Appendix

Appendix File 1 Search strategies used for each electronic database searched.

Search strategies used for PubMed, the Cochrane Register of Controlled Trials (CENTRAL) and all databases in ISI Web of Science (Web of Science Core Collection, MEDLINE, SciELO, Russian Science Citation Index and KCI-Korean Journal Database) is given below:

PubMed:

((Itca AND 650)) OR Efpeglenatide OR Exenatide OR Liraglutide OR Lixisenatide OR Albiglutide OR Dulaglutide OR Semaglutide OR Taspoglutide OR Canagliflozin OR Empagliflozin OR Dapagliflozin OR Ipragliflozin OR Tofogliflozin OR Luseogliflozin OR Ertugliflozin OR Sotagliflozin

CENTRAL:

(Itca and 650) or Efpeglenatide or Exenatide or Liraglutide or Lixisenatide or Albiglutide or Dulaglutide or Semaglutide or Taspoglutide or Canagliflozin or Empagliflozin or Dapagliflozin or Ipragliflozin or Tofogliflozin or Luseogliflozin or Ertugliflozin or Sotagliflozin in Trials (Word variations have been searched)

ISI Web of Science:

TOPIC: (Itca AND 650) *OR* **TOPIC:** (Efpeglenatide) *OR* **TOPIC:** (Exenatide) *OR* **TOPIC:** (liraglutide) *OR* **TOPIC:** (lixisenatide) *OR* **TOPIC:** (albiglutide) *OR* **TOPIC:** (dulaglutide) *OR* **TOPIC:** (semaglutide) *OR* **TOPIC:** (taspoglutide) *OR* **TOPIC:** (Canagliflozin) *OR* **TOPIC:** (Empagliflozin) *OR* **TOPIC:** (Dapagliflozin) *OR* **TOPIC:** (Ipragliflozin) *OR* **TOPIC:** (Tofogliflozin) *OR* **TOPIC:** (Luseogliflozin) *OR* **TOPIC:** (Ertugliflozin) *OR* **TOPIC:** (Sotagliflozin)

Refined by: **[excluding]: DOCUMENT TYPES:** (REFERENCE MATERIAL OR EDITORIAL OR LETTER OR BOOK OR BIOGRAPHY OR MEETING OR CASE REPORT OR BIBLIOGRAPHY OR REVIEW OR NEWS)

DocType=All document types; Language=All languages;

Appendix Table 1 Protocol for systematic review and network meta-analysis following the PRISMA-P guideline

Section and topic	PRISMA-P Item No	Information
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Cardiovascular efficacy and safety of sodium-glucose co-transporter-2 inhibitors and glucagon-like peptide-1 receptor agonists: a systematic review and network meta-analysis
Update	1b	NA
Registration:		
-	2	NA
Authors:		
Contact	3a	• Corresponding author: Miss Humaira Hussein (Email: hh244@leicester.ac.uk). Department of Health Sciences, University of Leicester, Leicester, UK • Dr Francesco Zaccardi (fz43@leicester.ac.uk). Diabetes Research Centre, Leicester General Hospital, Leicester, UK. • Professor Melanie J. Davies (melanie.davies@uhl-tr.nhs.uk). Diabetes Research Centre, Leicester General Hospital, Leicester, UK. • Professor Kamlesh Khunti (kk22@leicester.ac.uk). Diabetes Research Centre, Leicester General Hospital, Leicester, UK. • Dr Samuel Seidu (sis11@leicester.ac.uk). Diabetes Research Centre, Leicester General Hospital, Leicester, UK. • Dr Laura J. Gray (lg48@leicester.ac.uk). Department of Health Sciences, University of Leicester, Leicester, UK.
Contributions	3b	All authors contributed to the design of this systematic review and network meta-analysis, revising for important content and drafting the protocol.
Amendments	4	NA
Support:		
Sources	5a	This report is the independent research of HH supported by the National Institute of Health Research Collaborations for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC - EM) as part of a PhD project. FZ is a Clinical Research Fellow supported by the NIHR CLAHRC – EM.
Sponsor	5b	NA
Role of sponsor or funder	5c	No role of funders on the development of this protocol.
INTRODUCTION		
Rationale:		
-	6	Sodium-glucose co-transporter 2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are two classes of glucose-lowering therapies that have been associated with reducing the risk of cardiovascular (CV) complications in patients with type 2 diabetes mellitus (T2DM). Although meta-analyses have been conducted looking at the CV risk within these classes of

		drug, comparisons have not been made across these two drug classes. Further, direct (head-to-head) comparisons are not currently available comparing SGLT-2is to GLP-1RAs, with no distinction in guidelines as to which is the preferred therapy in reducing cardiovascular risk.
Objectives:		
-	7	The aim of this systematic review and network meta-analysis (NMA) is to compare the CV efficacy and safety of SGLT-2is with GLP-1RAs in adults (≥18 years old) with T2DM.
METHODS		
Eligibility criteria:		
-	8	Randomised controlled trials (RCTs) of any duration conducted in adults (≥18 years old) with T2DM that have specifically been designed to access CV efficacy and safety will be included (CV outcome trials). SGLT-2is and GLP-1RAs drug names included have been defined in the search strategy, which are the intervention while the control is placebo. RCTs must consist of *at least* two arms comparing SGLT-2i(s) vs placebo, GLP-1RA(s) vs placebo or SGLT-2i(s) vs GLP-1RA(s). Trials will be excluded if primary outcome is unavailable. RCTs in entirely Asian populations will be excluded due to the systematically lower dosage of drug given to this population. Arms with ipragliflozin, tofogliflozin and luseogliflozin will be excluded as these drugs only have approval in Japan.
Information sources:		
-	9	The following electronic databases will be searched from inception of the database: PubMed, the Cochrane Register of Controlled Trials (CENTRAL) and all databases in ISI Web of Science (i.e. Web of Science Core Collection, MEDLINE, SciELO, Russian Science Citation Index and the KCI-Korean Journal Database). Further, reference list of included papers will be searched to additional appropriate RCTs.
Search strategy:		
-	10	Example search in PubMED: ((Itca AND 650)) OR Efpeglenatide OR Exenatide OR Liraglutide OR Lixisenatide OR Albiglutide OR Dulaglutide OR Semaglutide OR Taspoglutide OR Canagliflozin OR Empagliflozin OR Dapagliflozin OR Ipragliflozin OR Tofogliflozin OR Luseogliflozin OR Ertugliflozin OR Sotagliflozin
Study records:		
Data management	11a	Literature search papers will be imported into EndNote X7.3.1 for screening.
Selection process	11b	Two independent researchers will screen papers for relevant studies meeting the eligibility criteria (HH and FZ) with discrepancies discussed and resolved by a third reviewer.
Data collection process	11c	Data will be extracted independently by two researchers (HH and SS) using pre-defined forms in Excel. Data will be extracted using an intention to treat principle, were possible. Agreement between two researchers will be assessed, with ≤80% agreement requiring further evaluation.
Data items:		
-	12	Data extracted will include first author name, ClinicalTrials.gov trial number, year of publication, median follow-up length of trial (years), sample size, treatment given in each arm and baseline characteristics of participants (i.e. mean age (years), gender (%), mean duration of diabetes (years) and HbA1c (%)).

Outcomes and prioritization:		
-	13	The primary outcome in this study is the number of participants to have a 3-point major cardiovascular event (3-point MACE) which is a composite measure of the number of participants first to have a non-fatal stroke, non-fatal myocardial infarction (MI) or CV death. Secondary outcomes will include the number of participants to have a non-fatal stroke, non-fatal MI, CV mortality, all-cause mortality and hospital admission due to heart failure. Safety outcomes analysed will include the number of participants to have at least one hypoglycaemic event, bone fracture, amputation, urinary tract infection (UTI), pancreatitis or diabetic ketoacidosis (DKA). For all outcomes, the arm-specific number of participants randomised and participants with events will be extracted for analysis.
Risk of bias in individual studies:		
-	14	Risk of bias will be assessed using the Cochrane Risk of Bias Tool. Sensitivity analysis will be conducted removing trials reporting high risk of bias in any domain.
Data synthesis:		
-	15a	A Bayesian NMA approach will be used fitting random effects generalised linear models using Markov Chain Monte Carlo (MCMC) simulations in WinBUGS. Treatments will be ranked for each outcome in each simulation run to give the percentage of each treatment ranking highest. This is the percentage probability of a particular treatment being the most effective in reducing risk of a particular outcome. Vague priors will be used for all parameters. History and trace plots will be inspected to assess convergence. Results will be presented using comparison tables and network plots (created in Stata).
	15b	Pairwise meta-analysis will be conducted for each outcome between direct comparisons available. I^2 statistics will be used to assess heterogeneity within direct comparisons. A continuity correction factor of 0.5 will be added for trials that report zero events in one arm. For models fitted in WinBUGS, a burn of 10,000 simulations with a sample length of 50,000 simulations will be used. For CV outcomes, hazard ratios will be estimated by fitting a binomial likelihood with composite log-log link function. Safety (dichotomous) outcomes, odds ratios will be estimated by fitting a binomial likelihood with logit link. Residual deviances will be estimated and compared to the number of data points to assess overall model fit.
	15c	Sensitivity analysis will include analysing the effect of varying burn in and simulation length on effect estimates. Further sensitivity analysis will include varying vague prior distributions and starting values of parameters.
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned: NA
Meta-bias(es):		
-	16	Publication bias and small study effects will be assessed by visually inspecting comparison adjusted funnel plots. Further, tables will be presented reporting the number of events and participants randomised for each outcome in each trial to study selective reporting.
Confidence in cumulative evidence:		

-	17	Results will be interpreted in line of current evidence and the limitations of the study.
Date protocol finalised:		March 2018

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix Table 2 PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis.

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**3**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**5-6**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**6**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**7**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or*	**7-8**

		merged into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**7**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Appendix File 1**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**7**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**8**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**8-9**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**8-9**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**8**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**8-9**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**8-10**
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**NA**

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**8**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**9-10**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**Appendix Figure 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Figure 1**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**11-12**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**11, Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**Appendix Table 4**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**11-13, Appendix Table 3, Appendix Figure 2, Appendix Figure 4.**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	**11-13, Table 2, Appendix Table 5, Appendix Figure 3, Appendix Figure 5.**

Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**NA**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**Appendix Figure 6-7.**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**13, Appendix Table 6-7.**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**14-16**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**16-18**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**18**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**4**

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

Appendix Table 3 Number of participants randomised and to have an event in each trial for each outcome analysed.

Cardiovascular Outcomes												
	3-point MACE		Non-fatal stroke		Non-fatal myocardial infarction		Cardiovascular mortality		All-cause mortality		Hospital admission for heart failure	
	event	n	event	n	event	n	event	n	event	n	event	n
EMPA-REG OUTCOME (24)	772	7020	210	7020	334	7020	309	7020	463	7020	221	7020
CANVAS (25)	658	4330	159	4330	238	4330	322	4330	476	4330	138	4330
CANVAS-R (25)	353	5812	115	5812	136	5812	131	5812	205	5812	105	5812
ELIXA (26)	786	6068	127	6068	531	6068	786	6068	434	6068	249	6068
LEADER (27)	1302	9340	336	9340	598	9340	497	9340	828	9340	466	9340
SUSTAIN-6 (28)	254	3297	71	3297	111	3297	90	3297	122	3297	113	3297
EXSCEL (29)	1744	14752	332	14752	925	14752	723	14752	1091	14752	450	14752
HARMONY (30)	766	9463	-	-	-	-	252	9463	401	9463	-	-
Safety Outcomes												
	Hypoglycaemia		Bone fracture		Amputation		Pancreatitis		Urinary tract infection		Diabetic ketoacidosis	
	event	n	event	n	event	n	event	n	event	n	event	n
EMPA-REG OUTCOME (24)	1953	7020	270	7020	131	7020	10	7020	1265	7020	4	7020
CANVAS (25)	1204	4330	368	4330	117	4327	-	-	962	4330	-	-
CANVAS-R (25)	-	-	151	5812	70	5807	-	-	-	-	-	-
ELIXA (26)	1163	6063	-	-	3	6063	13	6063	37	6063	4	6063
LEADER (27)	4169	9340	82	9340	-	-	41	9340	118	9340	18	9340
SUSTAIN-6 (28)	719	3297	-	-	-	-	21	3297	-	-	4	3297
EXSCEL (29)	-	-	219	14716	263	14733	48	14716	-	-	-	-
HARMONY (30)	-	-	-	-	-	-	17	9643	-	-	-	-

- represent data unavailable. Events represent the number of participants to have an event and n is the total number of participants.
Abbreviation: MACE, major adverse cardiovascular events.

Appendix Table 4 Risk of bias assessment table.

Trial Name	Random Sequence Generation	Allocation Concealment	Blinding Participants and Personnel	Blinding Out Assessment	Incomplete Outcome Data	Selective Reporting
EMPA-REG OUTCOME (24)	low	low	low	low	low	low
CANVAS (25)	low	low	low	low	low	low
CANVAS-R (25)	low	low	low	low	low	low
ELIXA (26)	low	low	low	low	low	low
LEADER (27)	low	low	low	low	low	low
SUSTAIN-6 (28)	low	low	low	low	low	low
EXSCEL (29)	low	low	low	low	low	low
HARMONY (30)	low	low	low	low	low	low

Appendix Table 5 Comparison of sodium-glucose co-transporter-2 inhibitors (SGLT-2is), glucagon-like peptide-1 receptor agonists (GLP-1RAs) and placebo concerning safety outcomes.

A. Hypoglycaemia		
		GLP-1RAs
	SGLT-2is	0.98 (0.63, 1.53)
Placebo	1.05 (0.74, 1.47)	1.02 (0.79, 1.36)
B. Bone fracture		
		GLP-1RAs
	SGLT-2is	1.24 (0.32, 5.12)
Placebo	1.12 (0.46, 2.66)	1.39 (0.48, 4.12)
C. Amputation		
		GLP-1RAs
	SGLT-2is	0.69 (0.09, 9.35)
Placebo	1.57 (0.40, 6.38)	1.09 (0.22, 9.30)
D. Pancreatitis		
		GLP-1RAs
	SGLT-2is	1.22 (0.20, 6.70)
Placebo	0.77 (0.15, 4.29)	0.94 (0.52, 1.63)
E. Urinary tract infection		
		GLP-1RAs
	SGLT-2is	0.71 (0.10, 5.57)
Placebo	1.04 (0.26, 4.68)	0.74 (0.20, 3.39)
F. Diabetic ketoacidosis		
		GLP-1RAs
	SGLT-2is	0.03 (0.00, 685.60)
Placebo	11.39 (0.00, 266100)	0.44 (0.00, 41.25)

Comparisons are reported as odds ratio (95% credible intervals) for column vs. row (i.e. for A. Hypoglycaemia: GLP-1RAs vs. placebo odds ratio (95% credible interval): 1.02 (0.79, 1.36)).

Appendix Table 6 Subgroup analysis comparing sodium glucose co-transporter 2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), split by duration of action and molecular formulation, for 3-point major adverse cardiovascular events.

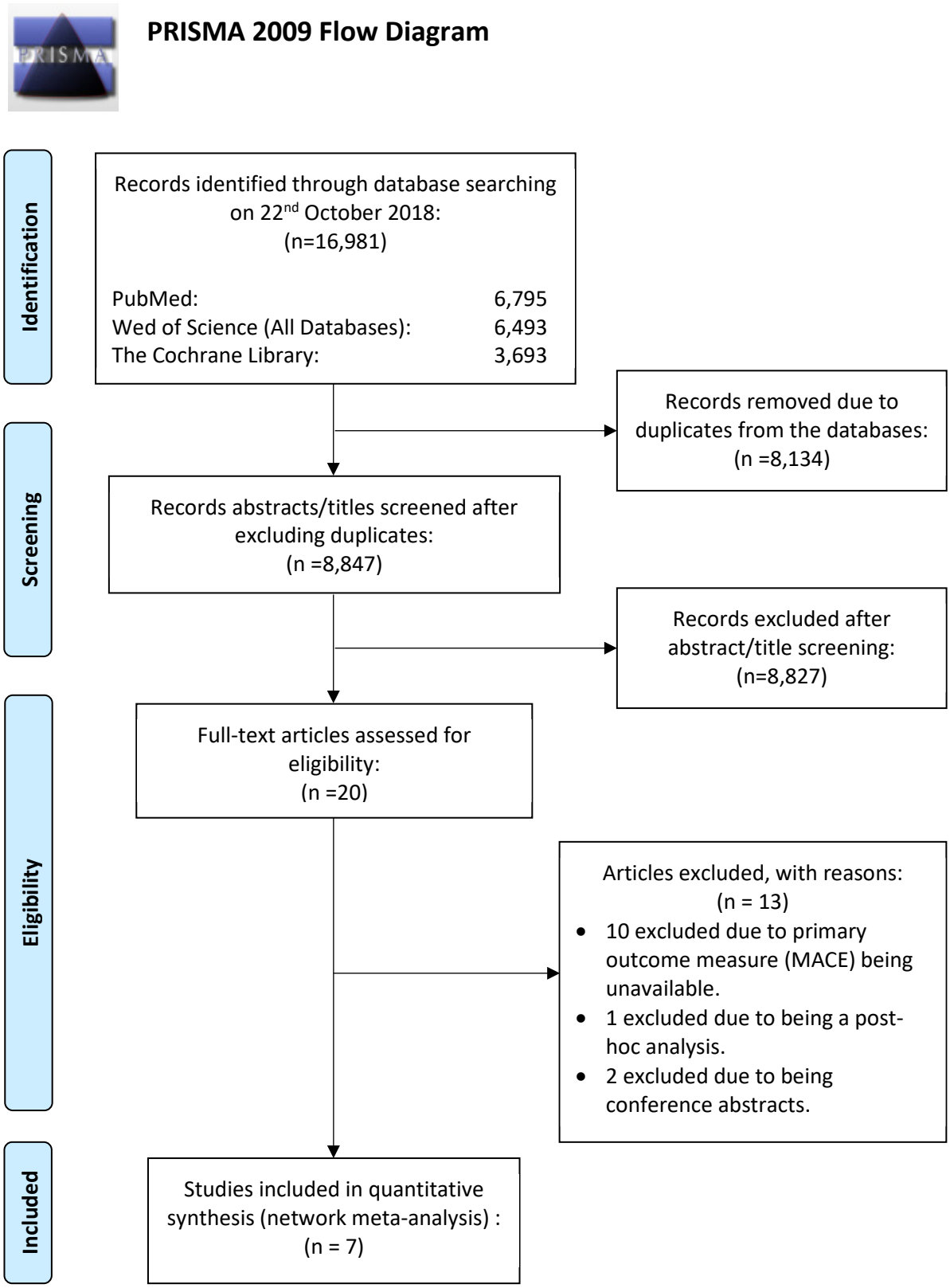
GLP-1RAs split by duration of action			
			Long acting GLP-1RAs
		Short acting GLP-1RAs	0.83 (0.62. 1.08)
	SGLT-2is	1.18 (0.89, 1.58)	0.99 (0.80, 1.18)
Placebo	0.86 (0.74, 1.00)	1.02 (0.80, 1.30)	0.85 (0.74, 0.95)
GLP-1RAs split by molecular formulation			
			GLP-1RA (Non-Exendin Base)
		GLP-1RA (Exendin Base)	0.85 (0.69, 1.01)
	SGLT-2is	1.11 (0.92, 1.37)	0.94 (0.78, 1.12)
Placebo	0.86 (0.75, 0.99)	0.96 (0.84, 1.12)	0.81 (0.71, 0.92)

Appendix Table 7 Residual deviance for each outcome analysed to assess model fit.

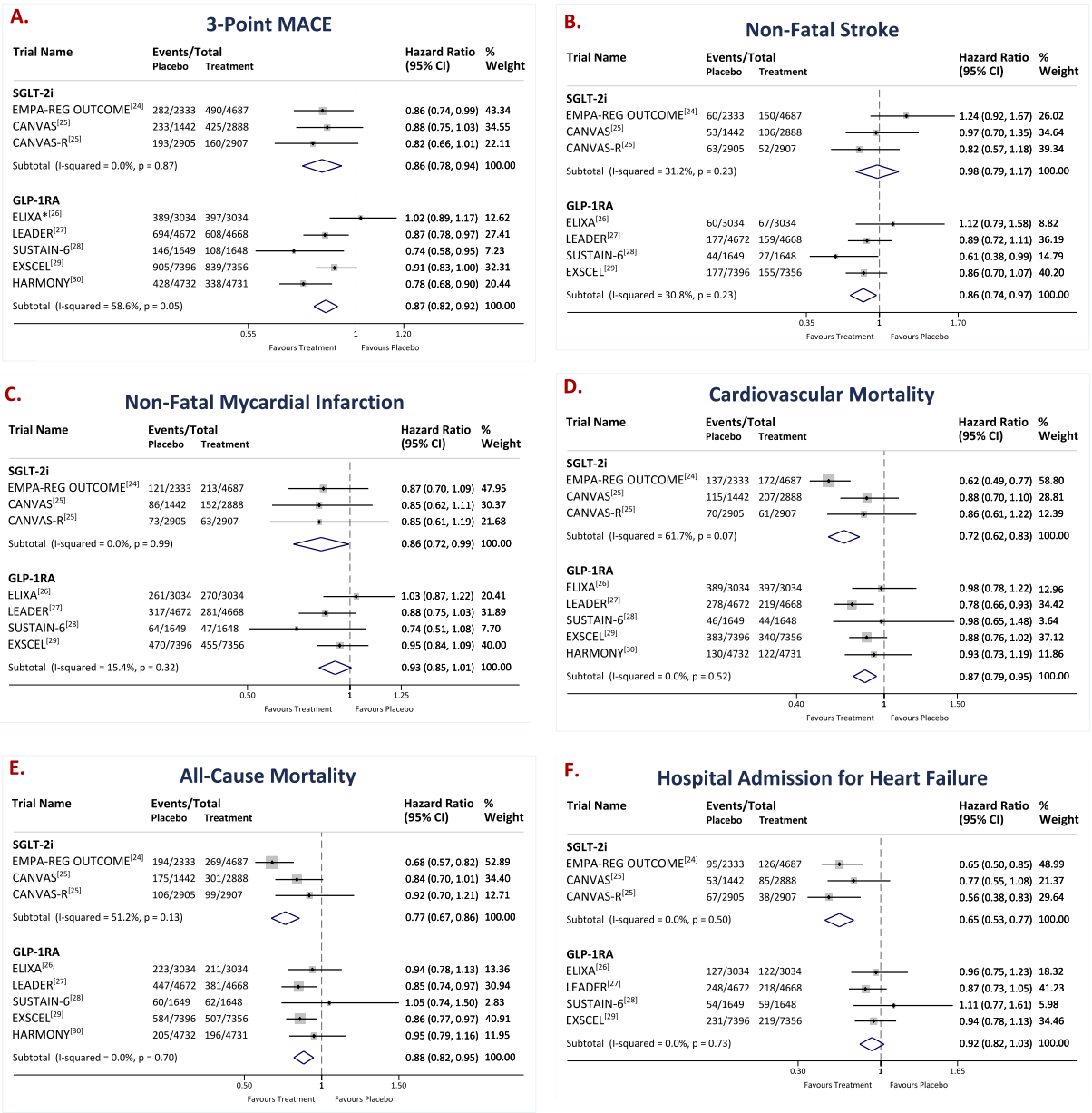
Outcome	Residual Deviance	Data Points
Cardiovascular		
3-point MACE	16.33	16
Non-fatal stroke	14.57	14
Non-fatal myocardial infarction	12.72	14
Cardiovascular mortality	16.06	16
All-cause mortality	15.58	16
Hospital admission for heart failure	12.26	14
Safety		
Hypoglycaemia	10.11	10
Bone fracture	10.11	10
Amputation	9.80	10
Pancreatitis	10.81	12
Urinary tract infection	7.79	8
Diabetic ketoacidosis	8.43	8

Abbreviation: MACE, major adverse cardiovascular events.

Appendix Figure 1 PRISMA flow diagram for study inclusion.

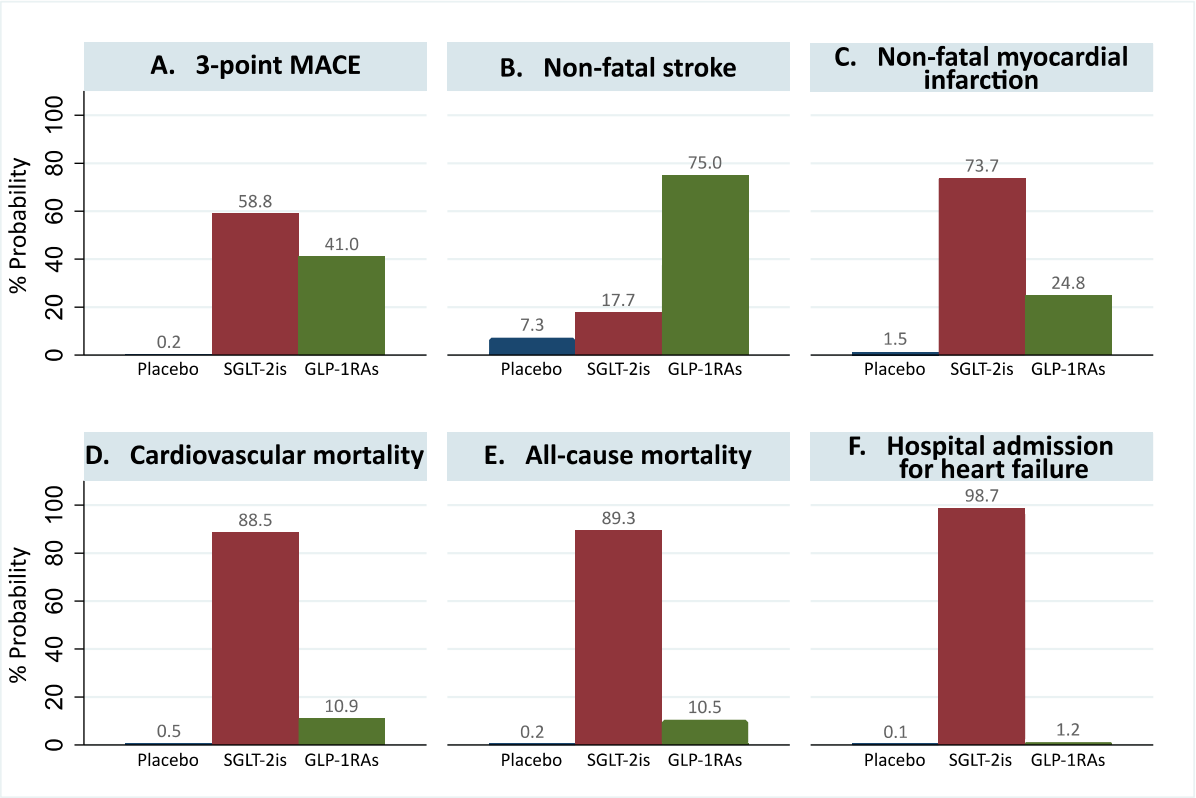


Appendix Figure 2 Pairwise forest plots for primary and secondary cardiovascular outcomes.



Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; MACE, major adverse cardiovascular events; SGLT-2is, sodium-glucose co-transporter 2 inhibitors.

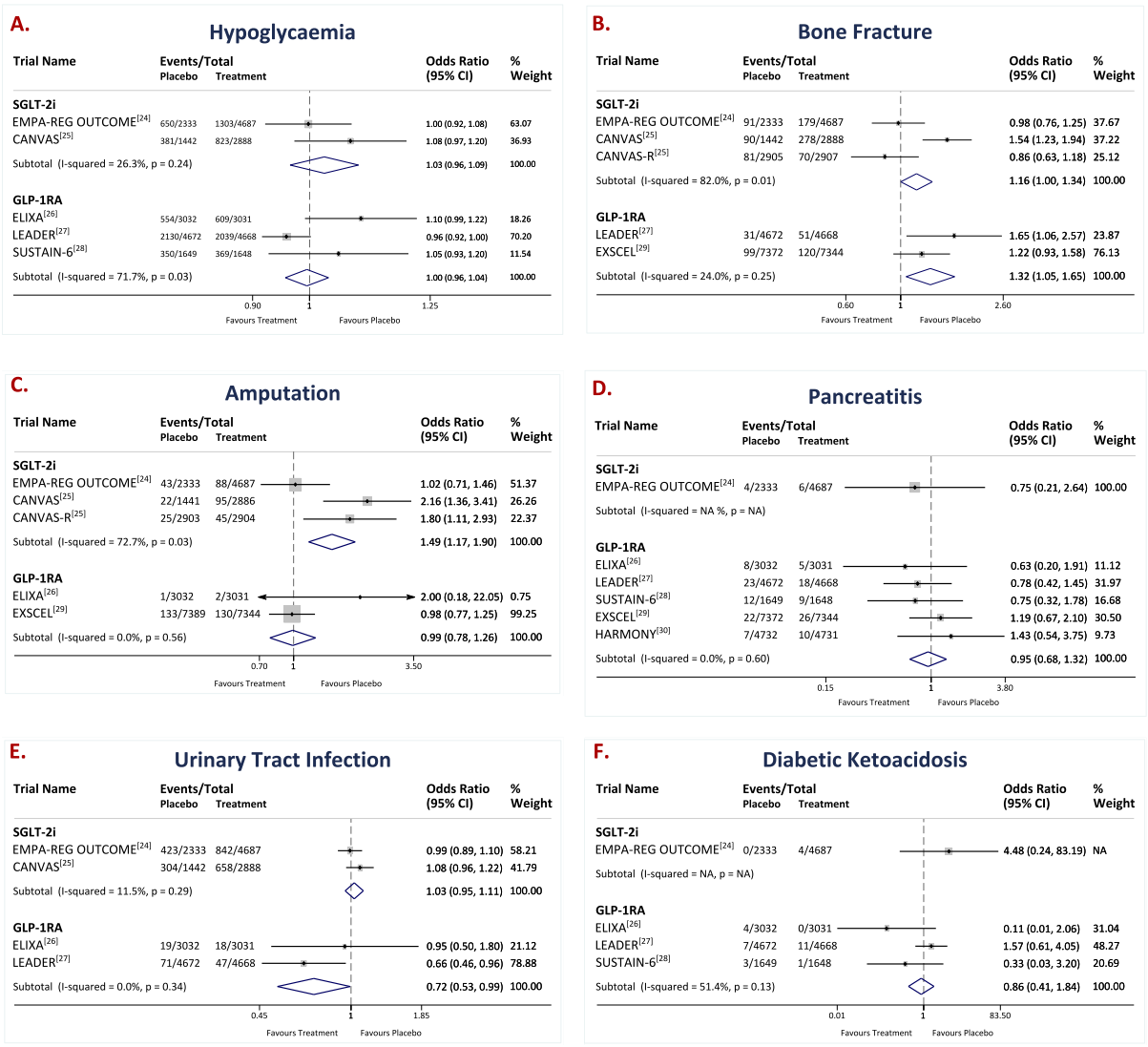
Appendix Figure 3 Bar charts of ranking of treatments (%) for primary and secondary cardiovascular outcomes.



These graphs present the probability of a treatment being the most effective.

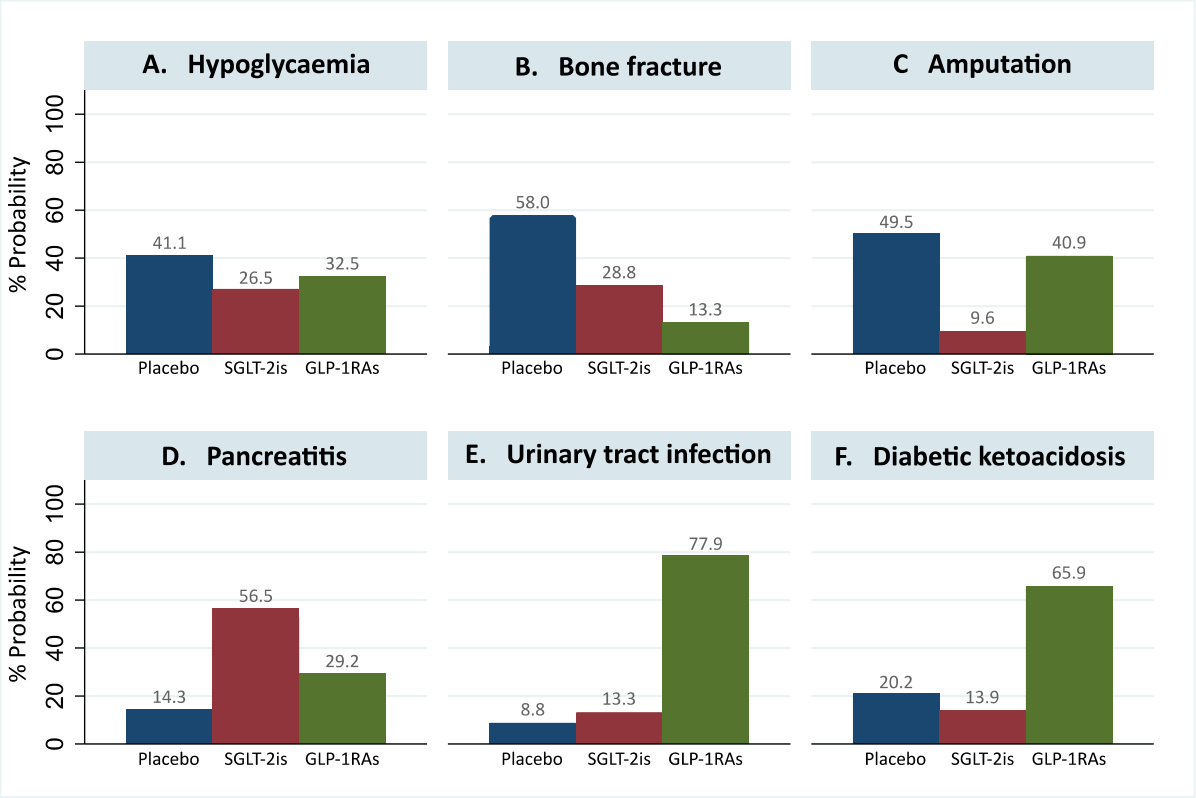
Abbreviations: MACE, major adverse cardiovascular events; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT-2is, sodium-glucose co-transporter 2 inhibitors.

Appendix Figure 4 Pairwise forest plots for safety outcomes.



Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT-2is, sodium-glucose co-transporter 2 'inhibitors.

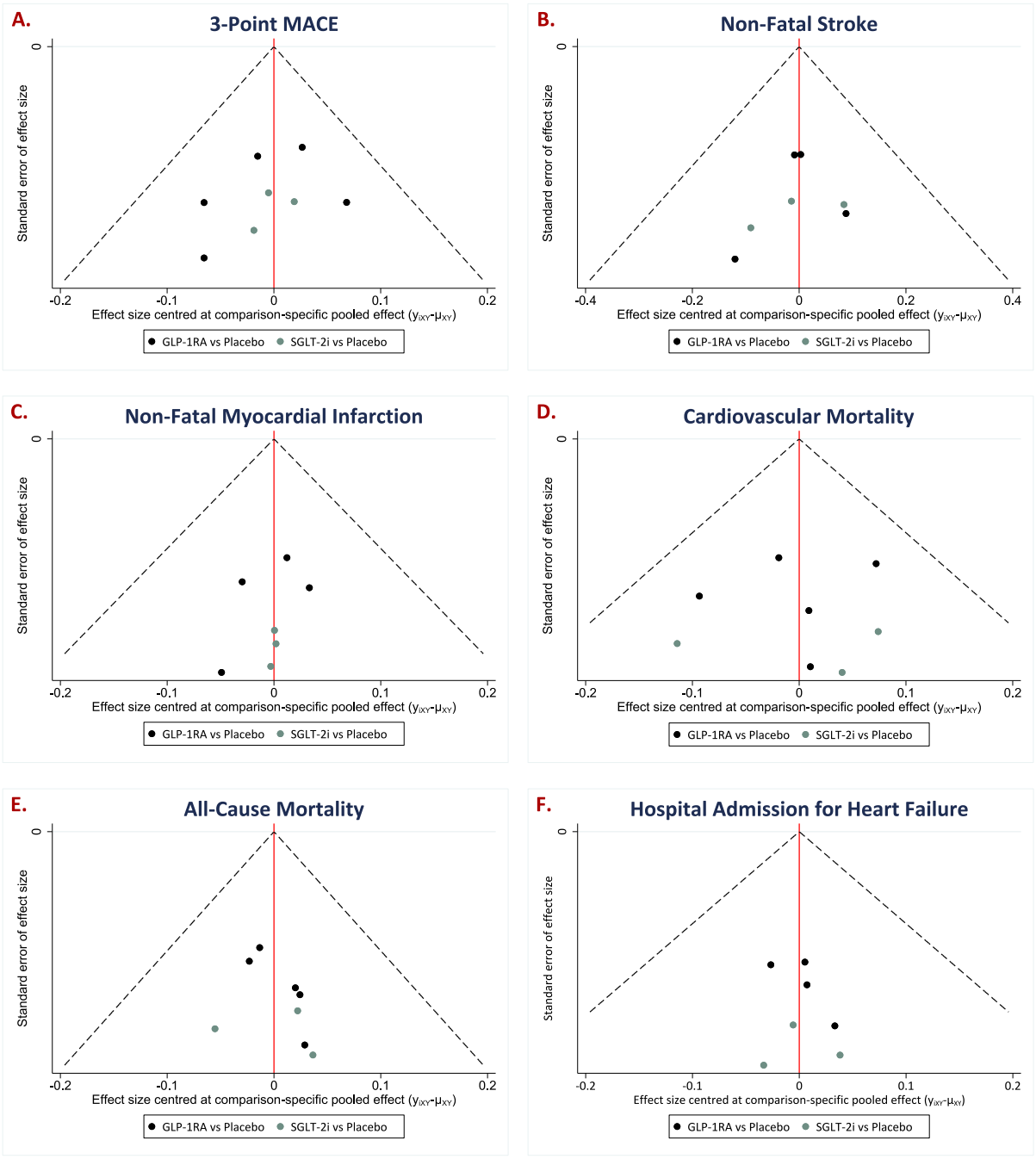
Appendix Figure 5 Bar charts of ranking of treatments (%) for safety outcomes.



These graphs present the probability of a treatment being the most effective.

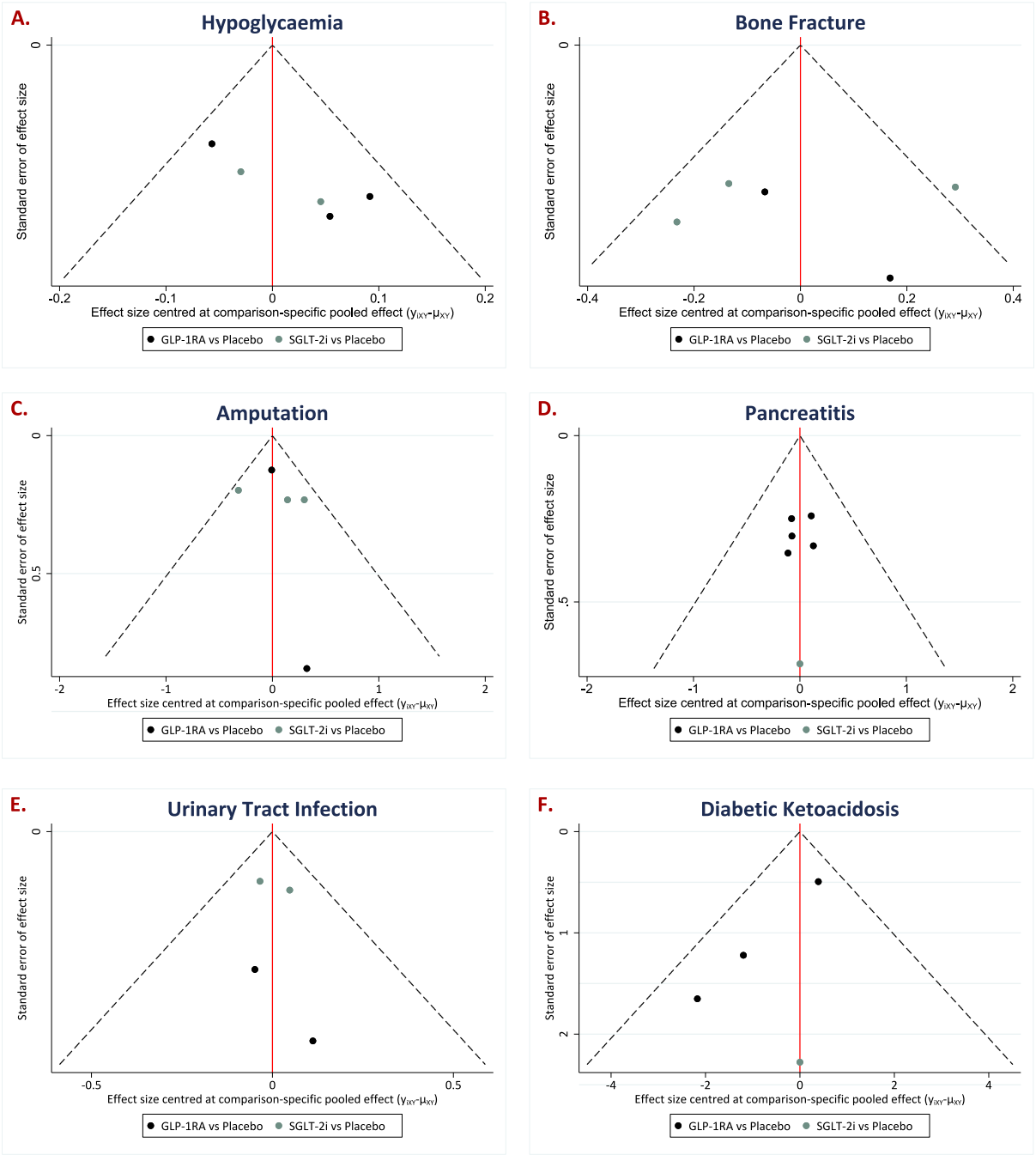
Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT-2is, sodium-glucose co-transporter 2 inhibitors.

Appendix Figure 6 Comparison adjusted funnel plots for primary and secondary cardiovascular outcomes.



Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; MACE, major adverse cardiovascular events; SGLT-2is, sodium-glucose co-transporter 2 inhibitors.

Appendix Figure 7 Comparison adjusted funnel plots for safety outcomes.



Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT-2is, sodium-glucose co-transporter 2 inhibitors.