67, 56.49) NC	45.5 (0.63, 6333.17) NC	4.7 (0.67, 58.46) NC	6.53 (0.87, 80.93) NC	Line	0.23 (0.02, 1.43) NC	NA	NA	0.25 (0, 11.05) NC	NA	NA	NA	NA	NA	NA	NA
INS	1.11 (0.48, 2.49) NC	1.08 (0.46, 2.53) NC	0.98 (0.41, 2.3) NC	8.99 (0.18, 750.94) NC	0.97 (0.4, 2.23) NC	1.34 (0.51, 3.59) NC	0.21 (0.02, 1.25) NC	Line	1.26 (0.06, 25.71) NC	NA	0.67 (0.25, 1.72) NC	0.22 (0, 8.62) NC	NA	NA	NA	NA	0.96 (0.05, 17.45) NC	1.36 (0.64, 3.11) NC

Line	PCO	DAPA	DULA	EMPA	EXEN	GLIM	IDeg Lira	INS	IGlar Lixi	LINA	LIRA	LIXI	MET	PIO	SAXA	SEMA-O	SEMA-S	SITA
IGlar Lixi	1.27 (0.07, 25) NC	1.24 (0.07, 24.92) NC	1.13 (0.06, 22.8) NC	10.74 (0.09, 1890.01) NC	1.12 (0.06, 21.44) NC	1.56 (0.08, 33.07) NC	0.23 (0.01, 7.93) NC	1.17 (0.07, 22.29) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA	NA
LINA	0.88 (0.6, 1.33) NC	0.86 (0.56, 1.37) NC	0.79 (0.47, 1.3) NC	7.12 (0.17, 619.61) NC	0.77 (0.49, 1.24) NC	1.07 (0.74, 1.54) NC	0.16 (0.01, 1.2) NC	0.8 (0.32, 2) NC	0.69 (0.03, 12.7) NC	Line	NA	NA	NA	NA	NA	NA	NA	NA
LIRA	0.95 (0.74, 1.2) NC	0.93 (0.69, 1.26) NC	0.85 (0.58, 1.23) NC	7.72 (0.18, 618.02) NC	0.83 (0.59, 1.16) NC	1.15 (0.63, 2.08) NC	0.18 (0.01, 1.28) NC	0.85 (0.38, 1.97) NC	0.74 (0.04, 13.17) NC	1.08 (0.68, 1.71) NC	Line	NA	NA	NA	NA	NA	NA	NA
LIXI	0.24 (0, 9.19) NC	0.24 (0, 8.78) NC	0.22 (0, 8.1) NC	1.89 (0.01, 429.24) NC	0.21 (0, 8.27) NC	0.28 (0, 11.02) NC	0.04 (0, 2.75) NC	0.22 (0, 8.67) NC	0.19 (0, 11.75) NC	0.27 (0, 10.3) NC	0.26 (0, 9.62) NC	Line	NA	NA	NA	NA	NA	NA
MET	0.43 (0, 36) NC	0.42 (0, 38.16) NC	0.38 (0, 33.9) NC	3.64 (0.01, 2157.35) NC	0.38 (0, 31.81) NC	0.52 (0, 42.2) NC	0.07 (0, 11.25) NC	0.4 (0, 37.76) NC	0.33 (0, 69.65) NC	0.49 (0, 43.43) NC	0.46 (0, 38.77) NC	1.97 (0, 880.33) NC	Line	5.82 (0.16, 499.86) NC	NA	NA	NA	NA
PIO	15.39 (0.55, 983.82) NC	14.96 (0.54, 998.67) NC	13.56 (0.49, 897.61) NC	131.24 (0.98, 37498.1) NC	13.6 (0.47, 901.2) NC	18.53 (0.64, 1240.82) NC	2.71 (0.05, 224.93) NC	14.09 (0.46, 948.67) NC	11.88 (0.13, 1689.4) NC	17.45 (0.59, 1131.17) NC	16.18 (0.59, 1020.46) NC	71.77 (0.5, 25774.85) NC	30.85 (0.39, 14825.57) NC	Line	NA	NA	NA	NA
SAXA	1.19 (0.88, 1.61) NC	1.17 (0.83, 1.64) NC	1.06 (0.7, 1.62) NC	9.63 (0.23, 755.63) NC	1.04 (0.71, 1.53) NC	1.44 (0.79, 2.67) NC	0.22 (0.02, 1.6) NC	1.08 (0.45, 2.65) NC	0.92 (0.05, 17.76) NC	1.35 (0.82, 2.22) NC	1.25 (0.86, 1.85) NC	4.92 (0.13, 554.5) NC	2.76 (0.03, 387.02) NC	0.08 (0, 2.19) NC	Line	NA	NA	NA
SEMA-O	1.01 (0.75, 1.34) NC	0.99 (0.7, 1.38) NC	0.9 (0.58, 1.38) NC	8.09 (0.18, 666.06) NC	0.88 (0.61, 1.27) NC	1.22 (0.67, 2.23) NC	0.19 (0.02, 1.37) NC	0.9 (0.39, 2.18) NC	0.79 (0.04, 14.84) NC	1.14 (0.7, 1.9) NC	1.06 (0.73, 1.53) NC	4.15 (0.11, 457.5) NC	2.33 (0.03, 332.24) NC	0.07 (0, 1.83) NC	0.84 (0.56, 1.27) NC	Line	NA	0.44 (0.03, 2.57) NC

Line	PCO	DAPA	DULA	EMPA	EXEN	GLIM	IDegLira	INS	IGlarLixi	LINA	LIRA	LIXI	MET	PIO	SAXA	SEMA-O	SEMA-S	SITA
SEMA-S	0.83 (0.48, 1.42) NC	0.81 (0.46, 1.42) NC	0.73 (0.4, 1.37) NC	6.7 (0.14, 549.69) NC	0.73 (0.4, 1.3) NC	1.01 (0.46, 2.16) NC	0.16 (0.01, 1.22) NC	0.75 (0.29, 2.03) NC	0.66 (0.03, 12.6) NC	0.94 (0.48, 1.84) NC	0.87 (0.49, 1.59) NC	3.38 (0.09, 359.29) NC	1.93 (0.02, 286.18) NC	0.05 (0, 1.67) NC	0.69 (0.38, 1.31) NC	0.82 (0.44, 1.55) NC	Line	NA
SITA	1.35 (0.63, 2.89) NC	1.32 (0.61, 2.86) NC	1.2 (0.53, 2.66) NC	11.16 (0.25, 969.24) NC	1.18 (0.54, 2.62) NC	1.62 (0.66, 4.17) NC	0.25 (0.02, 1.75) NC	1.22 (0.56, 2.73) NC	1.05 (0.05, 19.65) NC	1.52 (0.66, 3.58) NC	1.42 (0.69, 3.03) NC	5.44 (0.15, 620.35) NC	3.08 (0.04, 444.47) NC	0.09 (0, 2.47) NC	1.12 (0.5, 2.55) NC	1.35 (0.61, 2.92) NC	1.62 (0.67, 4.01) NC	Line

6.1.8. Hospitalisation for heart failure

Table 20: 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	NA	6.12 (0.3, 529.47) NC	0.67 (0.52, 0.88) FI	0.73 (0.61, 0.88) FI	NA	0.93 (0.77, 1.12) NC	NA	0.94 (0.78, 1.14) NC	NA	NA	NA	NA	0.9 (0.74, 1.08) NC	0.87 (0.72, 1.05) NC	NA	0.74 (0.15, 3.21) NC	2.56 (0.26, 35.56) NC	1.27 (1.07, 1.5) FC	0.87 (0.7, 1.07) NC	1.08 (0.76, 1.57) NC	NA	NA
ALO	6.93 (0.36, 509.13) NC	NA	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, 1.91) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DAPA	0.73 (0.6, 0.88) FI	0.11 (0, 2.1) NC	1.08 (0.79, 1.49) NC	NA	0.4 (0, 28.47) NC	NA	NA	NA	8.62 (0.2, 921.88) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DAPA/SAXA	0.21 (0, 6.66) NC	0.03 (0, 3.85) NC	0.31 (0, 10.37) NC	0.28 (0, 9.49) NC	NA	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, 2.58) NC	1.39 (1.01, 1.91) FC	1.28 (0.98, 1.68) NC	4.52 (0.14, 364.91) NC																	
EMPA	0.47 (0.03, 4.62) NC	0.06 (0, 3.1) NC	0.69 (0.05, 7.23) NC	0.64 (0.04, 6.29) NC	2.26 (0.02, 332.31) NC	0.5 (0.03, 5.05) NC														1.9 (0.2, 25.06) NC			
EXEN	0.94 (0.79, 1.14) NC	0.14 (0, 2.68) NC	1.41 (1.01, 1.95) FC	1.3 (1, 1.69) FC	4.51 (0.14, 363.68) NC	1.01 (0.78, 1.31) NC	2.03 (0.2, 31.66) NC															
GLIM	0.75 (0.54, 1.05) NC	0.11 (0, 2.2) NC	1.13 (0.73, 1.72) NC	1.04 (0.71, 1.53) NC	3.64 (0.11, 281.2) NC	0.81 (0.56, 1.18) NC	1.64 (0.16, 25.38) NC	0.8 (0.55, 1.16) NC					1.22 (0.93, 1.58) NC				2.48 (0.54, 15.14) NC					
IDegLira	0.76 (0.05, 7.96) NC	0.1 (0, 4.91) NC	1.14 (0.07, 12.3) NC	1.04 (0.07, 11.13) NC	3.67 (0.04, 426.98) NC	0.83 (0.06, 8.78) NC	1.59 (0.05, 59.06) NC	0.81 (0.05, 8.6) NC	1.02 (0.07, 10.7) NC		1.89 (0.19, 23.49) NC											
INS	1.7 (0.8, 3.65) NC	0.25 (0, 5.33) NC	2.52 (1.15, 5.69) FC	2.33 (1.08, 5.22) FC	8.19 (0.22, 712.46) NC	1.82 (0.85, 4) NC	3.71 (0.34, 68.22) NC	1.81 (0.85, 3.93) NC	2.26 (0.99, 5.09) NC	2.21 (0.23, 33.87) NC		0.1 (0, 2.33) NC		0.15 (0, 3.87) NC						1.15 (0.68, 1.94) NC	3.48 (0.1, 466.62) NC	

IGlarLixi	0.14 (0, 3.34) NC	0.02 (0, 1.74) NC	0.2 (0, 5.18) NC	0.19 (0, 4.56) NC	0.65 (0, 161.2) NC	0.15 (0, 3.48) NC	0.31 (0, 19.13) NC	0.15 (0, 3.37) NC	0.18 (0, 4.25) NC	0.19 (0, 9.99) NC	0.08 (0, 1.8) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LINA	0.9 (0.75, 1.09) NC	0.13 (0, 2.6) NC	1.35 (0.98, 1.85) NC	1.24 (0.95, 1.62) NC	4.37 (0.13, 350.78) NC	0.97 (0.75, 1.27) NC	1.95 (0.2, 29.75) NC	0.96 (0.74, 1.23) NC	1.2 (0.9, 1.57) NC	1.18 (0.11, 17.74) NC	0.53 (0.24, 1.15) NC	6.6 (0.27, 527.78) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LIRA	0.87 (0.73, 1.04) NC	0.12 (0, 2.48) NC	1.3 (0.95, 1.78) NC	1.2 (0.92, 1.56) NC	4.27 (0.13, 345.03) NC	0.93 (0.73, 1.2) NC	1.88 (0.19, 29.26) NC	0.92 (0.72, 1.19) NC	1.16 (0.8, 1.68) NC	1.14 (0.11, 16.83) NC	0.51 (0.24, 1.08) NC	6.3 (0.26, 537.48) NC	0.96 (0.75, 1.24) NC	NA	NA	NA	NA	NA	NA	NA	NA	2.12 (1.12, 3.83) FC	NA
LIXI	0.21 (0, 5.49) NC	0.02 (0, 3.5) NC	0.31 (0, 8.23) NC	0.29 (0, 7.62) NC	0.97 (0, 248.87) NC	0.22 (0, 5.89) NC	0.45 (0, 37.39) NC	0.22 (0, 5.78) NC	0.28 (0, 7.38) NC	0.27 (0, 19.99) NC	0.12 (0, 3.14) NC	1.54 (0.01, 351.55) NC	0.23 (0, 5.87) NC	0.24 (0, 6.14) NC	NA	NA	NA	NA	NA	NA	NA	NA	NA
MET	0.73 (0.16, 3.3) NC	0.1 (0, 3.18) NC	1.09 (0.23, 5.03) NC	1 (0.22, 4.43) NC	3.61 (0.07, 317.44) NC	0.78 (0.17, 3.51) NC	1.64 (0.1, 32.1) NC	0.77 (0.17, 3.48) NC	0.96 (0.21, 4.46) NC	1.01 (0.06, 21.99) NC	0.42 (0.08, 2.35) NC	5.4 (0.17, 521.32) NC	0.81 (0.18, 3.66) NC	0.83 (0.18, 3.75) NC	3.59 (0.09, 457.99) NC	NA	NA	NA	NA	NA	NA	NA	NA
PIO	2.14 (0.56, 10.36) NC	0.3 (0, 9.09) NC	3.23 (0.84, 16.39) NC	2.91 (0.78, 14.42) NC	10.83 (0.24, 1006.98) NC	2.28 (0.59, 11.33) NC	4.73 (0.32, 119.84) NC	2.27 (0.6, 11.14) NC	2.82 (0.75, 13.95) NC	2.96 (0.19, 60.75) NC	1.28 (0.26, 6.98) NC	16.73 (0.47, 1584.27) NC	2.38 (0.63, 11.46) NC	2.44 (0.64, 12.52) NC	10.98 (0.27, 1306.95) NC	2.9 (0.4, 27.5) NC	NA	NA	NA	NA	NA	NA	NA

SAXA	1.27 (1.07, 1.52) FC	0.18 (0, 3.58) NC	1.89 (1.39, 2.58) FC	1.74 (1.36, 2.24) FC	6.1 (0.19, 494.59) NC	1.36 (1.06, 1.78) FC	2.73 (0.27, 42.05) NC	1.35 (1.05, 1.72) FC	1.67 (1.17, 2.43) FC	1.67 (0.15, 24.89) NC	0.75 (0.34, 1.61) NC	9.25 (0.39, 750.69) NC	1.4 (1.09, 1.81) FC	1.46 (1.14, 1.85) FC	6.16 (0.22, 610.41) NC	1.74 (0.37, 7.98) NC	0.59 (0.12, 2.28) NC	NA	NA	NA	NA	NA
SEMA-O	0.87 (0.71, 1.07) NC	0.12 (0, 2.48) NC	1.3 (0.93, 1.81) NC	1.19 (0.9, 1.57) NC	4.2 (0.13, 334.61) NC	0.93 (0.71, 1.22) NC	1.87 (0.19, 29) NC	0.92 (0.69, 1.2) NC	1.15 (0.78, 1.69) NC	1.14 (0.11, 16.86) NC	0.51 (0.24, 1.08) NC	6.36 (0.26, 510.12) NC	0.96 (0.73, 1.27) NC	0.99 (0.76, 1.31) NC	4.2 (0.16, 422.92) NC	1.19 (0.26, 5.48) NC	0.41 (0.08, 1.54) NC	0.69 (0.52, 0.89) FI	NA	NA	2.3 (0.64, 8.3) NC	NA
SEMA-S	1.09 (0.75, 1.56) NC	0.15 (0, 3.08) NC	1.63 (1.04, 2.54) FC	1.5 (0.98, 2.22) NC	5.24 (0.16, 398.51) NC	1.17 (0.77, 1.76) NC	2.33 (0.22, 36.24) NC	1.15 (0.75, 1.74) NC	1.44 (0.87, 2.35) NC	1.41 (0.13, 21.54) NC	0.64 (0.27, 1.46) NC	7.95 (0.32, 671.95) NC	1.21 (0.79, 1.81) NC	1.25 (0.82, 1.87) NC	5.27 (0.2, 535.12) NC	1.46 (0.32, 7.05) NC	0.51 (0.1, 2.05) NC	0.86 (0.57, 1.28) NC	1.25 (0.82, 1.91) NC	NA	NA	NA
SITA	1.92 (1.09, 3.41) FC	0.28 (0, 5.87) NC	2.86 (1.51, 5.41) FC	2.64 (1.45, 4.88) FC	9.33 (0.27, 797.7) NC	2.06 (1.14, 3.74) FC	4.15 (0.38, 69.37) NC	2.03 (1.13, 3.71) FC	2.54 (1.32, 4.83) FC	2.58 (0.25, 37) NC	1.12 (0.67, 1.88) NC	13.84 (0.6, 1162.64) NC	2.13 (1.16, 3.88) FC	2.2 (1.27, 3.84) FC	9.21 (0.36, 974.02) NC	2.67 (0.53, 13.19) NC	0.9 (0.17, 3.89) NC	1.5 (0.85, 2.74) NC	2.22 (1.22, 4.05) FC	1.76 (0.92, 3.55) NC	NA	NA
TIRZE	4.78 (0.11, 550.54) NC	0.67 (0, 218.63) NC	7.26 (0.17, 835.45) NC	6.53 (0.16, 773.32) NC	27.1 (0.11, 13222.76) NC	5.23 (0.12, 580.31) NC	11.53 (0.12, 2269.04) NC	5.13 (0.12, 574.89) NC	6.43 (0.16, 720.31) NC	6.64 (0.09, 1439.36) NC	2.85 (0.06, 340.55) NC	43.09 (0.25, 21377.66) NC	5.38 (0.13, 592.88) NC	5.59 (0.13, 630.05) NC	26.7 (0.15, 15413.26) NC	6.77 (0.12, 925.31) NC	2.2 (0.04, 307) NC	3.87 (0.09, 405.9) NC	5.55 (0.13, 624.65) NC	4.42 (0.1, 549.52) NC	2.55 (0.06, 297.03) NC	NA

1

6.1.9. Development of end-stage renal failure

Table 21: 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 22: 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	3.25 (0.5, 34.12)	122 more per 1,000, 30 fewer to 819 more	8 treated for an additional harmful outcome in 1 person, 34 NNTB to 1 NNTH
Canagliflozin	0.88 (0.73, 1.06)	7 fewer per 1,000, 16 fewer to 3 more	143 treated for an additional beneficial outcome in 1 person, 63 NNTB to 287 NNTH
Dapagliflozin	1.00 (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	0.82 (0.06, 8.67)	11 fewer per 1,000, 56 fewer to 355 more	95 treated for an additional beneficial outcome in 1 person, 18 NNTB to 3 NNTH
Dapagliflozin + Saxagliptin	0.14 (0, 3.19)	51 fewer per 1,000, 60 fewer to 119 more	19 treated for an additional beneficial outcome in 1 person, 17 NNTB to 8 NNTH
Dulaglutide	0.91 (0.79, 1.06)	5 fewer per 1,000, 12 fewer to 3 more	191 treated for an additional beneficial outcome in 1 person, 81 NNTB to 287 NNTH
Empagliflozin	4.62 (0.46, 100.48)	189 more per 1,000, 32 fewer to 938 more	5 treated for an additional harmful outcome in 1 person, 31 NNTB to 1 NNTH
Empagliflozin + Linagliptin	15.96 (0.34, 871.31)	568 more per 1,000, 39 fewer to 940 more	2 treated for an additional harmful outcome in 1 person, 26 NNTB to 1 NNTH
Ertugliflozin	1.99 (0.25, 33.78)	56 more per 1,000, 45 fewer to 816 more	18 treated for an additional harmful outcome in 1 person, 22 NNTB to 1 NNTH
Ertugliflozin + Sitagliptin	0.26 (0, 13.2)	44 fewer per 1,000, 60 fewer to 498 more	23 treated for an additional beneficial outcome in 1 person, 17 NNTB to 2 NNTH
Exenatide	0.88 (0.76, 1.02)	7 fewer per 1,000, 14 fewer to 1 more	143 treated for an additional beneficial outcome in 1 person, 71 NNTB to 860 NNTH
Gliclazide	6.82 (0.14, 651.97)	284 more per 1,000, 51 fewer to 940 more	4 treated for an additional harmful outcome in 1 person, 19 NNTB to 1 NNTH
Glimepiride	0.99 (0.75, 1.3)	1 fewer per 1,000, 15 fewer to 17 more	1000 treated for an additional beneficial outcome in 1 person, 68 NNTB to 58 NNTH

Intervention compared to placebo	Hazard ratio	Absolute effect per 1000 people	Number needed to treat per 1000 people
Glipizide	6.05 (1.2, 44.7)	252 more per 1,000, 12 more to 877 more	4 treated for an additional harmful outcome in 1 person, 86 NNTH to 1 NNTH
IDegLira	0.48 (0.07, 2.44)	31 fewer per 1,000, 56 fewer to 80 more	33 treated for an additional beneficial outcome in 1 person, 18 NNTB to 12 NNTH
IGlarLixi	1.32 (0.7, 2.59)	18 fewer per 1,000, 18 fewer to 88 more	54 treated for an additional beneficial outcome in 1 person, 57 NNTB to 11 NNTH
Insulin	0.38 (0.03, 2.77)	37 more per 1,000, 58 fewer to 98 more	27 treated for an additional harmful outcome in 1 person, 17 NNTB to 10 NNTH
Linagliptin	0.98 (0.83, 1.15)	1 fewer per 1,000, 10 fewer to 9 more	859 treated for an additional beneficial outcome in 1 person, 101 NNTB to 115 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 (0.13, 3.19)	18 fewer per 1,000, 52 fewer to 119 more	57 treated for an additional beneficial outcome in 1 person, 19 NNTB to 8 NNTH
Metformin type unspecified	1.63 (0.27, 11.47)	36 more per 1,000, 43 fewer to 448 more	28 treated for an additional harmful outcome in 1 person, 23 NNTB to 2 NNTH
Pioglitazone	1.01 (0.09, 10.8)	1 fewer per 1,000, 54 fewer to 427 more	1000 treated for an additional harmful outcome in 1 person, 18 NNTB to 2 NNTH
Pioglitazone + Alogliptin	0.11 (0, 5.7)	53 fewer per 1,000, 60 fewer to 237 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	0.9 (0.77, 1.03)	6 fewer per 1,000, 13 fewer to 2 more	171 treated for an additional beneficial outcome in 1 person, 74 NNTB to 574 NNTB
Semaglutide; Subcutaneous	0.95 (0.66, 1.39)	3 fewer per 1,000, 20 fewer to 22 more	343 treated for an additional beneficial outcome in 1 person, 50 NNTB to 49 NNTH
Sitagliptin	1.28 (0.75, 2.12)	16 more per 1,000, 15 fewer to 63 more	62 treated for an additional harmful outcome in 1 person, 68 NNTB to 16 NNTH
Tirzepatide	1.39 (0.31, 9.3)	22 more per 1,000, 41 fewer to 378 more	45 treated for an additional harmful outcome in 1 person, 24 NNTB to 3 NNTH
Vildagliptin	1.2 (0.19, 8)	12 more per 1,000, 48 fewer to 330 more	86 treated for an additional harmful outcome in 1 person, 21 NNTB to 3 NNTH

1

6.2.2. 3-item MACE

Table 23: 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 (0.87 , 1.31)	8 more per 1,000, 15 fewer to 35 more	126 treated for an additional harmful outcome in 1 person, 67 NNTB to 29 NNTH
IDegLira	1.62 (0.43 , 6.62)	68 more per 1,000, 68 fewer to 445 more	15 treated for an additional harmful outcome in 1 person, 15 NNTB to 2 NNTH
Insulin	1.17 (0.71 , 1.93)	19 more per 1,000, 34 fewer to 100 more	52 treated for an additional harmful outcome in 1 person, 30 NNTB to 10 NNTH
Linagliptin	1.04 (0.9 , 1.19)	5 more per 1,000, 11 fewer to 21 more	219 treated for an additional harmful outcome in 1 person, 87 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 , 2.48)	43 more per 1,000, 23 fewer to 154 more	23 treated for an additional harmful outcome in 1 person, 43 NNTB to 7 NNTH
Saxagliptin	1.00 (0.9 , 1.12)	0 fewer per 1,000, 11 fewer to 14 more	1000 treated for an additional beneficial outcome in 1 person, 1000 NNTB to 1000 NNTH
Semaglutide; Oral	0.85 (0.77 , 0.95)	17 fewer per 1,000, 27 fewer to 6 fewer	58 treated for an additional beneficial outcome in 1 person, 37 NNTB to 175 NNTH
Semaglutide; Subcutaneous	0.74 (0.58 , 0.94)	30 fewer per 1,000, 49 fewer to 6 fewer	33 treated for an additional beneficial outcome in 1 person, 20 NNTB to 145 NNTB
Sitagliptin	1.25 (0.86 , 1.82)	28 more per 1,000, 16 fewer to 89 more	36 treated for an additional harmful outcome in 1 person, 62 NNTB to 11 NNTH
Tirzepatide	0.93 (0.29 , 3.6)	8 fewer per 1,000, 85 fewer to 252 more	124 treated for an additional beneficial outcome in 1 person, 12 NNTB to 4 NNTH

6.2.3. 4-item MACE

Table 24: 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	0.71 (0.09, 5.61)	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	0.53 (0.07, 4.27)	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	0.79 (0.10, 6.10)	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	0.92 (0.13, 6.88)	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 25: 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 26: 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	3.1 (1.21, 82.27)	128 more per 1,000, 14 fewer to 929 more	8 treated for an additional harmful outcome in 1 person, 73 NNTB to 1 NNTH
Canagliflozin	0.85 (0.72, 1.77)	10 fewer per 1,000, 19 fewer to 49 more	101 treated for an additional beneficial outcome in 1 person, 54 NNTB to 20 NNTH
Dapagliflozin	0.87 (0.73, 1.65)	9 fewer per 1,000, 18 fewer to 42 more	117 treated for an additional beneficial outcome in 1 person, 56 NNTB to 24 NNTH
Dulaglutide	0.94 (0.81, 1.8)	4 fewer per 1,000, 13 fewer to 51 more	253 treated for an additional beneficial outcome in 1 person, 80 NNTB to 20 NNTH
Exenatide	0.9 (0.76, 1.57)	7 fewer per 1,000, 16 fewer to 37 more	152 treated for an additional beneficial outcome in 1 person, 63 NNTB to 27 NNTH
Gliclazide	1.97 (0.88, 30.88)	62 more per 1,000, 8 fewer to 818 more	16 treated for an additional harmful outcome in 1 person, 126 NNTB to 1 NNTH
Glimepiride	1.2 (0.97, 2.69)	13 more per 1,000, 2 fewer to 105 more	77 treated for an additional harmful outcome in 1 person, 507 NNTB to 10 NNTH
Glipizide	4.62 (1.68, 122.73)	210 more per 1,000, 44 fewer to 932 more	5 treated for an additional harmful outcome in 1 person, 23 NNTB to 1 NNTH
IDegLira	1.49 (0.85, 8.76)	32 more per 1,000, 10 fewer to 392 more	32 treated for an additional harmful outcome in 1 person, 101 NNTB to 3 NNTH
Insulin	0.94 (0.55, 4.39)	4 fewer per 1,000, 30 fewer to 198 more	253 treated for an additional beneficial outcome in 1 person, 33 NNTB to 5 NNTH
Linagliptin	1.16 (0.99, 2.27)	10 more per 1,000, 1 fewer to 80 more	96 treated for an additional harmful outcome in 1 person, 1000 NNTB to 13 NNTH
Liraglutide	0.9 (0.79, 1.92)	7 fewer per 1,000, 14 fewer to 58 more	152 treated for an additional beneficial outcome in 1 person, 72 NNTB to 17 NNTH
Lixisenatide	5.7 (1.58, 492.75)	263 more per 1,000, 37 fewer to 932 more	4 treated for an additional harmful outcome in 1 person, 27 NNTB to 1 NNTH
Pioglitazone	0.72 (0.48, 2.25)	19 fewer per 1,000, 35 fewer to 79 more	54 treated for an additional beneficial outcome in 1 person, 29 NNTB to 13 NNTH
Saxagliptin	0.95 (0.82, 1.97)	3 fewer per 1,000, 12 fewer to 62 more	304 treated for an additional beneficial outcome in 1 person, 84 NNTB to 16 NNTH
Semaglutide; Oral	0.83 (0.73, 1.42)	11 fewer per 1,000, 18 fewer to 27 more	89 treated for an additional harmful outcome in 1 person, 56 NNTB to 37 NNTH

Intervention compared to placebo	Hazard ratio	Absolute effect per 1000 people	Number needed to treat per 1000 people
Semaglutide; Subcutaneous	0.7 (0.57, 1.43)	20 fewer per 1,000, 29 fewer to 28 more	50 treated for an additional beneficial outcome in 1 person, 35 NNTB to 36 NNTH
Sitagliptin	1.38 (0.88, 5.31)	25 more per 1,000, 8 fewer to 244 more	41 treated for an additional harmful outcome in 1 person, 126 NNTB to 4 NNTH
Tirzepatide	7.92 (2.44, 544.57)	360 more per 1,000, 90 more to 932 more	3 treated for an additional harmful outcome in 1 person, 11 NNTB to 1 NNTH

6.2.6. Non-fatal stroke

Table 27: 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 (0.7, 2.64)	4 fewer per 1,000, 11 fewer to 59 more	268 treated for an additional beneficial outcome in 1 person, 89 NNTB to 17 NNTH
Dapagliflozin	1.04 (0.84, 3.46)	2 fewer per 1,000, 6 fewer to 87 more	671 treated for an additional harmful outcome in 1 person, 167 NNTB to 11 NNTH
Dulaglutide	0.95 (0.76, 4.22)	2 fewer per 1,000, 9 fewer to 113 fewer	536 treated for an additional beneficial outcome in 1 person, 111 NNTB to 9 NNTB
Empagliflozin	0.73 (0.28, 14.88)	10 fewer per 1,000, 27 fewer to 400 more	99 treated for an additional beneficial outcome in 1 person, 37 NNTB to 2 NNTH
Exenatide	0.9 (0.72, 2.92)	4 fewer per 1,000, 10 fewer to 69 more	268 treated for an additional beneficial outcome in 1 person, 95 NNTB to 15 NNTH
Gliclazide	0.09 (0.02, 4.14)	35 fewer per 1,000, 37 fewer to 110 more	29 treated for an additional beneficial outcome in 1 person, 27 NNTB to 9 NNTH
Glimepiride	1.39 (1.02, 5.37)	14 more per 1,000, 1 more to 150 more	69 treated for an additional harmful outcome in 1 person, 1000 NNTB to 7 NNTH
IDegLira	0.47 (0.27, 2.75)	20 fewer per 1,000, 28 fewer to 63 more	50 treated for an additional beneficial outcome in 1 person, 36 NNTB to 16 NNTH
IGlarLixi	0.28 (0.17, 1.17)	27 fewer per 1,000, 31 fewer to 6 more	37 treated for an additional beneficial outcome in 1 person, 32 NNTB to 158 NNTH
Insulin	0.16 (0.04, 5.75)	32 fewer per 1,000, 36 fewer to 162 more	31 treated for an additional beneficial outcome in 1 person, 27 NNTB to 6 NNTH

Intervention compared to placebo	Hazard ratio	Absolute effect per 1000 people	Number needed to treat per 1000 people
Linagliptin	0.94 (0.76, 2.51)	2 fewer per 1,000, 9 fewer to 55 more	447 treated for an additional beneficial outcome in 1 person, 111 NNTB to 18 NNTH
Liraglutide	0.79 (0.61, 1.6)	8 fewer per 1,000, 15 fewer to 22 more	127 treated for an additional beneficial outcome in 1 person, 68 NNTB to 45 NNTH
Lixisenatide	4.35 (2.1, 64.72)	117 more per 1,000, 40 more to 881 more	9 treated for an additional harmful outcome in 1 person, 25 NNTB to 1 NNTH
Pioglitazone	0.87 (0.51, 4.06)	5 fewer per 1,000, 18 fewer to 108 more	206 treated for an additional beneficial outcome in 1 person, 54 NNTB to 9 NNTH
Pioglitazone + Exenatide	0.04 (0.01, 1.06)	36 fewer per 1,000, 38 fewer to 2 more	27 treated for an additional beneficial outcome in 1 person, 27 NNTB to 448 NNTB
Saxagliptin	1.11 (0.88, 2.97)	4 more per 1,000, 4 fewer to 71 more	244 treated for an additional harmful outcome in 1 person, 223 NNTB to 14 NNTH
Semaglutide; Oral	0.84 (0.69, 1.6)	6 fewer per 1,000, 12 fewer to 22 more	167 treated for an additional beneficial outcome in 1 person, 86 NNTB to 45 NNTH
Semaglutide; Subcutaneous	0.66 (0.5, 2.12)	13 fewer per 1,000, 19 fewer to 41 more	78 treated for an additional beneficial outcome in 1 person, 53 NNTB to 24 NNTH
Sitagliptin	0.38 (0.21, 1.9)	23 fewer per 1,000, 30 fewer to 33 more	43 treated for an additional beneficial outcome in 1 person, 33 NNTB to 30 NNTH
Tirzepatide	0.54 (0.26, 5.64)	17 fewer per 1,000, 28 fewer to 158 more	58 treated for an additional beneficial outcome in 1 person, 36 NNTB to 6 NNTH
Vildagliptin	0.32 (0.18, 1.67)	26 fewer per 1,000, 31 fewer to 25 more	39 treated for an additional beneficial outcome in 1 person, 32 NNTB to 41 NNTH

6.2.7. Unstable angina

Table 28: 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 (0.84, 1.21)	1 more per 1,000, 4 fewer to 6 more	1000 treated for an additional harmful outcome in 1 person, 234 NNTB to 179 NNTH
Dulaglutide	1.12 (0.83, 1.52)	3 more per 1,000, 5 fewer to 14 more	313 treated for an additional harmful outcome in 1 person, 220 NNTB to 73 NNTH

Intervention compared to placebo	Hazard ratio	Absolute effect per 1000 people	Number needed to treat per 1000 people
Empagliflozin	0.12 (0, 5.21)	24 fewer per 1,000, 27 fewer to 106 more	42 treated for an additional beneficial outcome in 1 person, 37 NNTB to 9 NNTH
Exenatide	1.14 (0.9, 1.43)	4 more per 1,000, 3 fewer to 11 more	269 treated for an additional harmful outcome in 1 person, 375 NNTB to 88 NNTH
Glimepiride	0.82 (0.48, 1.4)	5 fewer per 1,000, 14 fewer to 11 more	208 treated for an additional beneficial outcome in 1 person, 72 NNTB to 94 NNTH
IDegLira	5.31 (0.76, 64.72)	108 more per 1,000, 6 fewer to 803 more	9 treated for an additional harmful outcome in 1 person, 156 NNTB to 1 NNTH
IGlarLixi	1.11 (0.48, 2.48)	3 more per 1,000, 14 fewer to 39 more	342 treated for an additional harmful outcome in 1 person, 72 NNTB to 26 NNTH
Insulin	1.27 (0.07, 25.03)	7 more per 1,000, 25 fewer to 469 more	140 treated for an additional harmful outcome in 1 person, 40 NNTB to 2 NNTH
Linagliptin	0.88 (0.59, 1.32)	3 fewer per 1,000, 11 fewer to 8 more	312 treated for an additional beneficial outcome in 1 person, 91 NNTB to 118 NNTH
Liraglutide	0.95 (0.74, 1.2)	1 fewer per 1,000, 7 fewer to 5 more	750 treated for an additional beneficial outcome in 1 person, 144 NNTB to 188 NNTH
Lixisenatide	0.24 (0, 9.21)	20 fewer per 1,000, 27 fewer to 196 more	49 treated for an additional beneficial outcome in 1 person, 37 NNTB to 5 NNTH
Metformin type unspecified	0.43 (0, 35.87)	15 fewer per 1,000, 27 fewer to 598 more	65 treated for an additional beneficial outcome in 1 person, 37 NNTB to 2 NNTH
Pioglitazone	15.33 (0.55, 982.4)	316 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, 1.6)	5 more per 1,000, 3 fewer to 16 more	198 treated for an additional harmful outcome in 1 person, 312 NNTB to 63 NNTH
Semaglutide; Oral	1.01 (0.75, 1.34)	0 more per 1,000, 7 fewer to 9 more	1000 treated for an additional harmful outcome in 1 person, 150 NNTB to 111 NNTH
Semaglutide; Subcutaneous	0.83 (0.48, 1.42)	5 fewer per 1,000, 14 fewer to 11 more	220 treated for an additional beneficial outcome in 1 person, 72 NNTB to 90 NNTH
Sitagliptin	1.35 (0.63, 2.89)	9 more per 1,000, 10 fewer to 49 more	108 treated for an additional harmful outcome in 1 person, 101 NNTB to 20 NNTH

1

6.2.8. Hospitalisation for heart failure

Table 29: 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	6.96 (0.36, 507.76)	262 more per 1,000, 34 fewer to 947 more	4 treated for an additional harmful outcome in 1 person, 30 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 (0.6, 0.88)	14 fewer per 1,000, 21 fewer to 6 fewer	71 treated for an additional beneficial outcome in 1 person, 48 NNTB to 161 NNTB
Dapagliflozin + Saxagliptin	0.21 (0, 6.69)	42 fewer per 1,000, 53 fewer to 252 more	24 treated for an additional beneficial outcome in 1 person, 19 NNTB to 4 NNTH
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	0.47 (0.03, 4.62)	28 fewer per 1,000, 51 fewer to 169 more	36 treated for an additional beneficial outcome in 1 person, 19 NNTB to 6 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	0.76 (0.54, 1.05)	12 fewer per 1,000, 24 fewer to 3 more	80 treated for an additional beneficial outcome in 1 person, 42 NNTB to 388 NNTH
IDegLira	0.76 (0.05, 7.92)	12 fewer per 1,000, 50 fewer to 297 more	80 treated for an additional beneficial outcome in 1 person, 20 NNTB to 3 NNTH
IGlarLixi	1.7 (0.8, 3.67)	35 fewer per 1,000, 10 fewer to 128 more	28 treated for an additional beneficial outcome in 1 person, 96 NNTB to 8 NNTH
Insulin	0.14 (0, 3.35)	45 more per 1,000, 53 fewer to 114 more	22 treated for an additional harmful outcome in 1 person, 19 NNTB to 9 NNTH
Linagliptin	0.9 (0.75, 1.09)	5 fewer per 1,000, 13 fewer to 5 more	193 treated for an additional beneficial outcome in 1 person, 77 NNTB to 216 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, 5.47)	42 fewer per 1,000, 53 fewer to 205 more	24 treated for an additional beneficial outcome in 1 person, 19 NNTB to 5 NNTH
Metformin (type unspecified)	0.73 (0.16, 3.29)	14 fewer per 1,000, 44 fewer to 111 more	71 treated for an additional beneficial outcome in 1 person, 23 NNTB to 9 NNTH

Intervention compared to placebo	Hazard ratio	Absolute effect per 1000 people	Number needed to treat per 1000 people
Pioglitazone	2.14 (0.56, 10.38)	57 more per 1,000, 23 fewer to 379 more	18 treated for an additional harmful outcome in 1 person, 44 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	0.87 (0.7, 1.06)	7 fewer per 1,000, 16 fewer to 3 more	149 treated for an additional beneficial outcome in 1 person, 64 NNTB to 324 NNTH
Semaglutide; Subcutaneous	1.09 (0.75, 1.57)	5 more per 1,000, 13 fewer to 29 more	216 treated for an additional harmful outcome in 1 person, 77 NNTB to 35 NNTH
Sitagliptin	1.92 (1.09, 3.42)	46 more per 1,000, 5 more to 117 more	22 treated for an additional harmful outcome in 1 person, 216 NNTH to 9 NNTH
Tirzepatide	4.76 (0.11, 550.04)	175 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 30: 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 31: 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)
Alogliptin	26 (6 to 30)
Canagliflozin	11 (6 to 19)
Dapagliflozin	16 (9 to 22)
Dapagliflozin + Exenatide	10 (1 to 28)
Dapagliflozin + Saxagliptin	2 (1 to 26)
Dulaglutide	13 (7 to 20)
Empagliflozin	27 (5 to 30)
Empagliflozin + Linagliptin	29 (5 to 30)
Ertugliflozin	24 (3 to 30)
Ertugliflozin + Sitagliptin	4 (1 to 29)
Exenatide	11 (6 to 18)
Gliclazide	28 (3 to 30)
Glimepiride	16 (7 to 23)
Glipizide	28 (21 to 30)
IDegLira	5 (1 to 25)
Insulin	21 (8 to 26)
Insulin glargine/Lixisenatide	5 (1 to 25)
Linagliptin	15 (9 to 22)
Liraglutide	8 (4 to 13)
Lixisenatide	7 (2 to 26)
Metformin type unspecified	23 (3 to 29)
Pioglitazone	17 (2 to 29)
Pioglitazone + Alogliptin	2 (1 to 27)
Saxagliptin	17 (10 to 23)
Semaglutide; Oral	12 (6 to 19)
Semaglutide; Subcutaneous	14 (6 to 23)
Sitagliptin	21 (9 to 25)
Tirzepatide	21 (4 to 29)
Vildagliptin	20 (3 to 28)

6.3.2. 3-item MACE

Table 32: 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 (1 to 10)
Dapagliflozin	7 (3 to 12)
Dulaglutide	5 (2 to 10)
Exenatide	7 (3 to 11)
Glimepiride	12 (5 to 15)
IDegLira	15 (1 to 16)
Insulin	13 (2 to 16)
Linagliptin	11 (7 to 14)
Liraglutide	5 (2 to 9)
Pioglitazone	15 (3 to 16)
Saxagliptin	10 (6 to 14)
Semaglutide; Oral	4 (1 to 8)
Semaglutide; Subcutaneous	2 (1 to 8)
Sitagliptin	14 (5 to 16)
Tirzepatide	7 (1 to 16)

6.3.3. 4-item MACE

Table 33: 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 34: Median rankings for each treatment with 95% credible intervals for 5-item MACE.

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

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

6.3.5. Non-fatal myocardial infarction

Table 35: Median rankings for each treatment with 95% credible intervals for non-fatal myocardial infarction.

Treatment	Median rankings (95% credibility interval)
Placebo	11 (8 to 15)
Alogliptin	17 (1 to 20)
Canagliflozin	6 (2 to 13)
Dapagliflozin	7 (3 to 12)
Dulaglutide	9 (4 to 15)
Exenatide	9 (4 to 14)
Gliclazide	16 (1 to 20)
Glimepiride	13 (6 to 17)
Glipizide	18 (1 to 20)
IDegLira	15 (1 to 19)
Insulin	9 (1 to 18)
Linagliptin	13 (8 to 17)
Liraglutide	7 (3 to 13)
Lixisenatide	18 (1 to 20)
Pioglitazone	4 (1 to 17)
Saxagliptin	9 (4 to 15)
Semaglutide; Oral	4 (1 to 9)
Semaglutide; Subcutaneous	3 (1 to 12.03)
Sitagliptin	14 (1 to 19)
Tirzepatide	19 (1 to 20)

6.3.6. Non-fatal stroke

Table 36: 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)
Empagliflozin	10 (2 to 22)
Exenatide	13 (8 to 19)
Gliclazide	2 (1 to 21)

Treatment	Median rank (95% credible intervals)
Glimepiride	19 (10 to 21)
IDegLira	7 (2 to 21)
Insulin	5 (2 to 14)
Insulin glargine/Lixisenatide	3 (1 to 21)
Linagliptin	14 (7 to 20)
Liraglutide	13 (8 to 19)
Lixisenatide	22 (9 to 22)
Pioglitazone	12 (4 to 22)
Pioglitazone + Exenatide	2 (1 to 11)
Saxagliptin	19 (13 to 21)
Semaglutide; Oral	13 (8 to 19)
Semaglutide; Subcutaneous	9 (5 to 17)
Sitagliptin	6 (2 to 21)
Tirzepatide	7 (2 to 22)
Vildagliptin	6 (2 to 20)

6.3.7. Unstable angina

Table 37: Median rankings for each treatment with 95% credible intervals for unstable angina using the base case analysis.

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

6.3.8. Hospitalisation for heart failure

Table 38: 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	14 (10 to 17)
Alogliptin	21 (4 to 22)
Canagliflozin	6 (3 to 10)
Dapagliflozin	7 (3 to 11)
Dapagliflozin + Saxagliptin	3 (1 to 21)
Dulaglutide	12 (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	17 (14 to 19)
Semaglutide; Oral	10 (5 to 15)
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

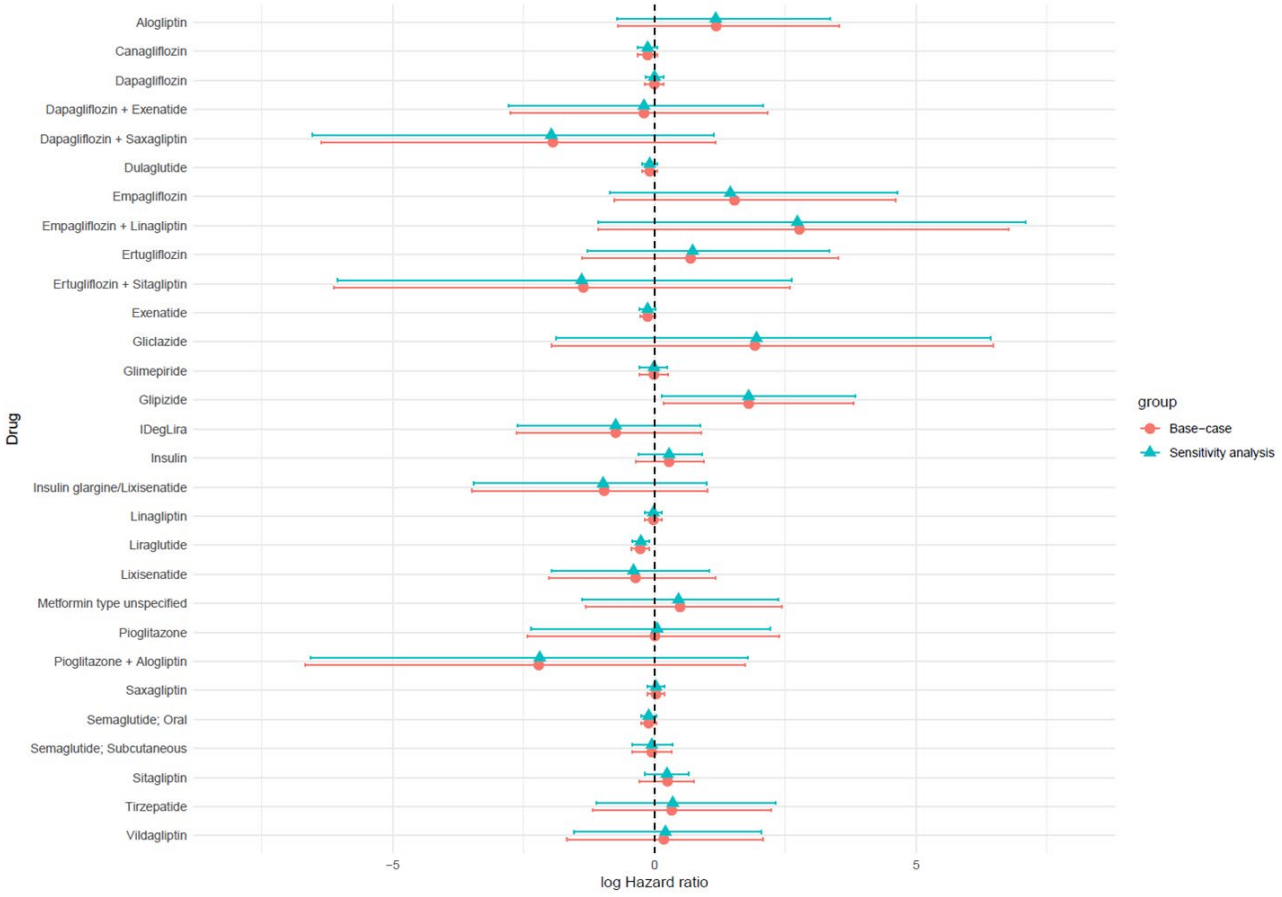
Table 39: Median rankings for each treatment with 95% credible intervals for development of end-stage renal failure.

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

6.4. Relative effectiveness plots

6.4.1. Cardiovascular mortality

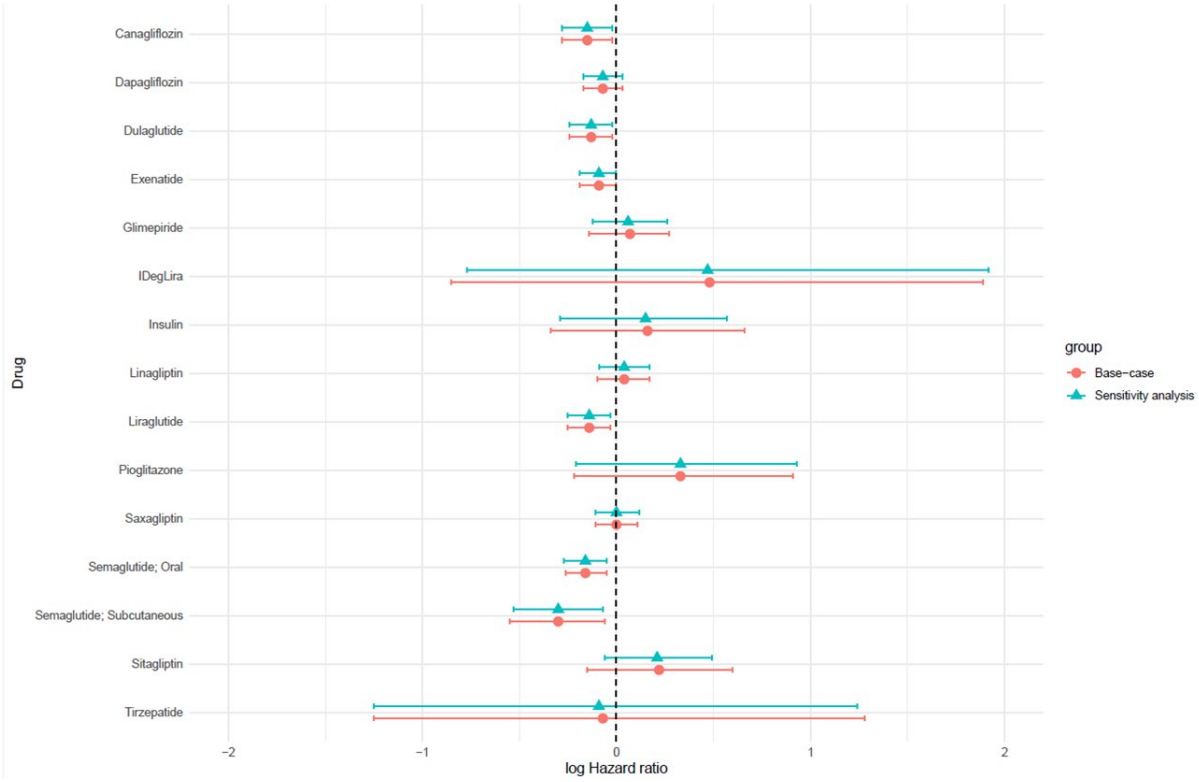
Figure 28: Log hazard ratios of all treatments compared with placebo for cardiovascular mortality showing the base case analysis results compared to sensitivity analysis results. Circles indicate the log HR, and lines indicate 95% credible intervals.



Favours treatment **Favours placebo**

6.4.2. 3-item MACE

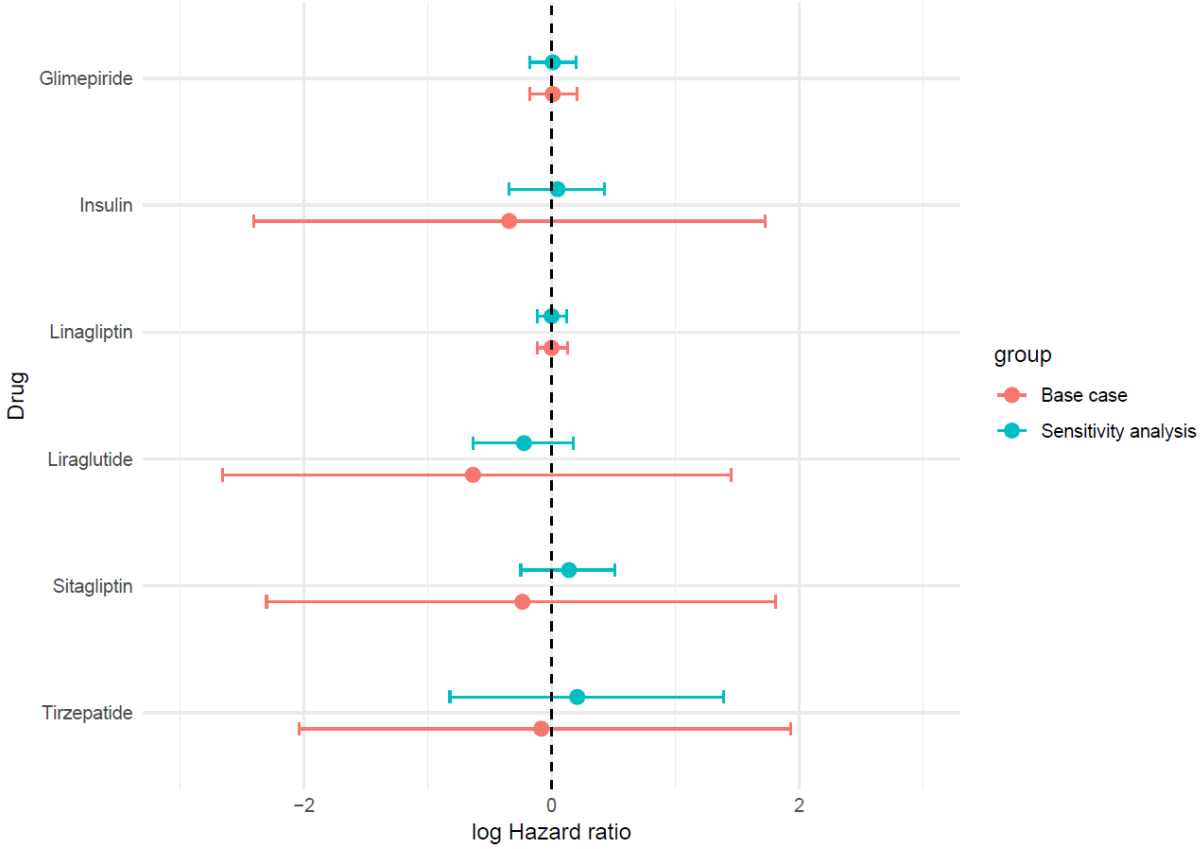
Figure 29: Log hazard ratios of all treatments compared with placebo for 3-item MACE showing the base case analysis results compared to the sensitivity analysis results. Circles indicate the log HR, and lines indicate 95% credible intervals.



Favours treatment **Favours placebo**

6.4.3. 4-item MACE

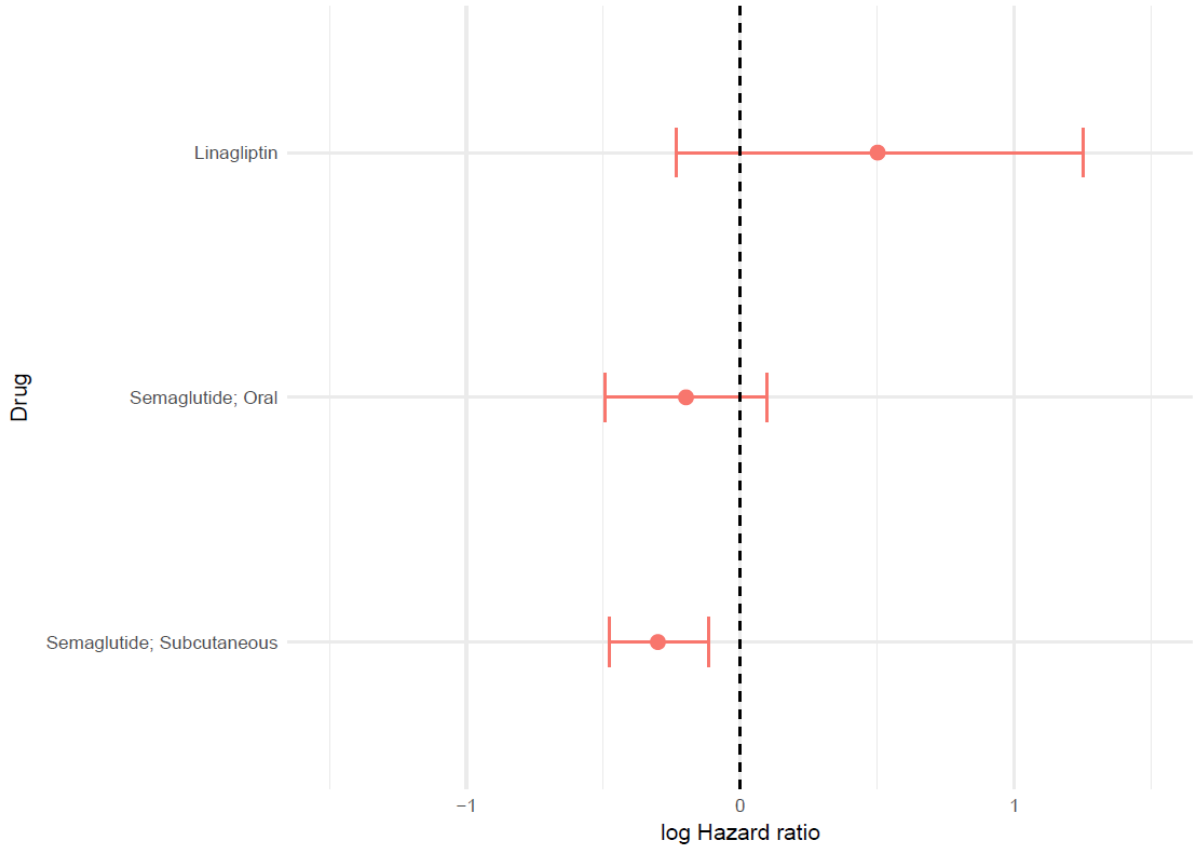
Figure 30: Log hazard ratios of all treatments compared with placebo for 4-item MACE showing the base case analysis results compared to the sensitivity analysis results. Circles indicate the log HR, and lines indicate 95% credible intervals.



Favours treatment **Favours placebo**

6.4.4. 5-item MACE

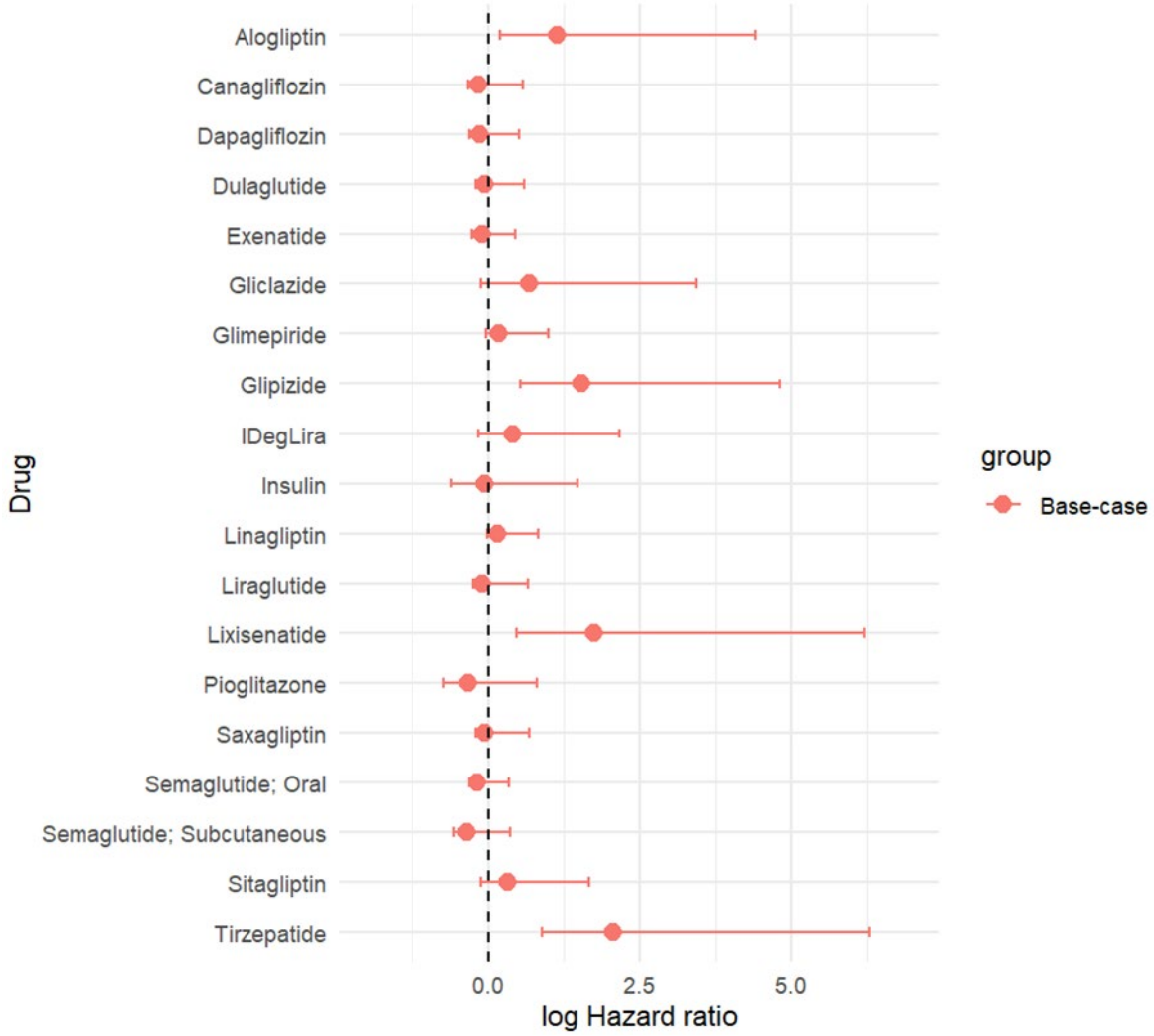
Figure 31: Log hazard ratios of all treatments compared with placebo for 5-item MACE. Circles indicate the log HR, and lines indicate 95% credible intervals.



Favours treatment **Favours placebo**

6.4.5. Non-fatal myocardial infarction

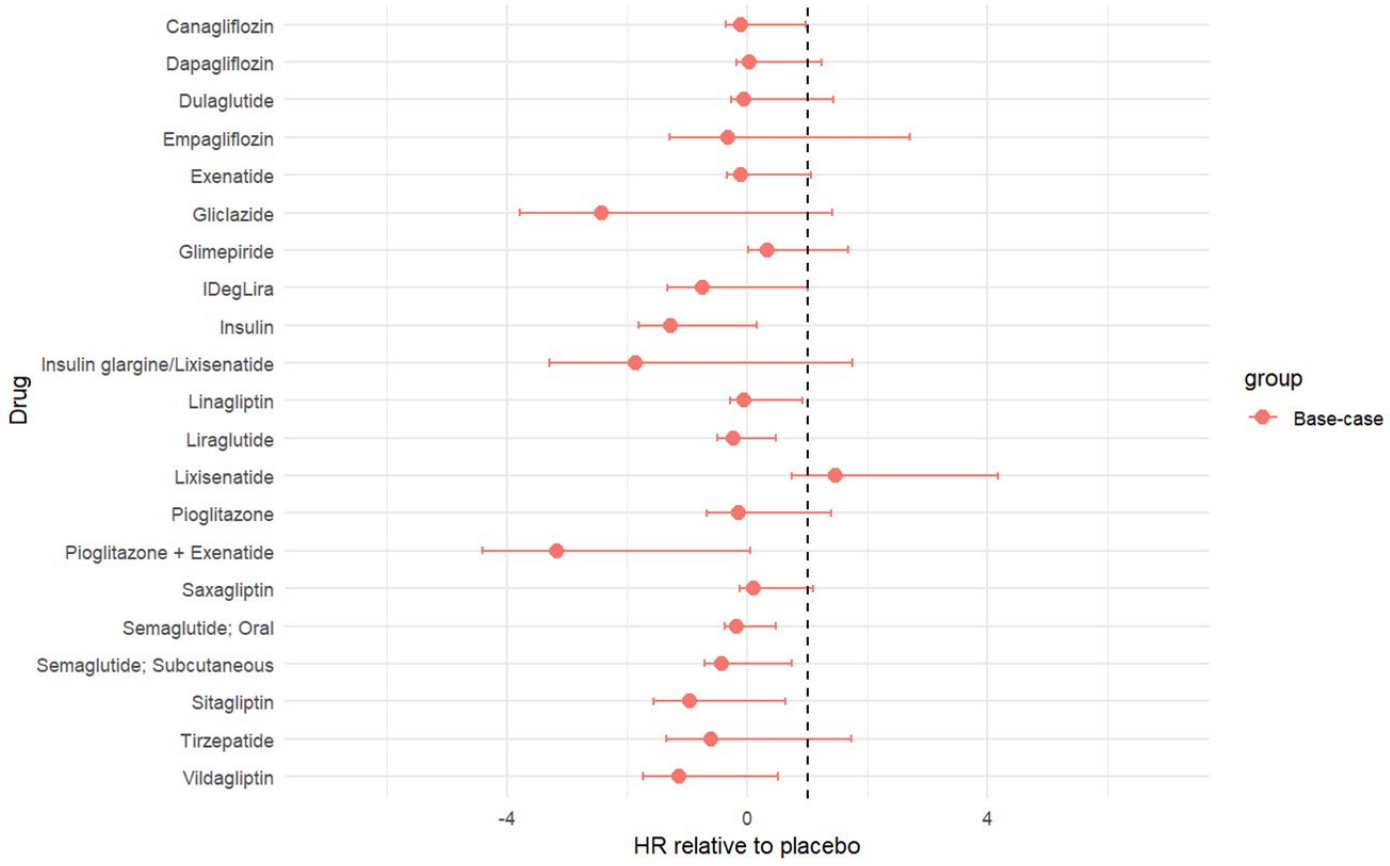
Figure 32: Log hazard ratios of all treatments compared with placebo for non-fatal myocardial infarction. Circles indicate the log HR, and lines indicate 95% credible intervals.



Favours treatment **Favours placebo**

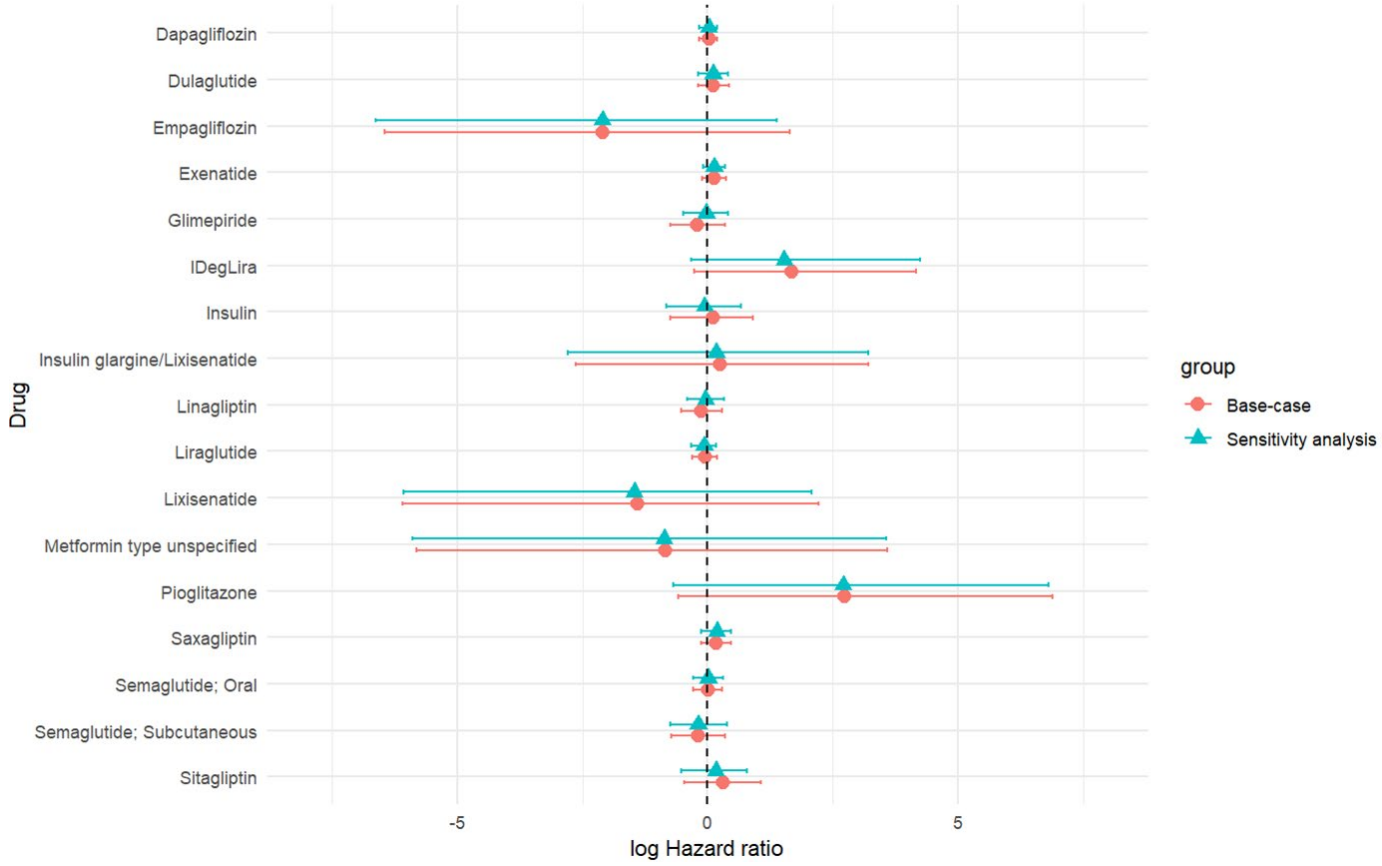
6.4.6. Non-fatal stroke

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.



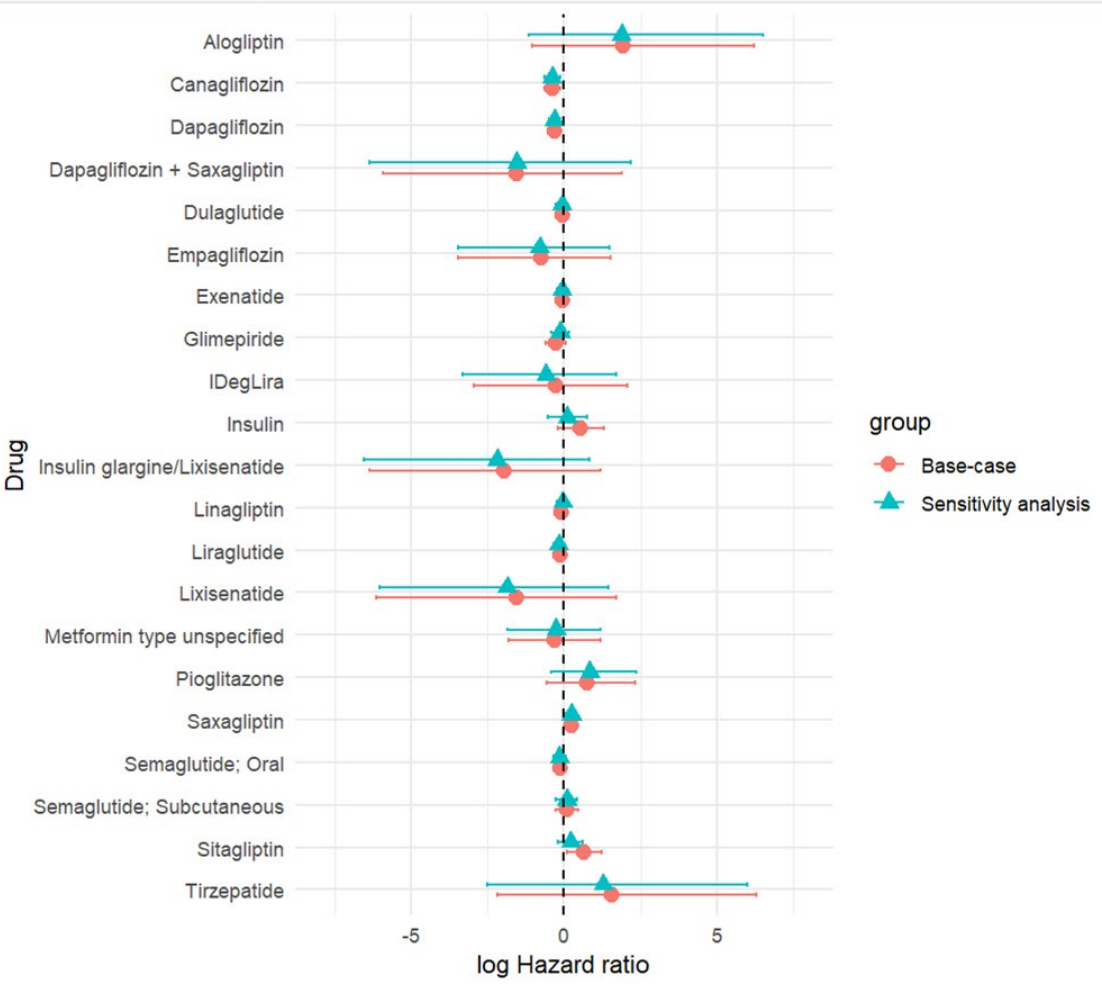
6.4.7. Unstable angina

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.



6.4.8. Hospitalisation for heart failure

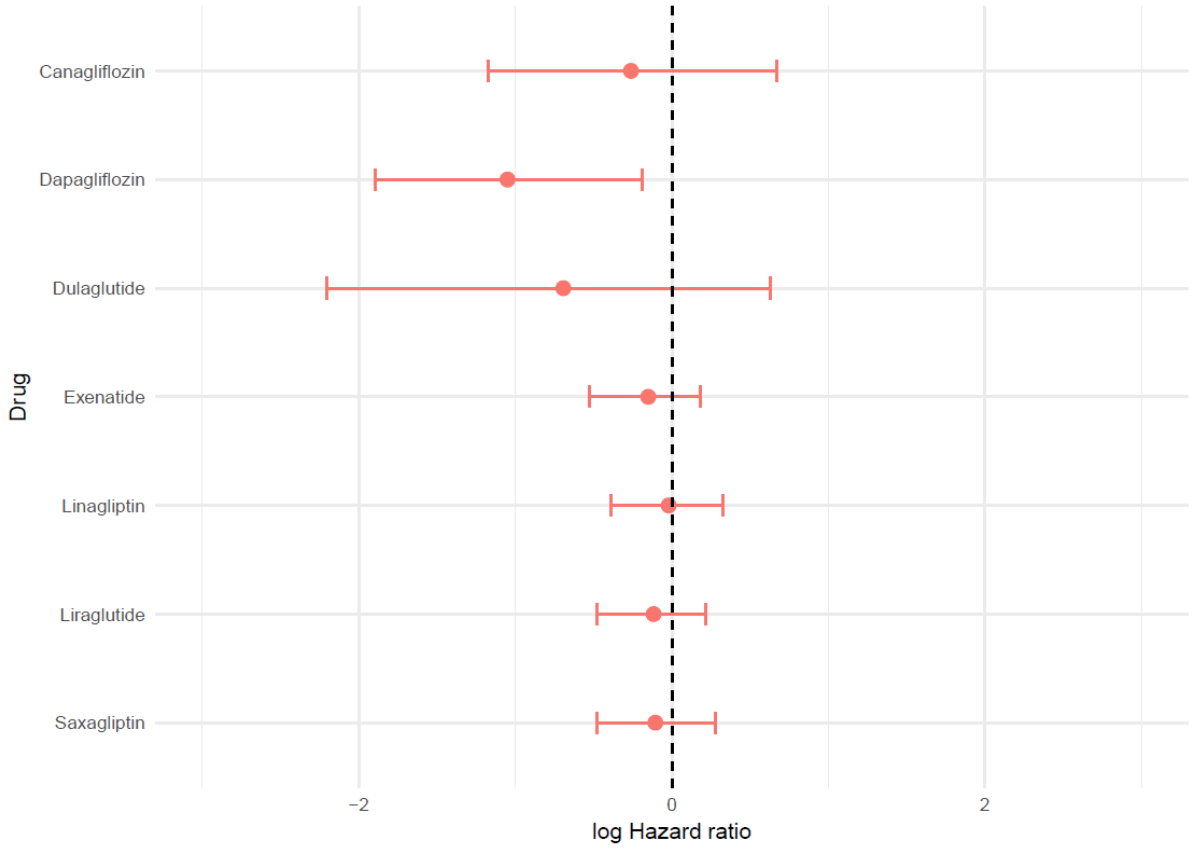
Figure 35: Log hazard ratios of all treatments compared with placebo for hospitalisation for heart failure showing the base case analysis results compared to the sensitivity analysis results. Circles indicate the log HR, and lines indicate 95% credible intervals.



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.

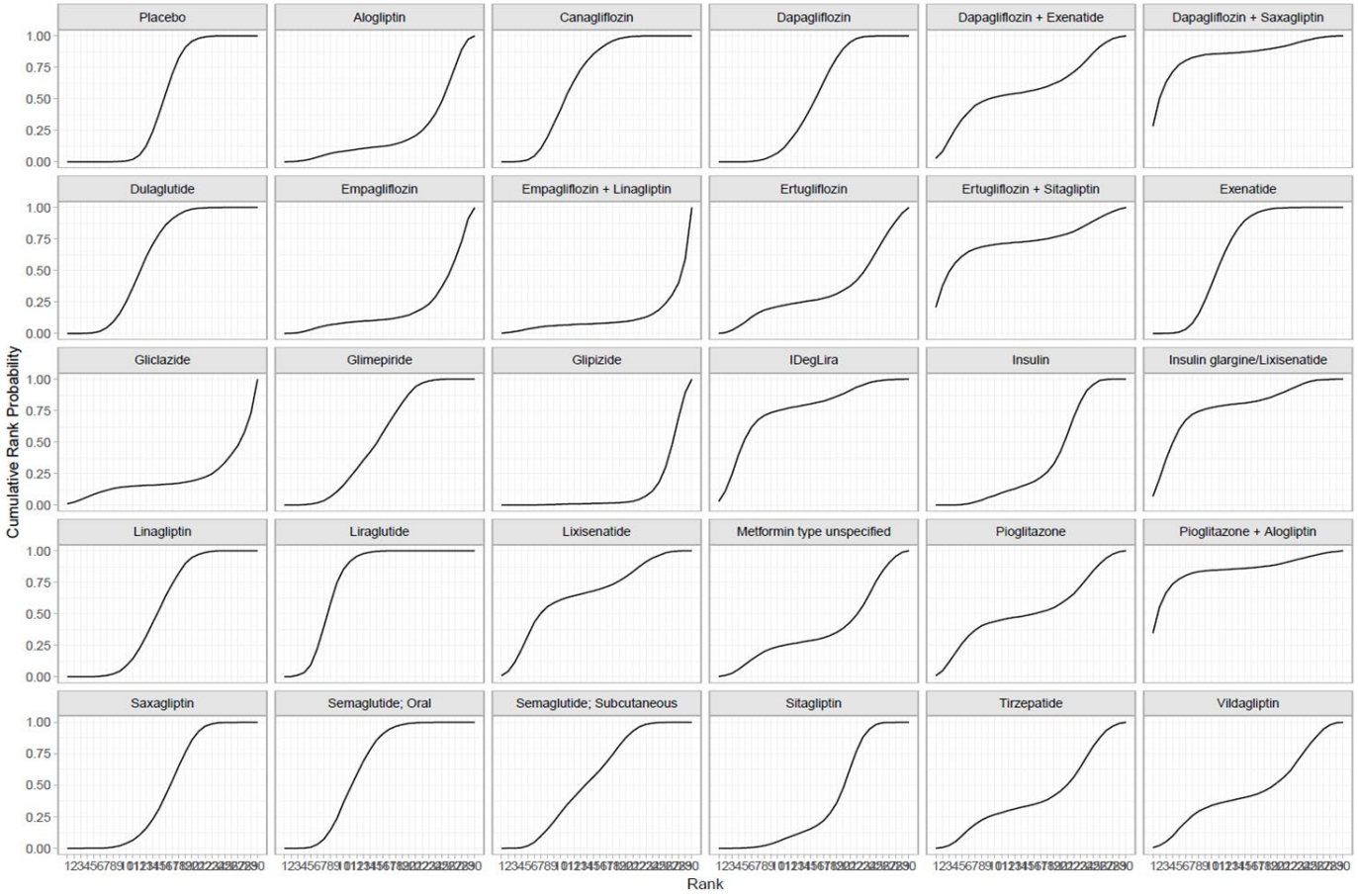


Favours treatment **Favours placebo**

6.5. Cumulative ranking probability plots

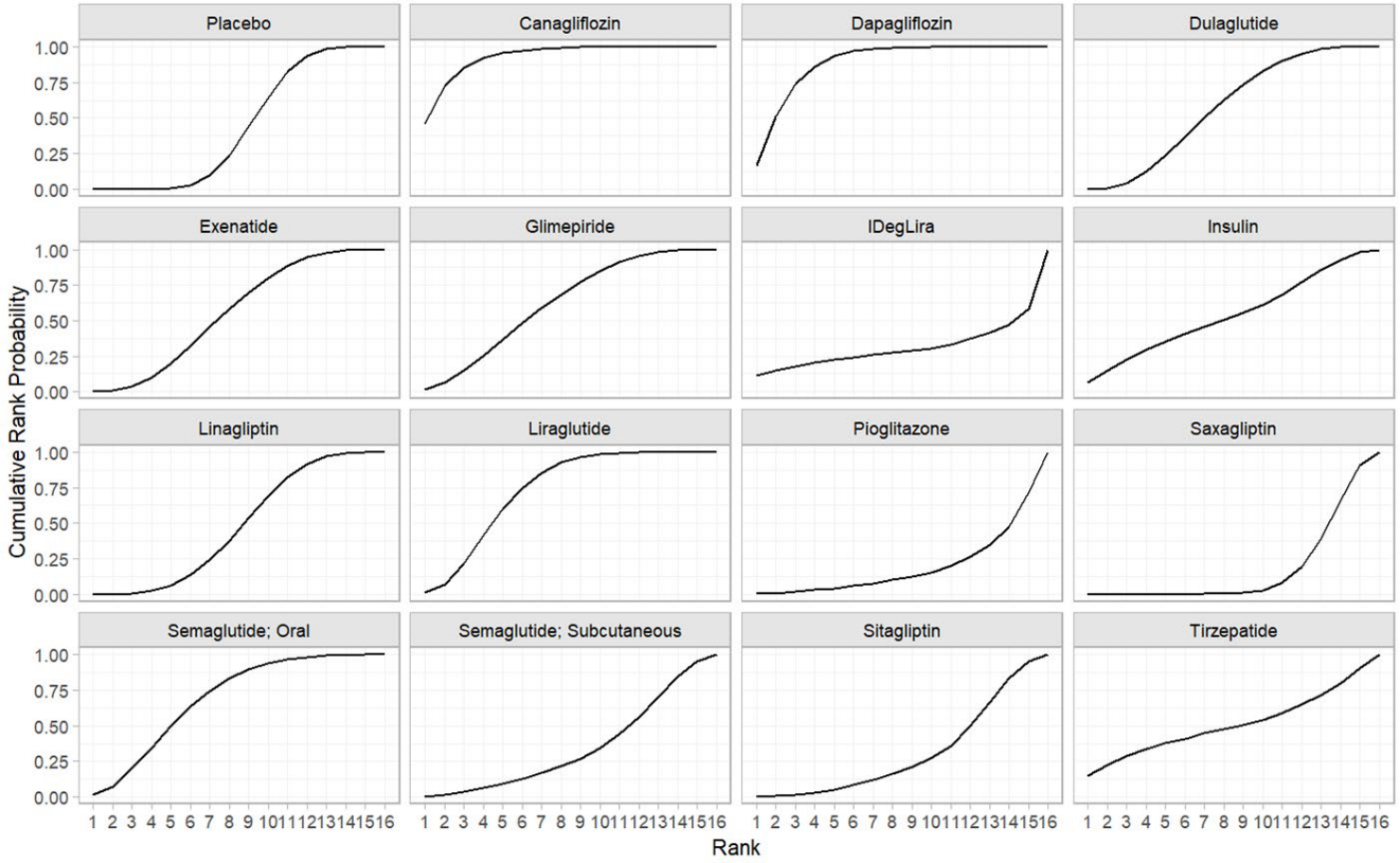
6.5.1. Cardiovascular mortality

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.



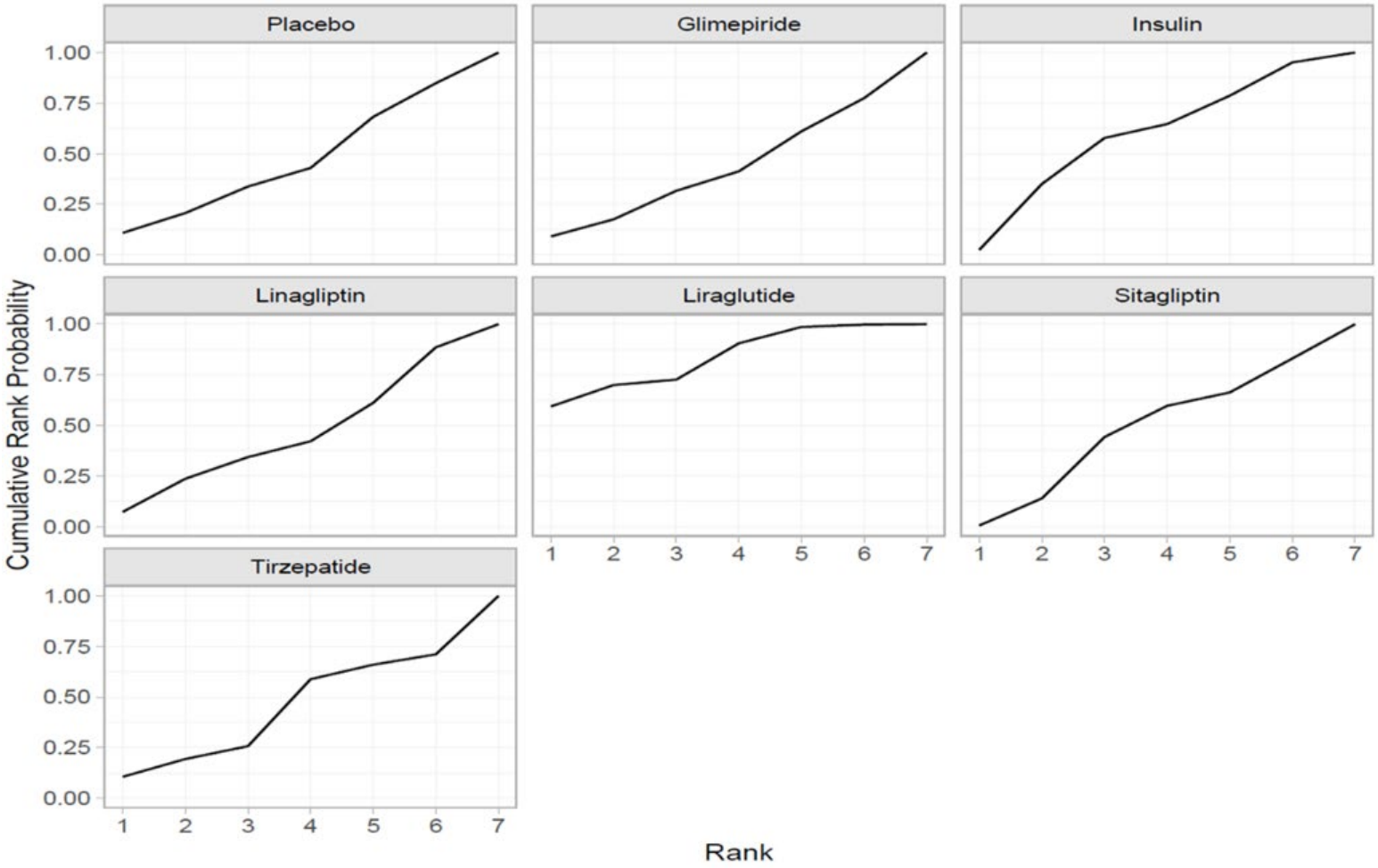
6.5.2. 3-item MACE

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.



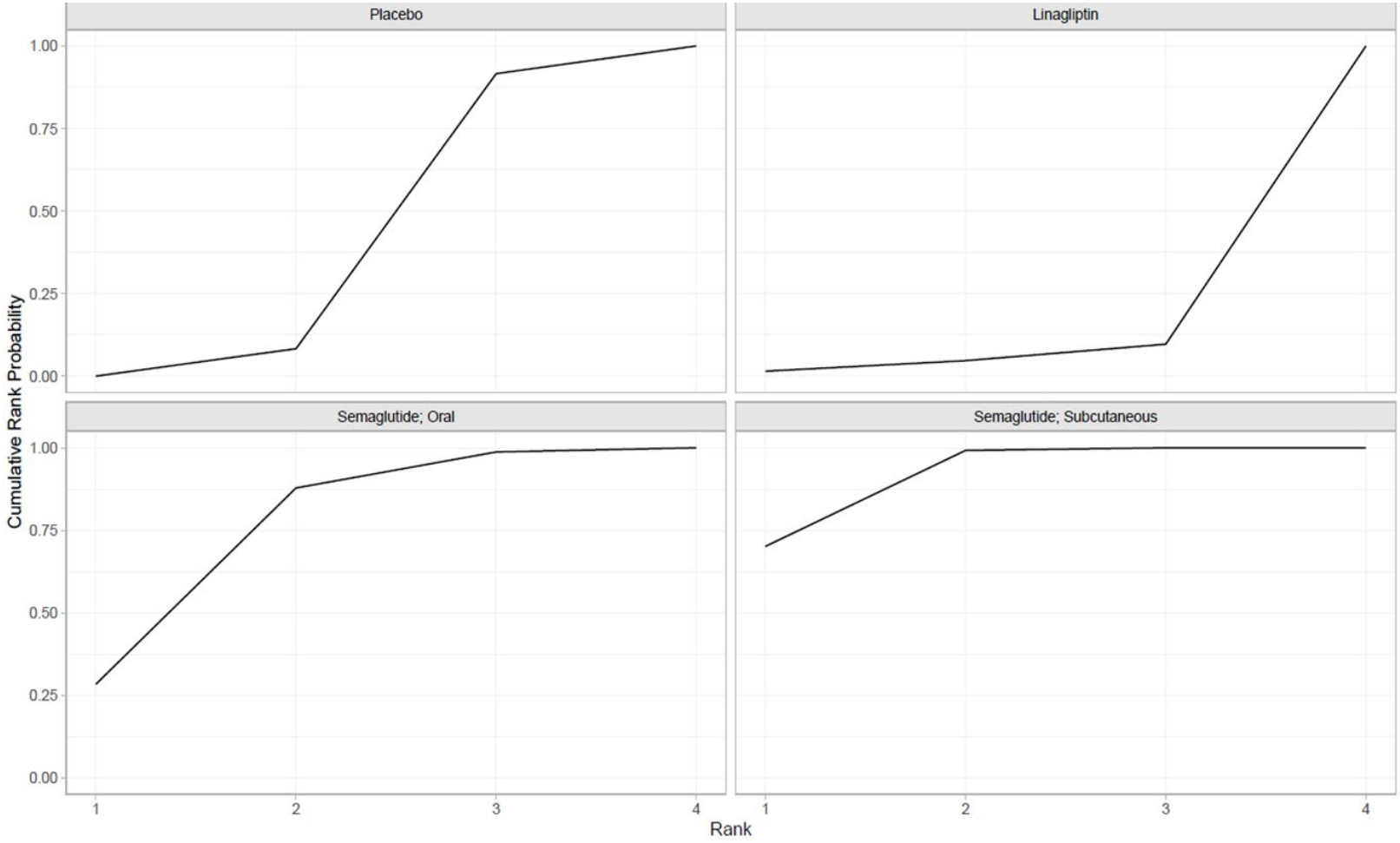
6.5.3. 4-item MACE

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.



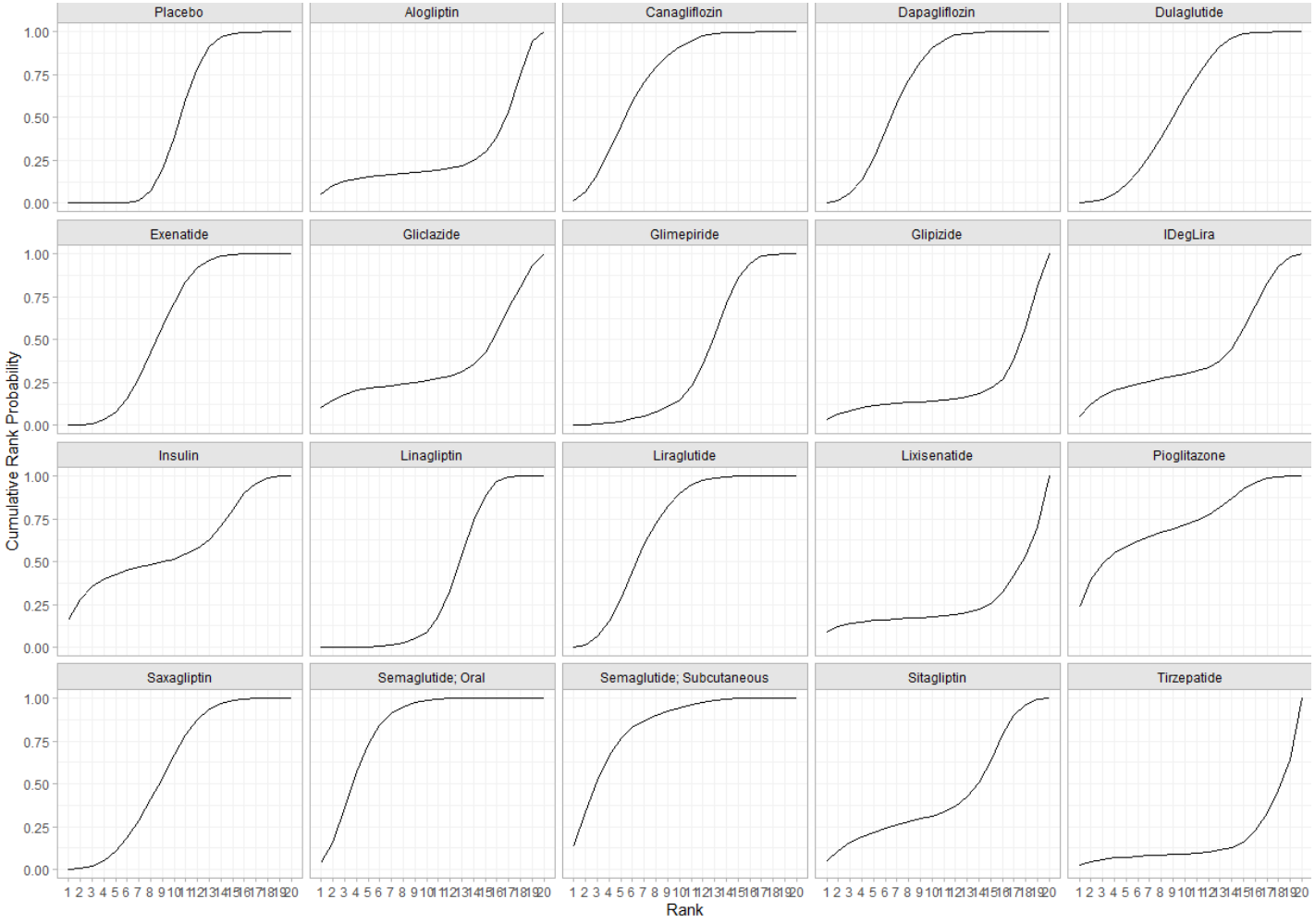
6.5.4. 5-item MACE

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.



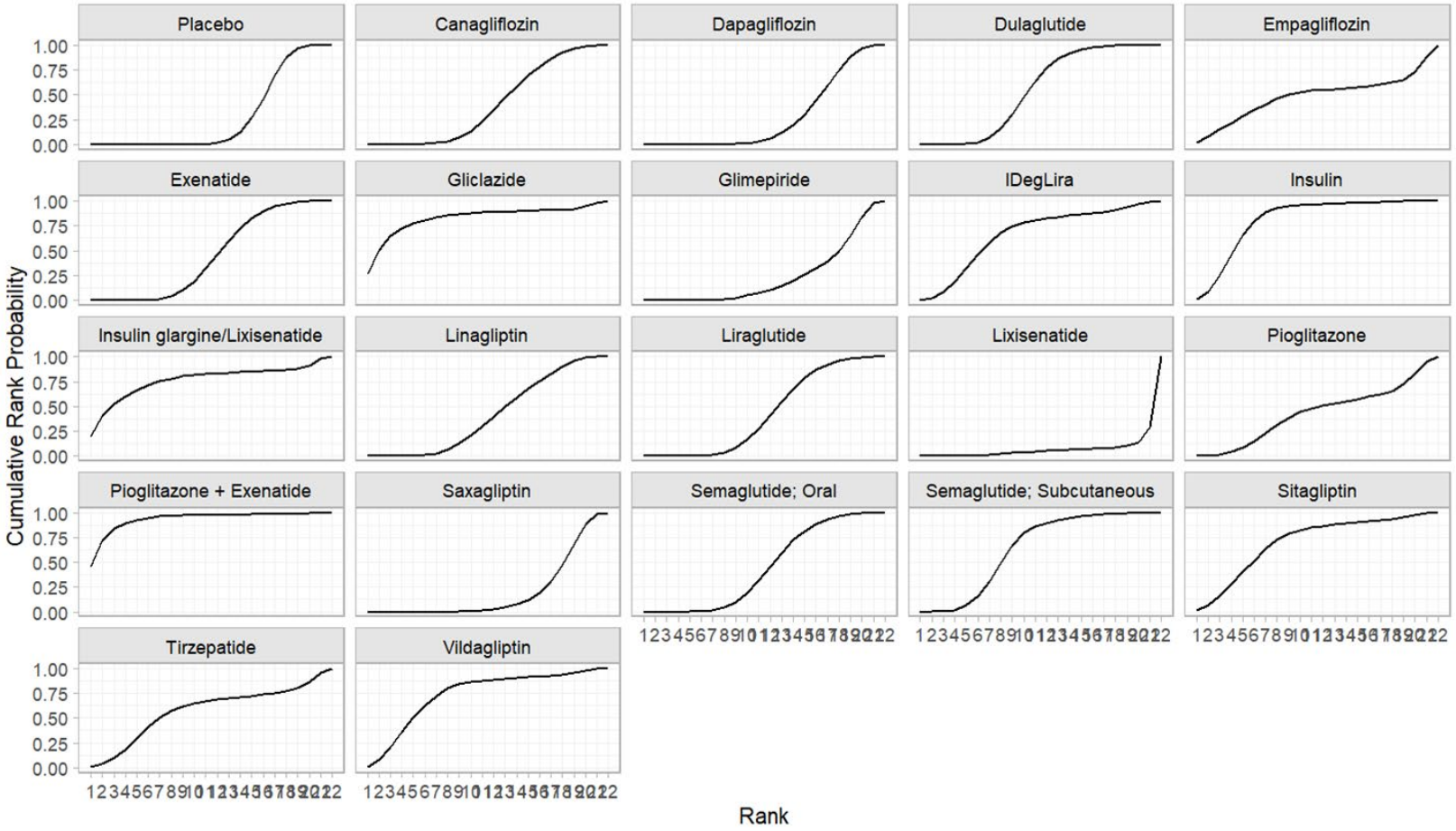
6.5.5. Non-fatal myocardial infarction

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.



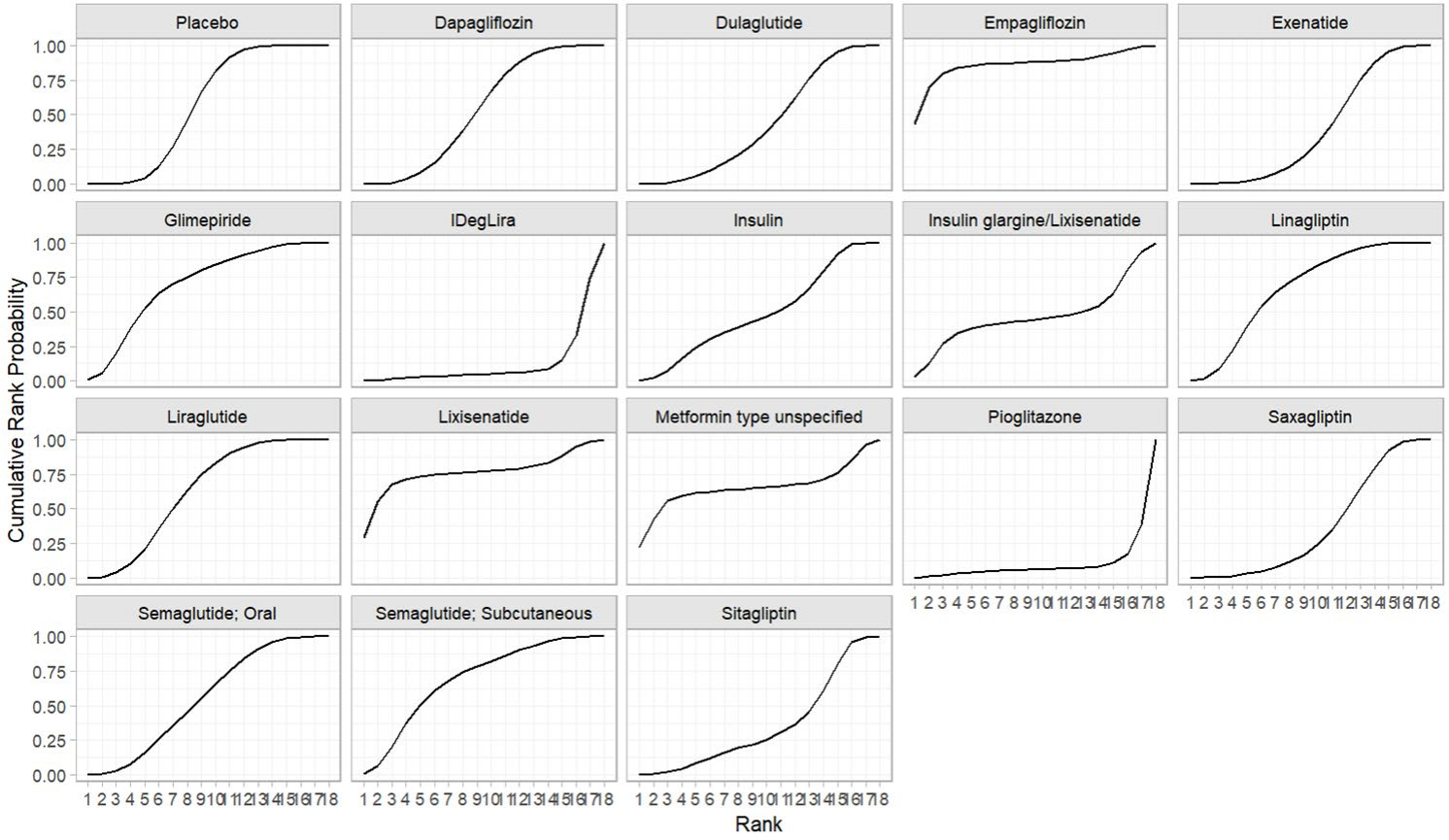
6.5.6. Non-fatal stroke

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.



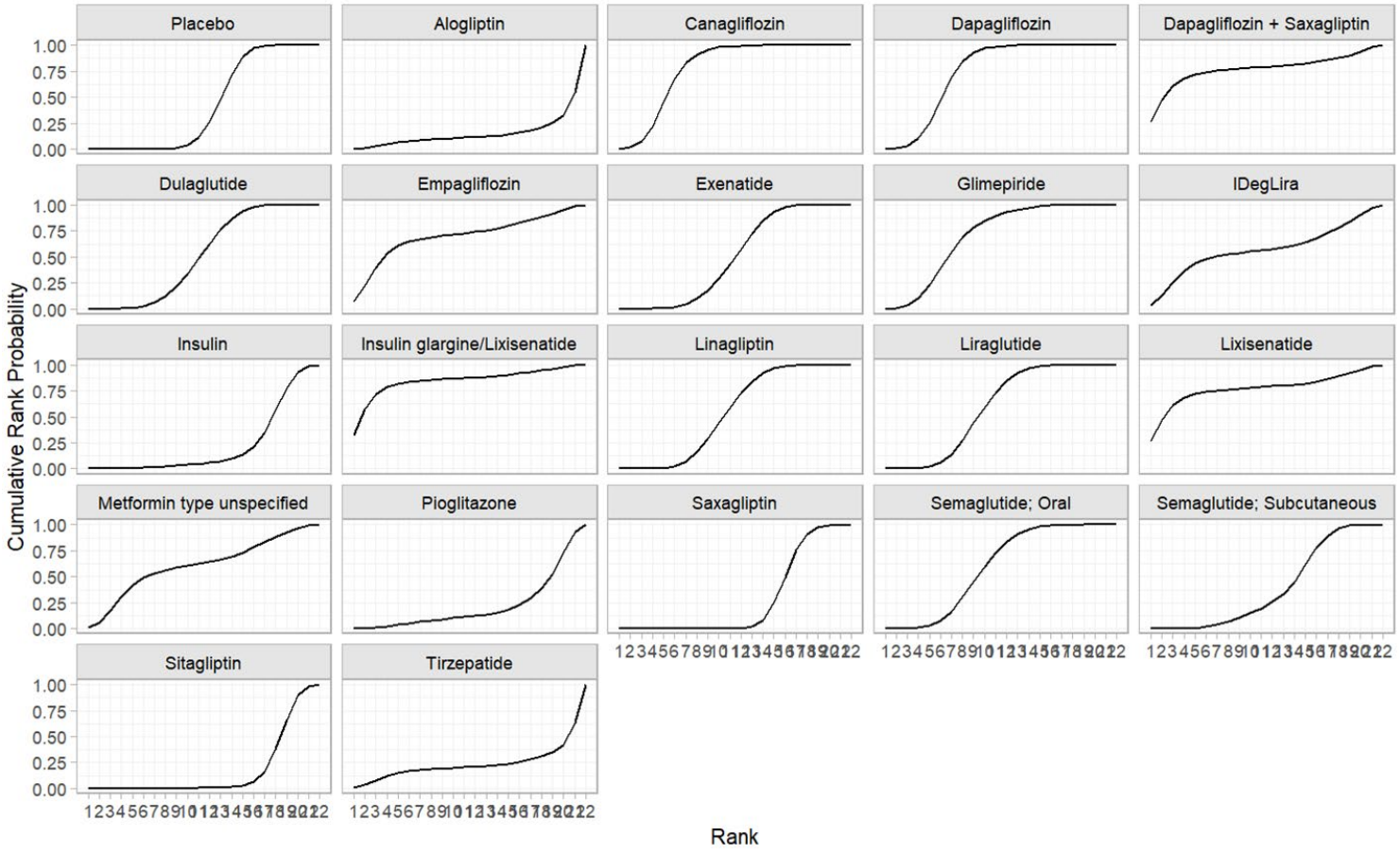
6.5.7. Unstable angina

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



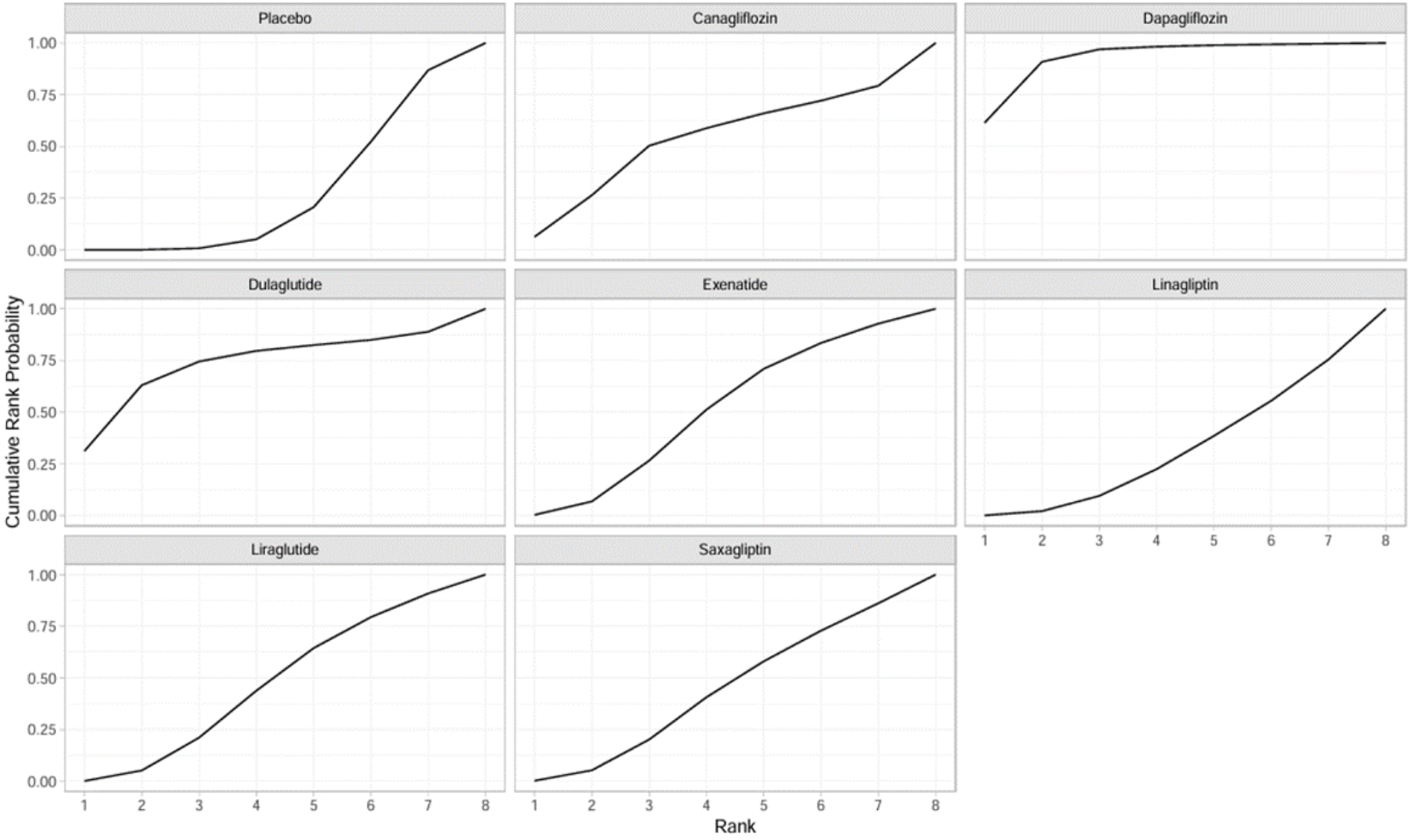
6.5.8. Hospitalisation for heart failure

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.



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.



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 40: 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
Derosa 2009	Low	NA
Dou 2018	High	High
Erem 2014	High	High

Study names	HbA1c change	Weight change
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
Moretto 2008	Moderate	Moderate
Mu 2017	High	High
Nauck 2016	Moderate	Moderate
Pan 2012A	High	High
Perez 2009	High	NA
Pfützner 2011A	High	NA

Study names	HbA1c change	Weight change
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 41: 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

Study names	Cardiovascular mortality	3-point MACE	Non-fatal myocardial infarction	Non-fatal stroke	Hospitalisation for heart failure	HbA1c change
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
Kosiborod 2024	Low	NA	NA	NA	Low	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 42: 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
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

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

Table 43: Pairwise meta-analysis risk of bias (RoB) assessment per NMA outcome - 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
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

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
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

Table 44: 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

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
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
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

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
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
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

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
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
Henriksen 2011	NA	NA	NA	NA	Some concerns	NA	NA	NA	NA
Hollander 2009	High	NA	NA	NA	NA	NA	NA	NA	NA
Hollander 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

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
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
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
McGuire 2025	Low	Low	NA	NA	Low	Low	Low	Low	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	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
Sitagliptin									
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
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

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
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
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

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
Strain 2013	Low	NA	NA	NA	NA	NA	NA	NA	NA
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 45: 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
Civera 2008	Moderate	Moderate	Moderate
Cusi 2019	High	High	High
da Silva 2016	High	High	High
Dagogo-Jack 2017	Low	Low	Low

Study names	HbA1c change	HbA1c change (regression)	Weight change
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
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

Study names	HbA1c change	HbA1c change (regression)	Weight change
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
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

Study names	HbA1c change	HbA1c change (regression)	Weight change
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
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

Study names	HbA1c change	HbA1c change (regression)	Weight change
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
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

Study names	HbA1c change	HbA1c change (regression)	Weight change
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
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

Study names	HbA1c change	HbA1c change (regression)	Weight change
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 46: 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 47: 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 48: 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 49: 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 50: 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 51: 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 52: 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 53: 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 54: 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 55: 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 56: 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 57: 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 58: 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 59: 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 60: 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 61: 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 62: 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 63: 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 64: 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 65: 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 66: 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 67: 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 68: 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 69: 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 70: 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 71: 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 72: 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