JAMA | Original Investigation

Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

A Systematic Review and Meta-analysis

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IMPORTANCE The comparative clinical efficacy of sodium-glucose cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors for treatment of type 2 diabetes is unknown.

OBJECTIVE To compare the efficacies of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors on mortality and cardiovascular end points using network meta-analysis.

DATA SOURCES MEDLINE, Embase, Cochrane Library Central Register of Controlled Trials, and published meta-analyses from inception through October 11, 2017.

STUDY SELECTION Randomized clinical trials enrolling participants with type 2 diabetes and a follow-up of at least 12 weeks were included, for which SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors were compared with either each other or placebo or no treatment.

DATA EXTRACTION AND SYNTHESIS Data were screened by 1 investigator and extracted in duplicate by 2 investigators. A Bayesian hierarchical network meta-analysis was performed.

MAIN OUTCOMES AND MEASURES The primary outcome: all-cause mortality; secondary outcomes: cardiovascular (CV) mortality, heart failure (HF) events, myocardial infarction (MI), unstable angina, and stroke; safety end points: adverse events and hypoglycemia.

RESULTS This network meta-analysis of 236 trials randomizing 176 310 participants found SGLT-2 inhibitors (absolute risk difference [RD], −1.0%; hazard ratio [HR], 0.80 [95% credible interval {CrI}, 0.71 to 0.89]) and GLP-1 agonists (absolute RD, −0.6%; HR, 0.88 [95% CrI, 0.81 to 0.94]) were associated with significantly lower all-cause mortality than the control groups. SGLT-2 inhibitors (absolute RD, −0.9%; HR, 0.78 [95% CrI, 0.68 to 0.90]) and GLP-1 agonists (absolute RD, −0.5%; HR, 0.86 [95% CrI, 0.77 to 0.96]) were associated with lower mortality than were DPP-4 inhibitors. DPP-4 inhibitors were not significantly associated with lower all-cause mortality (absolute RD, 0.1%; HR, 1.02 [95% CrI, 0.94 to 1.11]) than were the control groups. SGLT-2 inhibitors (absolute RD, −0.8%; HR, 0.79 [95% CrI, 0.69 to 0.91]) and GLP-1 agonists (absolute RD, −0.5%; HR, 0.85 [95% CrI, 0.77 to 0.94]) were significantly associated with lower CV mortality than were the control groups. SGLT-2 inhibitors were significantly associated with lower rates of HF events (absolute RD, −1.1%; HR, 0.62 [95% CrI, 0.54 to 0.72]) and MI (absolute RD, −0.6%; HR, 0.86 [95% CrI, 0.77 to 0.97]) than were the control groups. GLP-1 agonists were associated with a higher risk of adverse events leading to trial withdrawal than were SGLT-2 inhibitors (absolute RD, 5.8%; HR, 1.80 [95% CrI, 1.44 to 2.25]) and DPP-4 inhibitors (absolute RD, 3.1%; HR, 1.93 [95% CrI, 1.59 to 2.35]).

CONCLUSIONS AND RELEVANCE In this network meta-analysis, the use of SGLT-2 inhibitors or GLP-1 agonists was associated with lower mortality than DPP-4 inhibitors or placebo or no treatment. Use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment.

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Animated Summary Video

Supplemental content

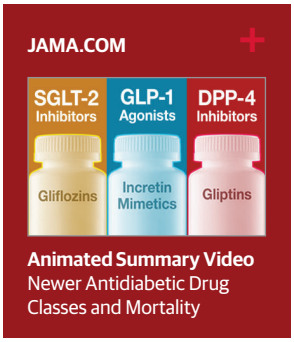
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The global type 2 diabetes epidemic is increasing.[1] Although there have been improvements in long-term outcomes, the excess mortality and cardiovascular morbidity remain a considerable challenge for health care systems.[2] Several drug classes have emerged that are efficacious in improving glycemic control. These include the incretin-based therapies: dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) agonists,[3] and sodium-glucose cotransporter 2 (SGLT-2) inhibitors. International guidelines recommend escalation to either SGLT-2 inhibitors or incretin-based treatments in people with type 2 diabetes not achieving target glycemic control with metformin.[4,5]



Animated Summary Video
Newer Antidiabetic Drug Classes and Mortality

The comparative clinical and cost-effectiveness of the 3 classes of glucose-lowering agents have not been explored, leading to clinical uncertainty about the optimal treatment pathway and a potential negative cost effect. Similarly, no cardiovascular outcome trials have directly compared the efficacy of these classes. When no head-to-head trial exists, network meta-analysis can be used to estimate the effect.

The purpose of this network meta-analysis was to compare the efficacy of SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 agonists in reducing mortality and cardiovascular outcomes in participants with type 2 diabetes and their relative safety profiles.

Key Points

Question How do sodium-glucose cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) agonists, and dipeptidyl peptidase 4 (DPP-4) inhibitors compare in reducing mortality and cardiovascular events in patients with type 2 diabetes?

Findings In this network meta-analysis that includes 236 trials with 176 310 participants, the use of SGLT-2 inhibitors or GLP-1 agonists was significantly associated with lower all-cause mortality compared with the control groups (placebo or no treatment) (hazard ratio [HR], 0.80, and HR, 0.88, respectively) and with DPP-4 inhibitors (HR, 0.78, and HR, 0.86, respectively).

Meaning In patients with type 2 diabetes, the use of SGLT-2 inhibitors or GLP-1 agonists was associated with better mortality outcomes than DPP-4 inhibitors.

Methods

This article has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-NMA).[6] The study protocol is available in Supplement 1.

Data Sources

A systematic search of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed from database inception through to October 11, 2017 (eMethods 1 in Supplement 2). The reference lists of included studies were searched for additional studies. Systematic reviews were identified and hand-screened for additional trials (**Figure 1**).

After removal of duplicates, the title and abstracts of search results were screened for relevance by a single author (S.L.Z. or A.J.R.). The full texts of remaining results were independently assessed in duplicate by 2 authors (S.L.Z. and A.J.R.) for inclusion based on predetermined criteria. The final list of included studies was decided on discussion between authors with full agreement required prior to inclusion. No disagreements required resolution by a third reviewer.

Study Selection

Trials were considered eligible if they (1) were a randomized clinical trial; (2) enrolled participants with type 2 diabetes mellitus; (3) compared SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors at market-approved doses with each other or with a control group (defined as placebo or no treatment) (eMethods 2 in Supplement 2); (4) had a follow-up of at least 12 weeks; (5) provided information on any of the prespecified primary, secondary, and safety end points; and (6) were published in the English language.

Data Extraction

Data were extracted using piloted forms, independently and in duplicate by 2 authors (S.L.Z. and A.J.R.), and were transcribed onto a dedicated database. The data extracted from each report included baseline participant characteristics, inclusion criteria, study drug and control treatments, follow-up duration, and end point data. Study status as a cardiovascular outcome trial was also recorded, defined by the US Food and Drug Administration regulatory approval process as a phase 3 trial used to determine cardiovascular safety. For studies registered to ClinicalTrials.gov, the entry was searched for additional clinical events. For trials with open-label extension periods, only data from the randomized controlled periods were used.

Risk of bias assessment was conducted by 2 authors in duplicate (S.L.Z. and A.J.R.) using the Cochrane Collaboration risk of bias tool across 5 domains (sequence generation, allocation concealment, blinding, detection bias, and attrition bias). The Egger test was used to identify asymmetry of funnel plots for publication bias.[7]

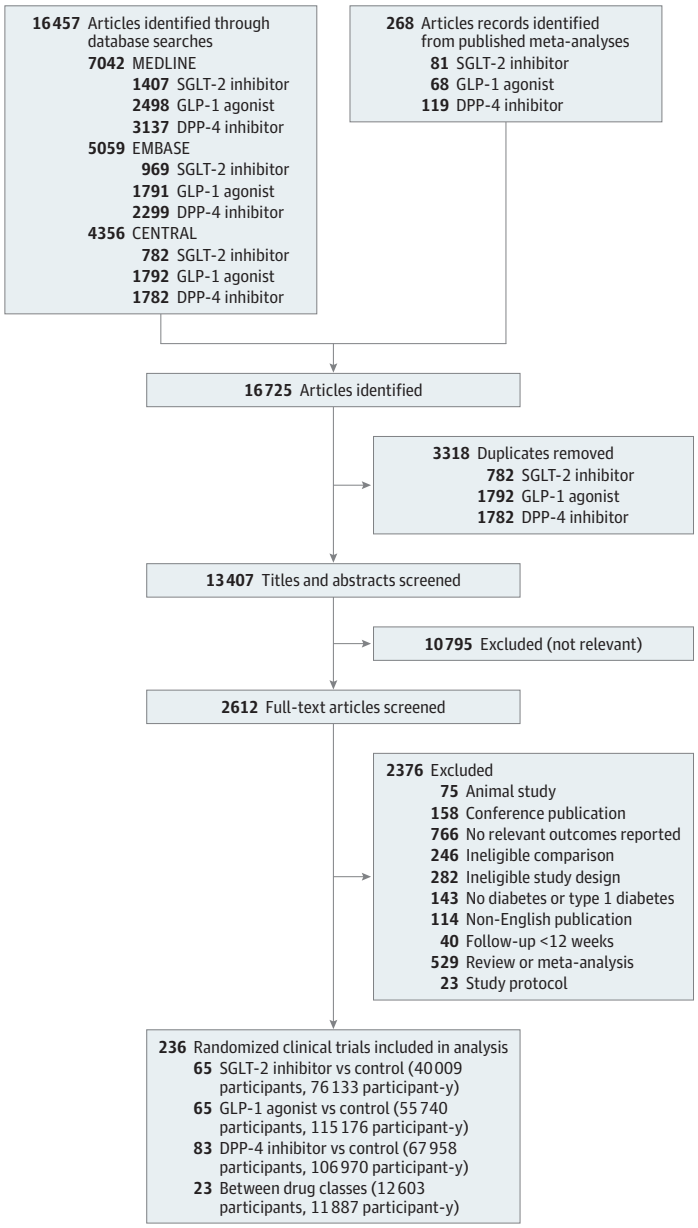
Outcomes

The primary outcome was all-cause mortality. Secondary outcomes included cardiovascular mortality, heart failure events, myocardial infarction (MI) (all and nonfatal), unstable angina, and stroke (all and nonfatal). Safety end points were adverse events (any, serious, and leading to study withdrawal), and hypoglycemia (minor and major) (eMethods 3 in Supplement 2). A composite cardiovascular outcome consisting of cardiovascular mortality, nonfatal MI, and nonfatal

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Figure 1. Summary of Study Retrieval and Identification for Network Meta-analysis



DPP-4 indicates dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; and SGLT-2, sodium-glucose cotransporter 2.

stroke was extracted and analyzed for the cardiovascular outcome trials alone.

Additional drug class-specific safety end points for SGLT-2 inhibitors were lower-limb amputation, urinary tract infection, and genital infection, for GLP-1 agonists were acute pancreatitis, and retinopathy, and for DPP-4 inhibitors was acute pancreatitis.

Data Synthesis

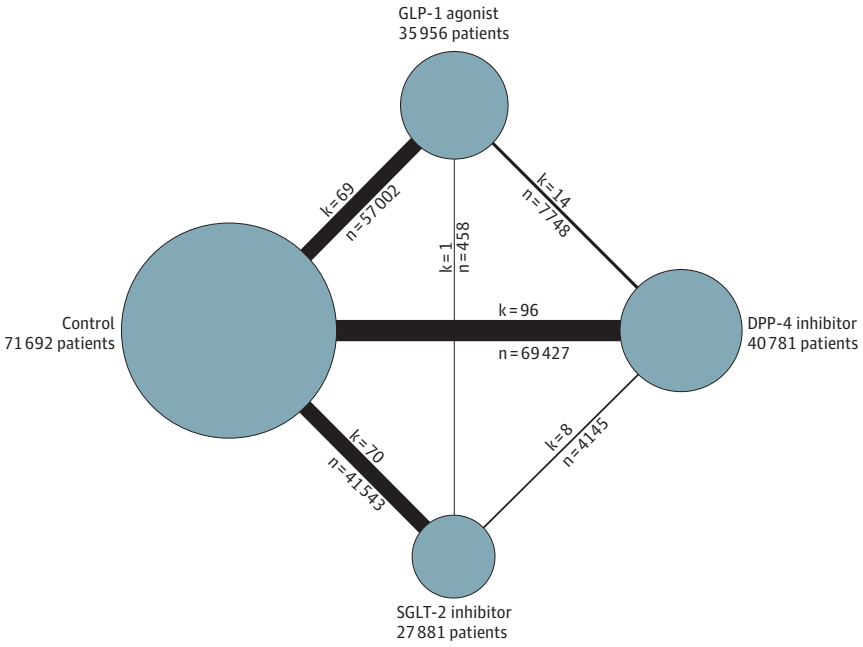
Network meta-analysis comprises direct and indirect comparisons between multiple interventions, allowing comparisons to be made when direct trial evidence is scarce. This approach respects randomization but does not represent randomized evidence.

A Bayesian hierarchical network meta-analysis was performed using the GeMTC package on R (version 3.4.1)[8] (eMethods 4 in Supplement 2). Fixed- or random-effects models were selected for each outcome based on the deviance information criterion (DIC), using the model with the smallest value (eTable 1). Analyses were performed using Markov-chain Monte Carlo methods. Results were presented as hazard ratios (HRs) with 95% credible intervals (CrIs). For studies that reported event counts only, differences in follow-up duration between studies were incorporated using the trial patient-years follow-up to estimate HRs using the Poisson likelihood and log link. Transitivity assumes similarity between sets of trials with respect to important effect modifiers. This was assessed by constructing summary tables

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Figure 2. Network Plot for All Studies



Graphical representation of network for all included trials. Connecting lines represent head-to-head comparisons between drugs, indicated by nodes. Multigroup trials contribute multiple comparisons, resulting in 258 comparisons from 236 trials. The thickness of lines between nodes is proportional to the number of trials comparing the treatments. The sizes of the nodes are proportional to the number of patients in each treatment. Patients may be included in multiple comparisons: for example, in a study of 3 groups consisting of control and 2 different drug classes, the control group is compared with each drug class. This is accounted for within the network model and does not constitute duplication of participants.

DPP-4 indicates dipeptidyl peptidase 4 GLP-1, glucagon-like peptide 1; k, the number of comparisons; n, the number of patients per comparison; and SGLT-2, sodium-glucose cotransporter 2.

organized by pair-wise comparisons to qualitatively assess baseline clinical similarity of trial populations. Between-study heterogeneity was assessed using the I^2 statistic.[9] The probability that each treatment class ranked in a given position from best to worst was estimated and presented in ranking plots. Network consistency was analyzed by calculating the ratio of direct and indirect treatment effects within each comparison with 95% CrIs.[10]

In addition to the primary analysis, a network meta-analysis of studies by individual drug type was performed for the primary outcome. A further network meta-analysis of primary and secondary outcomes was undertaken using data from cardiovascular outcome trials, with composite cardiovascular end points included as an outcome.

Absolute risk differences (RDs) and 95% CrIs were calculated by multiplying the HRs and 95% CrIs generated from meta-analysis to the risk of events in the comparison group. Negative values indicate a reduction in events with treatment, and positive values indicate an increase in events.

A frequentist random-effects network meta-analysis was also performed using the NetMeta package on R.[11] Results are presented as relative risks (RRs) with 95% CIs. Two-tailed P values of .05 were used for statistical significance. The P-score statistic was used to assess the mean probability of superiority of each drug class to alternative treatments for a given outcome. For additional drug class-specific adverse events, data from cardiovascular outcome trials were pooled using frequentist pair-wise meta-analysis. The model that was used was determined by the degree of heterogeneity, with random effects favored in the presence of heterogeneity (I^2 >30%). The sensitivity analysis that was performed was restricted to study participant type (excluding postacute coronary syndrome and low-cardiovascular risk trials), trial duration (excluding trials with <12 months of follow-up), and risk of bias (restricted to studies with low risk of bias across all domains). All data were represented graphically with network and forest plots using RStudio and Microsoft Excel. Changes to the study protocol are reported in eMethods 5 in Supplement 2.

Results

Study Search and Study Characteristics

Systematic searching through October 11, 2017, identified 16 725 articles, of which 236 articles comprising 258 drug-class comparisons were included for the network meta-analysis (Figure 1 and **Figure 2**). In total, 176 310 participants were enrolled, comprising 310 166 participant-years (**Table** and eTable 2 in Supplement 2). For direct comparisons, 14 trials compared a GLP-1 agonist with a DPP-4 inhibitor, 8 trials compared an SGLT-2 inhibitor with a DPP-4 inhibitor, and 1 trial compared an SGLT-2 inhibitor with a GLP-1 agonist. Of the 236 included studies, 9 were designed as cardiovascular outcome trials and enrolled 87 162 participants (247 034 participant-years) who were at increased risk of or who had cardiovascular disease (SGLT-2 inhibitor: EMPA-REG OUTCOME,[12] CANVAS[13]; GLP-1 agonist: ELIXA,[14] LEADER,[15] SUSTAIN-6,[16] EXSCEL[17]; and DPP-4 inhibitor: SAVOR-TIMI 53,[18] EXAMINE,[19] TECOS[20]) (eTable 3). Participants enrolled in the cardiovascular outcome trials made up 42.9% of all participants in the SGLT-2 inhibitor trials (17 162 of 40 009), 60.0% (33 457 of 55 740) in the GLP-1 agonist trials, and 53.8% (36 543 of 67 958) in the DPP-4 inhibitor trials.

The baseline characteristics of studies were deemed sufficiently similar based on sex, age, body mass index (BMI),

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Table. Study Participant Characteristics[a]

Drug Type	No. of Trials	Total No. Randomized	Mean (SD)			
			Men, %	Age, y	BMI	HbA_{1c}, %
DPP-4 inhibitor vs control	83	67 958	54.7 (9.4)	57.9 (5.3)	29.3 (2.9)	8.16 (0.61)
GLP-1 agonist vs control	65	55 740	55.1 (11.4)	57.1 (3.8)	31.5 (3.5)	8.11 (0.36)
SGLT-2 inhibitor vs control	65	40 009	57.9 (10.4)	58.0 (3.7)	29.3 (5.0)	8.05 (0.32)
DPP-4 inhibitor vs GLP-1 agonist	14	8024	50.9 (7.5)	52.9 (4.4)	32.6 (2.3)	8.2 (0.20)
DPP-4 inhibitor vs SGLT-2 inhibitor	8	4121	56.0 (5.5)	55.5 (2.1)	30.9 (1.2)	8.0 (0.39)
GLP-1 agonist vs SGLT-2 inhibitor	1	458				

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HbA_{1c}, hemoglobin A_{1c}; SLGT2, sodium-glucose cotransporter 2.

[a] The Table represents data from studies stratified by the intervention and comparator. Control refers to placebo or no treatment. There was 1 study assessing GLP-1 agonist compared with a SGLT-2 inhibitor.

and hemoglobin A_{1c} (HbA_{1c}) levels to permit network comparison. Baseline cardiovascular disease and background medical therapy for participants in cardiovascular outcome trials were deemed similar, although 2 studies (ELIXA[14] and EXAMINE[19]) enrolled participants after being diagnosed with acute coronary syndrome.

Risk of Bias and Publication Bias

Of 236 included studies, 104 (44.1%) were low risk of bias across all domains. Three (1.3%) were high risk of bias for allocation concealment, 16 (6.8%) for blinding, and 58 (24.6%) for attrition bias. No studies were high risk of bias for sequence allocation or detection (eFigure 1 and eTable 4 in Supplement 2). There was no evidence of publication bias (Egger test, 0.10; $P = .27$) (eFigure 2).

Primary Outcome: All-Cause Mortality

For all-cause mortality, 97 studies that had enrolled 134 160 participants reported at least 1 event in any group. In all, there were 6035 deaths: 714 (3.6%) of 19 587 participants treated with SGLT-2 inhibitors, 1171 (3.9%) of 30 178 treated with DPP-4 inhibitors, 1195 (4.4%) of 27 373 treated with GLP-1 agonists, and 2955 (5.2%) of 57 022 in the control groups. Compared with the control groups, both SGLT-2 inhibitors (HR, 0.80 [95% CrI, 0.71 to 0.89]; absolute RD, −1.0% [95% CrI, −1.5% to −0.6%]) and GLP-1 agonists (HR, 0.88 [95% CrI, 0.81 to 0.94]; absolute RD, −0.6% [95% CrI, −1.0% to −0.3%]) were associated with reductions in all-cause mortality (**Figure 3**). Dipeptidyl peptidase 4 inhibitors were not associated with a difference in mortality compared with the control groups (HR, 1.02 [95% CrI, 0.94 to 1.11]; absolute RD, 0.1% [95% CrI, −0.3% to 0.6%]). Both SGLT-2 inhibitors (HR, 0.78 [95% CrI, 0.68 to 0.90]; absolute RD, −0.9% [95% CrI, −1.2% to -0.4%]) and GLP-1 agonists (HR, 0.86 [95% CrI, 0.77 to 0.96]; absolute RD −0.5% [95% CrI, −0.9% to −0.2%]) were associated with reduced all-cause mortality when compared with DPP-4 inhibitors. There was no significant difference between SGLT-2 inhibitors and GLP-1 agonists (HR, 0.91 [95% CrI, 0.79 to 1.04]; absolute RD, −0.4% [95% CrI, −0.9% to 0.2%]).

Secondary Outcomes

Reporting of secondary outcomes was variable, with not all trials presenting data. Cardiovascular outcome trials accounted for the majority of events, with event data in other trials derived frequently from bias-prone safety outcomes reported in the publication or on the clinical trials database entry. The networks for secondary outcomes are shown in eFigure 3 in Supplement 2.

Cardiovascular Mortality

Compared with the control groups, both SGLT-2 inhibitors (HR, 0.79 [95% CrI, 0.69 to 0.91]; absolute RD, −0.8% [95% CrI, −1.1% to −0.3%]) and GLP-1 agonists (HR, 0.85 [95% CrI, 0.77 to 0.94]; absolute RD, −0.5% [95% CrI, −0.8% to −0.1%]) were associated with reductions in cardiovascular mortality (Figure 3). Dipeptidyl peptidase 4 inhibitors were not associated with change in cardiovascular mortality compared with the control groups (HR, 1.00 [95% CrI, 0.91 to 1.11]; absolute RD, 0% [95% CrI, −0.3% to 0.4%]). Compared with DPP-4 inhibitors, both SGLT-2 inhibitors (HR, 0.79 [95% CrI, 0.66 to 0.94]; absolute RD, −0.7% [95% CrI, −1.1% to −0.2%]) and GLP-1 agonists (HR, 0.85 [95% CrI, 0.74 to 0.98]; absolute RD −0.5% [95% CrI, −0.8% to −0.1%]) were associated with reduced cardiovascular mortality. There was no significant difference between SGLT-2 inhibitors and GLP-1 agonists on cardiovascular mortality (HR, 0.93 [95% CrI, 0.78 to 1.10]; absolute RD, −0.2% [95% CrI, −0.7% to 0.3%]).

Heart Failure Events

When compared with the control groups (HR, 0.62 [95% CrI, 0.54 to 0.72]; absolute RD, −1.1% [95% CrI, −1.3% to −0.8%]), with DPP-4 inhibitors (HR, 0.55 [95% CrI, 0.46 to 0.67]; absolute RD, −1.1% [95% CrI, −1.3% to −0.8%]), and with GLP-1 agonists (HR, 0.67 [95% CrI, 0.57 to 0.80]; absolute RD, −0.9% [95% CrI, −1.2% to −0.5%]), SGLT-2 inhibitors were associated with reduced heart failure events (Figure 3). Glucagon-like peptide 1 agonists and DPP-4 inhibitors had no significant difference compared with the control groups, but GLP-agonists were associated with reduced heart failure events compared with DPP-4 inhibitors (HR, 0.82 [95% CrI, 0.70 to 0.95]; absolute RD, −0.4% [95% CrI, −0.7% to −0.1%]).

MI and Unstable Angina

Only SGLT-2 inhibitors were associated with reduction in all MIs (HR, 0.86 [95% CrI, 0.77 to 0.97]; absolute RD, −0.6% [95% CrI, −0.9% to −0.1%]) and nonfatal MIs (HR, 0.84 [95% CrI, 0.72

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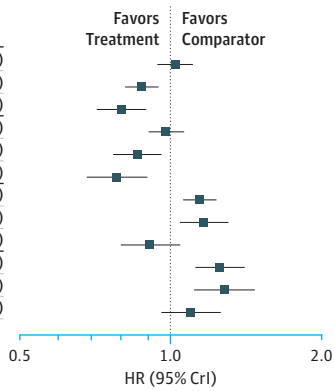
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Figure 3. Forest Plots for All-Cause Mortality, Cardiovascular Mortality, and Heart Failure

A Primary outcome: all-cause mortality, 97 trials; $I^2 = 12\%$

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.1 (−0.3 to 0.6)	1.02 (0.94 to 1.11)
GLP-1 agonist		−0.6 (−1.0 to −0.3)	0.88 (0.81 to 0.94)
SGLT-2 inhibitor		−1.0 (−1.5 to −0.6)	0.80 (0.71 to 0.89)
Control	vs DPP-4 inhibitor	−0.1 (−0.4 to 0.2)	0.98 (0.90 to 1.06)
GLP-1 agonist		−0.5 (−0.9 to −0.2)	0.86 (0.77 to 0.96)
SGLT-2 inhibitor		−0.9 (−1.2 to −0.4)	0.78 (0.68 to 0.90)
Control	vs GLP-1 agonist	0.6 (0.3 to 1.0)	1.14 (1.06 to 1.23)
DPP-4 inhibitor		0.7 (0.2 to 1.3)	1.17 (1.04 to 1.30)
SGLT-2 inhibitor		−0.4 (−0.9 to 0.2)	0.91 (0.79 to 1.04)
Control	vs SGLT-2 inhibitor	0.9 (0.4 to 1.5)	1.25 (1.12 to 1.40)
DPP-4 inhibitor		1.0 (0.4 to 1.7)	1.28 (1.11 to 1.47)
GLP-1 agonist		0.4 (−0.1 to 0.9)	1.10 (0.96 to 1.26)

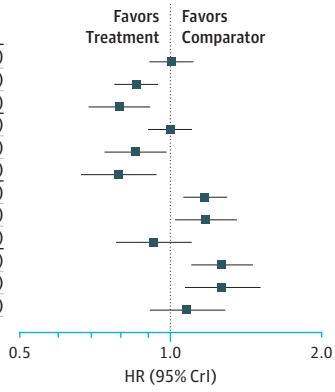
Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	88	2955 (5.2)	57022
DPP-4 inhibitor	49	1171 (3.9)	30178
GLP-1 agonist	32	1195 (4.4)	27373
SGLT-2 inhibitor	29	714 (3.6)	19587



B Cardiovascular mortality, 56 trials; $I^2 = 19\%$

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.0 (−0.3 to 0.4)	1.00 (0.91 to 1.11)
GLP-1 agonist		−0.5 (−0.8 to −0.1)	0.85 (0.77 to 0.94)
SGLT-2 inhibitor		−0.8 (−1.1 to −0.3)	0.79 (0.69 to 0.91)
Control	vs DPP-4 inhibitor	0.0 (−0.3 to 0.3)	1.00 (0.90 to 1.10)
GLP-1 agonist		−0.5 (−0.8 to −0.1)	0.85 (0.74 to 0.98)
SGLT-2 inhibitor		−0.7 (−1.1 to −0.2)	0.79 (0.66 to 0.94)
Control	vs GLP-1 agonist	0.5 (0.2 to 0.9)	1.17 (1.06 to 1.30)
DPP-4 inhibitor		0.5 (0.1 to 1.1)	1.18 (1.02 to 1.36)
SGLT-2 inhibitor		−0.2 (−0.7 to 0.3)	0.93 (0.78 to 1.10)
Control	vs SGLT-2 inhibitor	0.8 (0.3 to 1.3)	1.27 (1.10 to 1.46)
DPP-4 inhibitor		0.8 (0.2 to 1.5)	1.27 (1.07 to 1.51)
GLP-1 agonist		0.2 (−0.3 to 0.8)	1.08 (0.91 to 1.29)

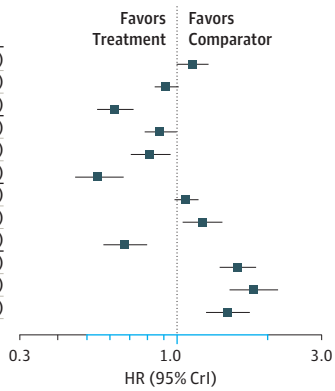
Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	50	1833 (3.6)	50869
DPP-4 inhibitor	27	763 (3.1)	24519
GLP-1 agonist	19	704 (3.0)	23554
SGLT-2 inhibitor	19	468 (2.5)	18407



C Heart failure events, 58 trials; $I^2 = 19\%$

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.4 (0.0 to 0.8)	1.13 (1.00 to 1.28)
GLP-1 agonist		−0.2 (−0.5 to 0.1)	0.93 (0.84 to 1.02)
SGLT-2 inhibitor		−1.1 (−1.3 to −0.8)	0.62 (0.54 to 0.72)
Control	vs DPP-4 inhibitor	−0.3 (−0.5 to 0.0)	0.88 (0.78 to 1.00)
GLP-1 agonist		−0.4 (−0.7 to −0.1)	0.82 (0.70 to 0.95)
SGLT-2 inhibitor		−1.1 (−1.3 to −0.8)	0.55 (0.46 to 0.67)
Control	vs GLP-1 agonist	0.2 (−0.1 to 0.5)	1.08 (0.98 to 1.18)
DPP-4 inhibitor		0.6 (0.1 to 1.1)	1.22 (1.05 to 1.42)
SGLT-2 inhibitor		−0.9 (−1.2 to −0.5)	0.67 (0.57 to 0.80)
Control	vs SGLT-2 inhibitor	1.0 (0.6 to 1.4)	1.60 (1.39 to 1.84)
DPP-4 inhibitor		1.3 (0.8 to 2.0)	1.81 (1.50 to 2.18)
GLP-1 agonist		0.8 (0.4 to 1.3)	1.48 (1.25 to 1.76)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	55	1370 (2.8)	48362
DPP-4 inhibitor	24	544 (2.4)	22327
GLP-1 agonist	21	638 (2.7)	23363
SGLT-2 inhibitor	19	266 (1.7)	15989



All outcomes are reported in hazard ratios (HRs) for treatment vs the comparator and 95% credible intervals (CrIs). Absolute risk differences (RDs) were calculated by multiplying the RD by the event rate in the comparator group. The 95% CrIs for absolute RDs are calculated by multiplying the 95% CrIs by the event rate in the comparator group. Heterogeneity was assessed using the I^2 statistic; low heterogeneity was determined by an I^2 of 25% or less. The x-axis scale shown in blue indicates the range of the HR from 0.5 to 2.0. Tables below the forest plots show, for each drug class, the number of trials, number of participants with events, and the total number of randomized participants. For example, for all-cause mortality, 88 trials randomized 57 022 participants to the control treatment with 2955 participants having events, and 49 trials randomized 30 178 participants to DPP-4 inhibitors with 1171 participants having events. Control represents either placebo or no treatment; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; and SGLT-2, sodium-glucose cotransporter 2.

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to 0.98]; absolute RD, −0.8% [95% CrI, −1.4% to −0.1%]) compared with the control groups (**Figure 4** and eFigure 4 in Supplement 2). There was no significant difference between drug classes. No drug class was associated with reduction in unstable angina (Figure 4).

Stroke

No drug class was associated with reduction in all stroke compared with the control groups (Figure 4); however, GLP-1 agonists were associated with reduction in nonfatal stroke compared with the control groups (HR, 0.87 [95% CrI, 0.76 to 0.99]; absolute RD −0.3% [95% CrI, −0.5% to −0.02%]) (eFigure 4 in Supplement 2). There was no associated difference between drug classes for nonfatal stroke.

Individual Drug Types

For 16 individual drug types compared with the control groups (eFigure 5), all-cause mortality was reduced only with 1 SGLT-2 inhibitor: empagliflozin (HR, 0.68 [95% CrI, 0.57 to 0.82]; absolute RD, −1.3% [95% CrI, −1.7% to −0.7%]), and 2 GLP-1 agonists: liraglutide (HR, 0.85 [95% CrI, 0.75 to 0.98]; absolute RD, −0.9% [95% CrI, −1.5% to −0.1%]) and exenatide (HR, 0.86 [95% CrI, 0.77 to 0.97]; absolute RD, −0.9% [95% CrI, −1.5% to −0.2%]) (eTable 5 and eFigure 6 in Supplement 2). No DPP-4 inhibitor individually reduced all-cause mortality.

Safety End Points

For any hypoglycemia, DPP-4 inhibitors (HR, 1.29 [95% CrI, 1.12 to 1.50]; absolute RD, 4.9% [95% CrI, 2.0% to 8.4%]), GLP-1 agonists (HR, 1.44 [95% CrI, 1.25 to 1.66]; absolute RD, 7.4% [95% CrI, 4.2% to 11.1%]), and SGLT-2 inhibitors (HR, 1.24 [95% CrI, 1.06 to 1.45]; absolute RD, 4.0% [95% CrI, 1.0% to 7.6%]) were all associated with an increased risk compared with the control groups (eFigure 7 in Supplement 2). There were no significant differences for major hypoglycemia. There was no difference between drug classes for any or major hypoglycemia.

Sodium-glucose cotransporter 2 inhibitors were associated with a reduction in serious adverse events compared with the control groups (HR, 0.90 [95% CrI, 0.85 to 0.96]; absolute RD, −1.8% [95% CrI, −2.7% to −0.7%]), DPP-4 inhibitor (HR, 0.91 [95% CrI, 0.84 to 0.98]; absolute RD, −1.1% [95% CrI, −2.0% to −0.3%]), and GLP-1 agonist (HR, 0.92 [95% CrI, 0.85 to 0.99]; absolute RD, −1.4% [95% CrI, −2.5% to −0.2%]). Glucagon-like peptide 1 agonists were associated with an increased risk of adverse events leading to trial withdrawal compared with the control groups (HR, 2.00 [95% CrI, 1.70 to 2.37]; absolute RD, 4.7% [95% CrI, 3.3% to 6.5%]), SGLT-2 inhibitors (HR, 1.80 [95% CrI, 1.44 to 2.25]; absolute RD, 5.8% [95% CrI, 3.2% to 9.0%]), and DPP-4 inhibitors (HR, 1.93 [95% CrI, 1.59 to 2.35]; absolute RD, 3.1% [95% CrI, 2.0% to 4.5%]).

Clinical Events in Cardiovascular Outcome Trials

Network meta-analysis of clinical end points from cardiovascular outcome trials were similar to the primary analysis for all-cause and cardiovascular mortality (eTable 6 in Supplement 2). Compared with placebo, SGLT-2 inhibitors were not associated with reductions in all MI and nonfatal MI, whereas GLP-1 agonists were not associated with a reduction in nonfatal stroke. Glucagon-like peptide 1 agonists were not associated with reduced heart failure events compared with DPP-4 inhibitors.

For pooled cardiovascular mortality, nonfatal MI, and nonfatal stroke, SGLT-2 inhibitors (HR, 0.88 [95% CrI, 0.79 to 0.97]; absolute RD, −1.3% [95% CrI, −2.3% to −0.3%]) and GLP-1 agonists (HR, 0.91 [95% CrI, 0.85 to 0.96]; absolute RD, −1.0% [95% CrI, −1.6% to −0.4%]) were associated with reduction in events compared with placebo. The DPP-4 inhibitors were not associated with reduction (HR, 0.99 [95% CrI, 0.92 to 1.07]). There was no associated reduction in events when drug classes were compared with each other.

Sodium-glucose contransporter 2 inhibitors were associated with an increased risk of genital infections (RR, 4.19 [95% CI, 3.45 to 5.09]; absolute RD, 6.0%; P = <.001) but not of urinary tract infection (eFigure 8 in Supplement 2). Sodium-glucose cotransporter 2 inhibitors were not associated with a significant increase in lower limb amputation (RR, 1.55 [95% CI, 0.96 to 2.50]; P = .07) with high heterogeneity (I^2, 73%). Dipeptidyl peptidase 4 inhibitors were associated with an increased risk of acute pancreatitis (RR, 1.58 [95% CI, 1.04 to 2.39]; absolute RD, 0.1%; P = .03). Glucagon-like peptide 1 agonists were not associated with acute pancreatitis or retinopathy.

Drug Class Rankings

For all-cause and cardiovascular mortality, SGLT-2 inhibitors were most likely to rank best, GLP-1 agonists second best, and DPP-4 inhibitors worst (**Figure 5**). The SGLT-2 inhibitors were most likely to rank best for heart failure and MI outcomes, and GLP-1 agonists were most likely to rank best for stroke outcomes.

Heterogeneity and Network Consistency

Heterogeneity (global I^2) was low for all primary, secondary, and safety outcomes (range, 0% to 25%). For all-cause mortality, heterogeneity was 12% when analyzed by drug class and by individual drug type. There was no evidence of inconsistency in all networks except for heart failure events (DPP-4 inhibitor vs GLP-1 agonist), nonfatal stroke (DPP-4 vs control), and adverse events leading to withdrawal (DPP-4 vs GLP-1, DPP-4 vs control, and GLP-1 vs control; eFigure 9 in Supplement 2).

Sensitivity Analysis

Sensitivity analyses did not affect the associations of SGLT-2 inhibitors and GLP-1 agonists with reduced all-cause mortality and cardiovascular mortality compared with the control groups and DPP-4 inhibitor inhibitors (eTable 7 in Supplement 2). Although the sensitivity analysis did not show that SGLT-2 inhibitors were associated with reduced risk of nonfatal MI, the analyses showed that the associations with all MIs remained. The sensitivity analyses also showed that GLP-1 agonists were not associated with reduced risk of nonfatal stroke.

Frequentist Meta-analysis

Frequentist network meta-analysis findings were similar to those using the Bayesian approach (eTable 8 in Supplement 2).

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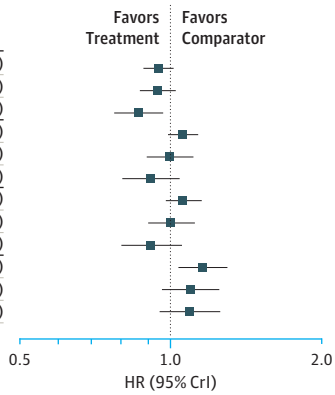
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Figure 4. Forest Plots for Myocardial Infarction, Unstable Angina, and Stroke

A All myocardial infarction, 97 trials; I^2 = 15%

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	−0.2 (−0.5 to 0.0)	0.94 (0.88 to 1.01)
GLP-1 agonist		−0.2 (−0.5 to 0.1)	0.94 (0.87 to 1.02)
SGLT-2 inhibitor		−0.6 (−0.9 to −0.1)	0.86 (0.77 to 0.97)
Control	vs DPP-4 inhibitor	0.1 (0.0 to 0.3)	1.06 (0.99 to 1.13)
GLP-1 agonist		0.0 (−0.2 to 0.2)	1.00 (0.90 to 1.11)
SGLT-2 inhibitor		−0.2 (−0.4 to 0.1)	0.91 (0.80 to 1.04)
Control	vs GLP-1 agonist	0.3 (−0.1 to 0.6)	1.06 (0.98 to 1.15)
DPP-4 inhibitor		0.0 (−0.4 to 0.5)	1.00 (0.90 to 1.12)
SGLT-2 inhibitor		−0.3 (−0.9 to 0.2)	0.92 (0.80 to 1.05)
Control	vs SGLT-2 inhibitor	0.4 (0.1 to 0.8)	1.16 (1.04 to 1.30)
DPP-4 inhibitor		0.3 (−0.1 to 0.6)	1.10 (0.96 to 1.25)
GLP-1 agonist		0.2 (−0.1 to 0.6)	1.09 (0.95 to 1.25)

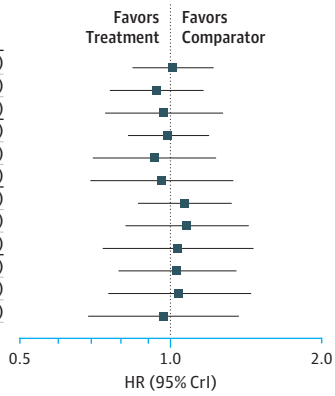
Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	87	2133 (4.0)	53 099
DPP-4 inhibitor	50	616 (2.2)	27 462
GLP-1 agonist	30	1140 (4.3)	26 400
SGLT-2 inhibitor	32	505 (2.5)	19 958



B Unstable angina, 50 trials; I^2 = 20%

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.0 (−0.2 to 0.3)	1.01 (0.84 to 1.22)
GLP-1 agonist		0.1 (−0.3 to 0.2)	0.94 (0.76 to 1.16)
SGLT-2 inhibitor		0.0 (−0.3 to 0.3)	0.97 (0.74 to 1.27)
Control	vs DPP-4 inhibitor	0.0 (−0.2 to 0.2)	0.99 (0.82 to 1.19)
GLP-1 agonist		−0.1 (−0.3 to 0.2)	0.93 (0.70 to 1.23)
SGLT-2 inhibitor		0.0 (−0.3 to 0.3)	0.96 (0.69 to 1.33)
Control	vs GLP-1 agonist	0.1 (−0.2 to 0.4)	1.07 (0.86 to 1.32)
DPP-4 inhibitor		0.1 (−0.2 to 0.5)	1.08 (0.81 to 1.43)
SGLT-2 inhibitor		0.0 (−0.3 to 0.5)	1.03 (0.73 to 1.46)
Control	vs SGLT-2 inhibitor	0.0 (−0.3 to 0.5)	1.03 (0.79 to 1.35)
DPP-4 inhibitor		0.1 (−0.4 to 0.7)	1.04 (0.75 to 1.45)
GLP-1 agonist		0.0 (−0.5 to 0.6)	0.97 (0.68 to 1.37)

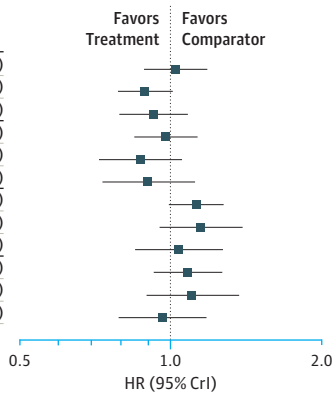
Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	48	470 (1.3)	36 362
DPP-4 inhibitor	21	227 (1.1)	21 211
GLP-1 agonist	18	165 (1.2)	14 278
SGLT-2 inhibitor	16	154 (1.6)	9875



C All stroke, 837 trials; I^2 = 18%

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.0 (−0.2 to 0.4)	1.02 (0.88 to 1.18)
GLP-1 agonist		−0.2 (−0.5 to 0.0)	0.89 (0.78 to 1.01)
SGLT-2 inhibitor		−0.2 (−0.4 to 0.2)	0.92 (0.79 to 1.08)
Control	vs DPP-4 inhibitor	0.0 (−0.2 to 0.2)	0.98 (0.85 to 1.13)
GLP-1 agonist		−0.2 (−0.4 to 0.1)	0.87 (0.72 to 1.05)
SGLT-2 inhibitor		−0.1 (−0.4 to 0.2)	0.90 (0.73 to 1.12)
Control	vs GLP-1 agonist	0.2 (0.0 to 0.5)	1.12 (0.99 to 1.27)
DPP-4 inhibitor		0.3 (−0.1 to 0.8)	1.15 (0.95 to 1.39)
SGLT-2 inhibitor		0.1 (−0.3 to 0.5)	1.04 (0.85 to 1.27)
Control	vs SGLT-2 inhibitor	0.1 (−0.1 to 0.4)	1.08 (0.92 to 1.27)
DPP-4 inhibitor		0.2 (−0.2 to 0.6)	1.11 (0.89 to 1.37)
GLP-1 agonist		−0.1 (−0.3 to 0.3)	0.96 (0.79 to 1.18)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	75	955 (2.1)	46 012
DPP-4 inhibitor	39	371 (1.5)	25 106
GLP-1 agonist	28	455 (2.0)	23 330
SGLT-2 inhibitor	30	243 (1.6)	15 333

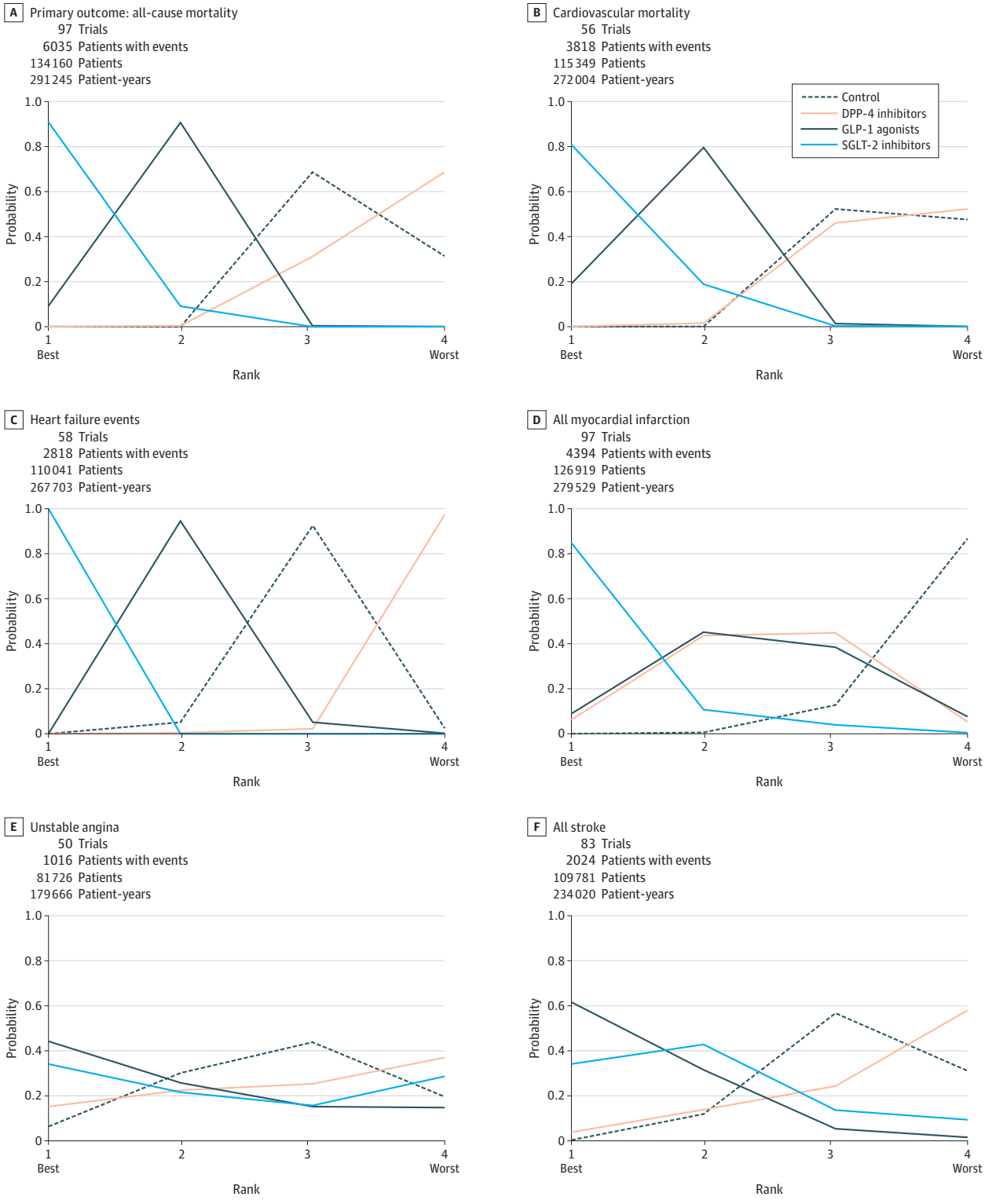


All outcomes are reported in hazard ratios (HRs) for treatment vs the comparator and 95% credible intervals (CrIs). Absolute risk differences (RDs) were calculated by multiplying the RD by the event rate in the comparator group. The 95% CrIs for absolute RDs are calculated by multiplying the 95% CrIs by the event rate in the comparator group. Heterogeneity was assessed using the I^2 statistic; low heterogeneity was determined by an I^2 of 25% or less. The x-axis scale shown in blue indicates the range of the HR from 0.5 to 2.0. Tables below the forest plots show for each drug class, the number of trials, number of participants with events, and the total number of randomized participants. For example, for all myocardial infarction, 87 trials randomized 53 099 participants to the control treatment with 2133 participants having events, and 50 trials randomized 27 462 participants to DPP-4 inhibitors with 616 participants having events. Control represents either placebo or no treatment; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; and SGLT-2, sodium-glucose cotransporter 2.

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Figure 5. Ranking Plots



Drug ranking plots for primary and secondary outcomes are stratified by treatment. Each line represents 1 drug class and shows the probability of its ranking from best to worst. The peak of the line represents the rank that the drug is most likely to be for each given outcome. For example, for all-cause mortality, sodium-glucose cotransporter 2 (SGLT-2) inhibitors are most likely to rank best; glucagon-like peptide 1 (GLP-1) agonists, second best; control, third best; and dipeptidyl peptidase 4 (DPP-4) inhibitors, worst. Control includes placebo and no treatment.

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Discussion

In this network meta-analysis of 236 trials enrolling 176 310 participants with type 2 diabetes, SGLT-2 inhibitors and GLP-1 agonists were associated with reductions in all-cause and cardiovascular mortality compared with DPP-4 inhibitors and the control groups. The SGLT-2 inhibitors were associated with additional cardiovascular benefits for heart failure events compared with incretin-based therapies and control groups and for MI events compared with control groups. Of the 3 classes tested, SGLT-2 inhibition may be preferred over the incretin-based therapies based on their association with lower mortality and their favorable adverse event profile.

Compared with control groups, the use of SGLT-2 inhibitors was associated with absolute risk reductions (RRs) in all-cause and cardiovascular mortality of 1% and 0.8%, respectively. For the same outcomes, GLP-1 agonists had more modest absolute RRs of 0.6% and 0.5%, respectively. Given that absolute RR depends on the baseline risk, it is probable that these estimates are greater in higher-risk populations, with a corresponding lower number needed to treat and better cost-effectiveness. The magnitudes of these absolute RRs using SGLT-2 inhibitors and GLP-1 agonists are important in the context of established standards of care in diabetes.[4] For example, the associated absolute RR in mortality has been shown to be 0.5% for lowering blood pressure[21] and 0.9% for lowering low-density lipoprotein cholesterol (per mmol/L reduction).[22]

To date, no randomized clinical trials with mortality or cardiovascular outcomes have directly compared the efficacy of these 3 classes. Within the limitations of observational studies, the CVD-REAL propensity-matched study[23,24] demonstrated that SGLT-2 inhibitor use was associated with lower rates of all-cause death compared with other glucose lowering agents (HR, 0.49).

The reductions in cardiovascular mortality in EMPA-REG OUTCOME occurred within the first few months of treatment, suggesting that diuretic effects and altered hemodynamics may be responsible. Blood pressure reductions without heart rate increases[25] and weight loss[25] may exert additional early cardiovascular benefits that are independent of glycemic control.[26] In EMPA-REG OUTCOME,[26] participants with heart failure with both modest and larger HbA_{1c} reductions benefited equally from empagliflozin suggesting that glycemic control alone is not responsible. This study supports the beneficial effects SGLT-2 inhibitors have on heart failure by demonstrating a lower risk than DPP-4 inhibitors (HR, 0.55; absolute RD, −1.1%) and GLP-1 agonists (HR, 0.67; absolute RD, −0.9%). To determine if the benefits of SGLT-2 inhibitors on heart failure extend beyond glycemic control, their effects in patients with heart failure without diabetes will be assessed with empagliflozin in EMPEROR-HF[26] and dapagliflozin in Dapa-HF.[27] In contrast, questions have been raised about whether DPP-4 inhibitors are responsible for an increase in heart failure events.[28]

The contrasting effects of the 2 incretin-based treatments on cardiovascular outcomes may be explained by their differing mechanisms of action.[15] Glucagon-like peptide 1 secretion is stimulated by an oral glucose load, leading to insulin release.[29] The GLP-1 half-life is short in vivo due to DPP-4-mediated degradation. Although DPP-4 inhibition increases GLP-1 levels, this elevation is small compared with the supraphysiological supplementation with GLP-1 agonists. This may help to explain the greater reduction in HbA_{1c} and fasting glucose levels and body weight that is seen with the use of GLP-1 agonists compared with DPP-4 inhibitors.[28,29] The UK Prospective Diabetes Study showed that long-term intensive glucose control could reduce mortality,[30] and it is possible that benefits of incretin-based therapies, if due to improved glycemic control, will take many years to become apparent.

All 3 classes resulted in significantly more hypoglycemic events than did control groups, despite SGLT-2 inhibitors and incretin-based therapies using glucose-dependent mechanisms with low theoretical risks of hypoglycemia.[15] One explanation is the heterogenous study definitions for hypoglycemia, which has been addressed by the International Hypoglycemia Study Group.[31] There were no significant differences in the more robustly defined major hypoglycemic events. Sodium-glucose cotransporter 2 inhibitors performed particularly well in reducing serious adverse events, whereas GLP-1 agonists were associated with the highest risk of adverse events of any type and with adverse events leading to participant withdrawal. The majority of these adverse events were gastrointestinal.[32] Current GLP-1 agonists are administered with subcutaneous injections; however, glycemic efficacy of the first oral GLP-1 agonist was demonstrated using semaglutide,[33] with a cardiovascular outcome trial ongoing.[34] Oral GLP-1 agonists may exhibit greater tolerability than subcutaneous counterparts.

Analysis of safety outcomes from cardiovascular outcome trials demonstrated that SGLT-2 inhibitors were associated with increased risk of genital infections but not urinary tract infections. There was a high degree of heterogeneity for lower-limb amputations driven by the significant increase in events with canagliflozin but neutral effects of empagliflozin. Our analyses do not rule out the possibility of a clinically meaningful safety signal for SGLT-2 inhibitors and amputation. Dipeptidyl peptidase 4 inhibitors were associated with increased risk of acute pancreatitis. Careful treatment selection may be necessary to minimize these outcomes in at-risk patients.

Limitations

This study has several limitations. First, the inherent limitations of meta-analysis exist, including the availability and quality of reported data.[35] The reporting of cardiovascular events was variable, with total events driven primarily by the 9 cardiovascular outcome trials. Adverse events reported on ClinicalTrials.gov were used to identify additional events using strict definitions. Given the potential for bias, additional analysis of primary and secondary outcomes was performed limited to event data from cardiovascular outcome trials. This showed consistent results confirming the validity of the main findings.

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Second, an important assumption of network meta-analysis is that participant characteristics that may affect the relative efficacy of interventions are similar across groups. A higher mean BMI in the GLP-1 agonist trials was noted, although the mean BMI was similar across drug classes in the cardiovascular outcome trials from which the majority of events were derived. Third, clinical efficacy and safety was evaluated by drug class rather than by individual drug type. Although this substantially increases power to detect treatment effects, there is a key assumption that within-class treatments are interchangeable. For the primary outcome, between-study heterogeneity was low and the same when evaluated by drug class and by individual drug type, suggesting little variability of treatment effects within drug classes. However, findings from cardiovascular outcome trials have been variable (for example, the same primary outcome was reduced with liraglutide [LEADER[36]] and semaglutide [SUSTAIN-6[16]] but not with lixisenatide [ELIXA[14]] and exenatide [EXSCEL[17]]). Whether this reflects true pharmacological differences or disparity of study design and trial populations is unknown.[15]

Fourth, although approximately half of all participants included in this study had low cardiovascular risk, short trial follow-up duration and low event rates limit the evaluation of these 3 agents in patients with low cardiovascular risk. Fifth, this network meta-analysis did not address the effect of treatments on HbA_{1c} and glycemic control. Although this has been reviewed previously,[37] the drive to maintain glycemic equipoise by modification of background therapy in cardiovascular outcome trials prevents conclusions on HbA_{1c} reduction from being drawn. Similarly, inclusion of cardiovascular outcome trials precludes effects to be stratified by baseline medication therapy. It will be important to test these 3 classes against and in addition to metformin monotherapy for cardiovascular outcomes to better determine treatment algorithms.

Conclusions

In this network meta-analysis, the use of SGLT-2 inhibitors or GLP-1 agonists was associated with lower mortality than DPP-4 inhibitors or placebo or no treatment. Use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment.

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