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Comparative Effect of Glucose-Lowering Drugs for Type 2 Diabetes Mellitus on Stroke Prevention: A Systematic Review and Network Meta-Analysis

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Background: There is still a lack of research on which diabetic drugs are more effective in preventing stroke. Our network meta-analysis aimed to compare cerebrovascular benefits among glucose-lowering treatments.
Methods: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov registry for clinical trials from inception through May 25, 2021. We included both prespecified cerebrovascular outcomes and cerebrovascular events reported as severe adverse events. Subgroup analyses were conducted by stroke subtype, publication type, age of patients, baseline glycosylated hemoglobin (HbA1c), duration of type 2 diabetes mellitus, and cardiovascular risks.
Results: Of 2,861 reports and 1,779 trials screened, 79 randomized controlled trials comprising 206,387 patients fulfilled the inclusion criteria. In the pairwise meta-analysis, the use of glucagon-like peptide-1 (GLP-1) agonist was associated with a lower risk of total stroke compared with placebo (relative risk [RR], –0.17; 95% confidence interval [CI], –0.27 to –0.07). In the network meta-analysis, only the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitor was associated with a reduction of total stroke, compared with placebo (RR, 0.81; 95% CI, 0.67 to 0.98). In the subgroup analyses, the use of SGLT-2 inhibitor and GLP-1 agonist was associated with a lower risk of stroke in those with high HbA1c (≥8.0) and low-risk of cardiovascular disease, respectively.
Conclusion: SGLT-2 inhibitors and GLP-1 agonists were shown to be beneficial for stroke prevention in patients with type 2 diabetes mellitus.

Keywords: Diabetes mellitus, type 2; Drug therapy, combination; Hypoglycemic agents; Stroke

INTRODUCTION

Diabetes and hyperglycemia are established risk factors of stroke [1]. There is evidence concerning the pathogenetic mechanisms and clinical conditions that may underlie the propensity for cerebrovascular diseases in diabetic patients [2,3]. Metformin is the preferred initial pharmacologic agent for treating type 2 diabetes mellitus (T2DM), and other glucose-lowering agents can be considered according to comorbidities or patient-centered treatment factors [4,5]. However, the optimal glucose-lowering treatment for preventing stroke is unclear.

Several large-scale studies have shown the superiority of newer antidiabetic medications for preventing poor cardiovascular outcomes and related mortality [6]. However, analyses about the effects of antidiabetic medications on stroke have shown inconsistent results [7,8]. Pioglitazone did not reduce stroke compared with placebo, but it had a significant effect in preventing stroke recurrence in the PROspective pioglitAzone

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Clinical Trial In macroVascular Events (PROactive) [9]. Sodium-glucose cotransporter-2 (SGLT-2) inhibitor use was associated with reduced cardiovascular events and mortality compared to placebo in the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients (EMPA-REG OUTCOME), CANagliflozin cardioVascular Assessment Study (CANVAS), and Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI58) trials. However, its effects on stroke were neutral or non-significant [10-13]. Semaglutide, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6), showed a significant reduction of nonfatal stroke compared to placebo. However, the trial was a noninferiority study and was not powered to show the superiority of specific stroke endpoints [13]. Furthermore, studies of other glucagon-like peptide-1 (GLP-1) analogs did not show significant reductions in stroke events [14-17]. In this study, we aimed to compare stroke events among glucose-lowering treatments, by conducting a network meta-analysis.

METHODS

Search strategy and selection criteria

The systematic review (PROSPERO: CRD42018082633) protocol was drafted based on the Preferred Reporting Items for

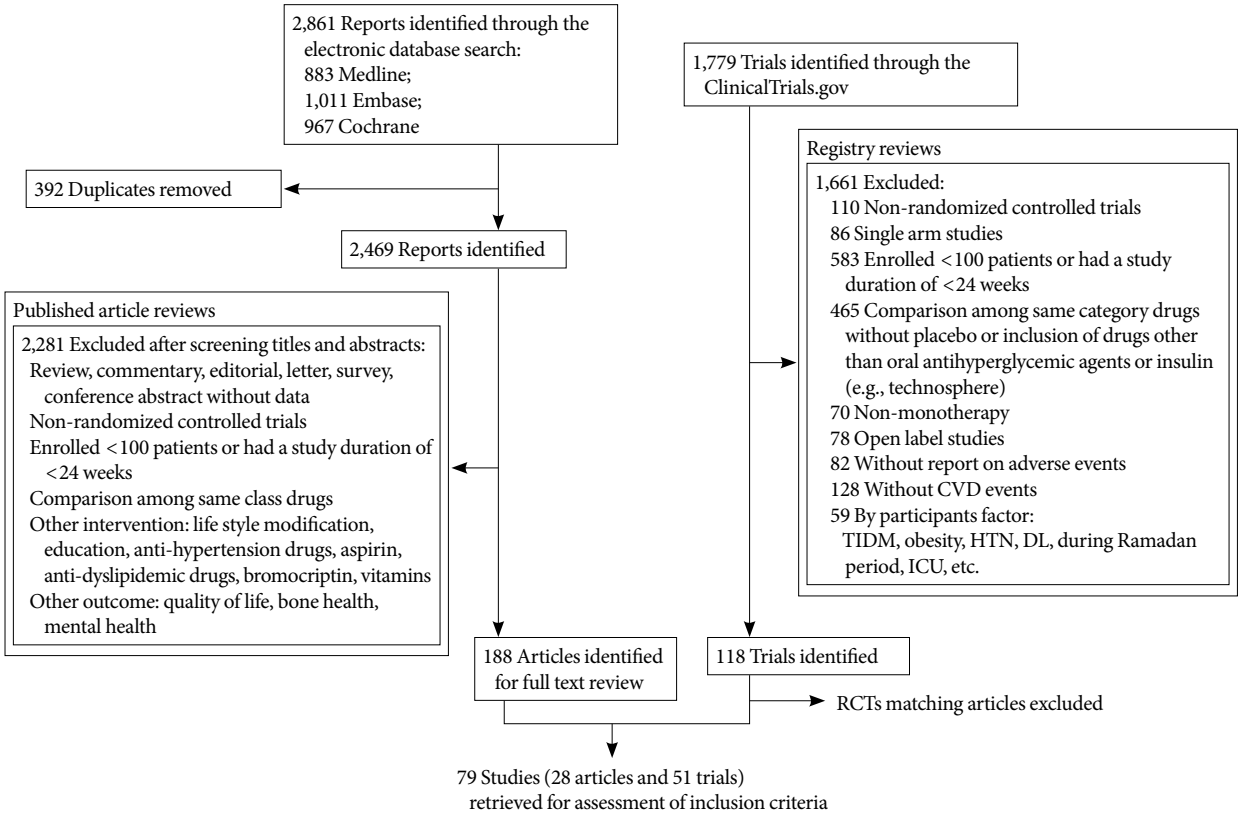

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Network Meta-Analysis (PRISMA-NMA) diagram. We searched the MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov registry for articles published through May 2021 (Supplementary Table 1). The antihyperglycemic agents targeted in our comparison were metformin, sulfonylureas, thiazolidinedione, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, alpha-glucosidase inhibitors, meglitinide, glucagon-like peptide-1 agonists, and insulin. When searching the ClinicalTrials.gov registry, we did not use the outcome keywords. As a result, we reviewed all registered clinical trials including unpublished reports about antihyperglycemic agents that met our comparison criteria. We included not only included prespecified cardiovascular outcome but also cardiovascular events reported as severe adverse events. CVD, cardiovascular disease; T1DM, type 1 diabetes mellitus; HTN, hypertension; DL, dyslipidemia; ICU, intensive care unit; RCT, randomized controlled trial.

Systematic reviews and Meta-Analyses Extension for Network Meta-Analysis (PRISMA-NMA) [18]. MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials were searched for articles published from inception through May 25, 2021 (Fig. 1 and Supplementary Tables 1, 2). The glucose-lowering drugs targeted in our comparison were metformin, sulfonylureas, thiazolidinedione, dipeptidyl peptidase 4 (DPP-4) inhibitors, SGLT-2 inhibitors, alpha-glucosidase inhibitors, meglitinide, GLP-1 agonist, and insulin. When searching the ClinicalTrials.gov registry, we did not use the outcome keywords. As a result, we reviewed all registered clinical trials including unpublished reports on antidiabetic drugs that met our comparison criteria. We included not only prespecified outcomes, but also cerebrovascular events reported as severe adverse events (SAEs). Additionally, publications were retrieved from the bibliographies of relevant manuscripts if they were considered pertinent. All citations were eligible for inclusion regardless of publication year or language.

After removing duplicate citations, two authors (J.S.K. and G.L.) independently screened the titles and abstracts to identify potentially relevant citations. Full texts were then reviewed to establish whether all prespecified inclusion criteria were met: participants were adults with T2DM; group allocation was based on antidiabetic drug use; the study reported at least two groups; comparison was among monotherapy treatment pertaining to different drug category; participants were followed up for at least 24 weeks; more than 100 participants were randomized; and the number of fatal or nonfatal strokes, including hemorrhagic stroke, ischemic stroke, or transient ischemic attack (TIA) was reported. Disagreements regarding study inclusion or exclusion were resolved by discussion with another author (S.W.O.).

Data extraction and risk of bias assessment

One author (J.S.K.) used a standardized form to extract data from each included study, and a second author (G.L.) verified data accuracy and completeness (Supplementary Table 2). The following were recorded: data sources (published articles and ClinicalTrials.gov registries); lead author and year of publication; study design and phase; duration of study; antidiabetic drug use at enrollment; participant age, percentage of male or female participants, ethnicity, and baseline glycosylated hemoglobin (HbA1c) level; duration of T2DM; duration of follow-up; prespecified outcomes or SAE measured; number of randomized participants allocated with each antidiabetic agent; and number of participants who experienced each outcome or SAEs.

We did not impose limitations on background medication. If there was no change in the use of a background medication, we did not include the particular background medication in the analyses. When trials switched from one drug to another or added a drug, we determined the group based on which treatment was administered for a longer duration. Separate drug dosages were not evaluated in the analyses. When results of one trial were published separately due to an extended study duration, we used the results from the extended duration. We prioritized published data when both published and unpublished data were available.

Cerebrovascular outcome or events consisted of ischemic stroke (ischemia, ischemic stroke, vertebrobasilar insufficiency, cerebrovascular insufficiency, and lacunar infarction) or TIA (including reversible ischemic neurologic deficit), hemorrhagic stroke (hemorrhage and cerebral hematoma), and unspecified stroke (cerebrovascular accident, cerebrovascular disorder, hemiplegia, and hemiparesis). We excluded cerebrovascular outcomes or events that could not be identified as ischemic stroke, TIA, hemorrhagic stroke, or unspecified stroke. Parts of a study duration that were not chosen for data extraction were also excluded. The Cochrane Collaboration tool for assessing the risk of bias was used to examine the quality of eligible randomized controlled trials (RCTs) [19]. Both the manuscript and protocol were reviewed for relevant information on quality (Supplementary Table 3 and Supplementary Fig. 1). The risk of bias was assessed by one author (J.S.K.) and cross-checked by a second author (S.W.O.).

Data synthesis and analysis

We undertook pairwise meta-analyses for within-study comparisons between one antidiabetic drug and placebo or other antidiabetic drugs using Mantel-Haenszel fixed-effects models [20]. Results were reported as relative risks (RRs) and corresponding 95% confidence intervals (CIs) [21]. Heterogeneity was measured with the I^2 statistic. Then, a network meta-analysis was constructed to combine the direct and indirect evidence. After generating network geometry, overall and local loop inconsistency tests were performed. Network forest plots, interval plot, and league table of effect size by treatment were used to display effect sizes. Treatments were ranked in order according to the superiority of their treatment effect based on the surface under the cumulative ranking curves (SUCRA) percentages. Lastly, we evaluated publication bias in the network

meta-analysis using a network funnel plot.

Subgroup analyses were conducted, stratified by stroke subtypes (ischemic stroke, hemorrhagic stroke, unspecified stroke, and TIA) and publication type (published by peer-reviewed journal or unpublished [Clinicaltrials.gov database-only]) (Supplementary Figs. 2-7). Subgroup analyses were also conducted according to age (<65 and ≥65 years), baseline HbA1c (<8.0 and ≥8.0), duration of type 2 diabetes mellitus (<10 and ≥10 years), and presence of low or high cardiovascular disease risk (history of renal impairment, heart failure, or old age) (Supplementary Figs. 8-15). All statistical analyses were performed using Stata version 16.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Fig. 1 shows the flow diagram of this study according to the PRISMA-NMA statement. The literature search identified 2,861 reports and 1,779 trials. After screening the titles and abstracts, 3,869 studies were excluded, because they did not meet the predetermined selection criteria. The full texts of 188 studies and 118 trials were reviewed. Finally, 79 RCTs were included in the final analysis. Supplementary Table 2 summarizes the characteristics of the included trials.

The RCTs focused on metformin, sulfonylureas, thiazolidinedione, DPP-4 inhibitors, SGLT-2 inhibitors, alpha-glucosidase inhibitors, GLP-1 agonists, and insulin. RCTs on insulin were excluded from the final analysis because no studies met the inclusion criteria. The mean patient age was 49 to 74 years. Baseline HbA1c levels were 6.8% to 9.5%, and the duration from diabetes diagnosis ranged from naïve to a mean of 18 years. Participants were diverse in terms of ethnicity (Caucasian, Asian, and multi-ethnicity). The results of the risk of bias assessment are presented in Supplementary Table 3 and Supplementary Fig. 1. Overall, 43 (54.4%) out of 79 RCTs provided details on randomization and allocation concealment procedures.

The final analysis included data from 79 RCTs reporting 4,625 (2.2%) total strokes in 206,387 patients. In the network plot of eligible comparisons (test of consistency; $P=0.953$), the most frequent studies compared placebo versus SGLT-2 inhibitor and placebo versus DPP-4 inhibitor (Fig. 2). An inconsistency test was performed to compare direct and indirect treatment in mixed treatment (Supplementary Table 4). A traditional pairwise and network meta-analyses for total stroke (Table 1) and corresponding network forest plot and interval plot (Supplementary Figs. 16 and 17, respectively) were used. In the pairwise meta-analysis, GLP-1 agonist use was associated with a lower risk of total stroke compared with placebo, based on data from 58,399 patients in 13 studies (855 events/38,921 subjects with placebo vs. 724 events/29,478 subjects with GLP-1 agonist; RR, –0.17; 95% CI, –0.27 to –0.07). In the network meta-analysis, only SGLT-2 inhibitor use was associated with a reduction in total stroke, compared with placebo (RR, 0.81; 95% CI, 0.67 to 0.98). There were no significant differences between the other antidiabetic drugs and placebo. Regarding the ranking of the most superior treatment, SGLT-2 inhibitor showed the leading effect (SUCRA 76.4%), followed by GLP-1 agonist (SUCRA 71.7%). The probability of SGLT-2 inhibitor being the best was 31.0%, and its probability to be at least the second best was 29.2% (Supplementary Fig. 18). Through the comparison-adjusted funnel plot, we confirmed these data were relatively symmetric, indicating rare small-study effects in the network (Supplementary Fig. 19).

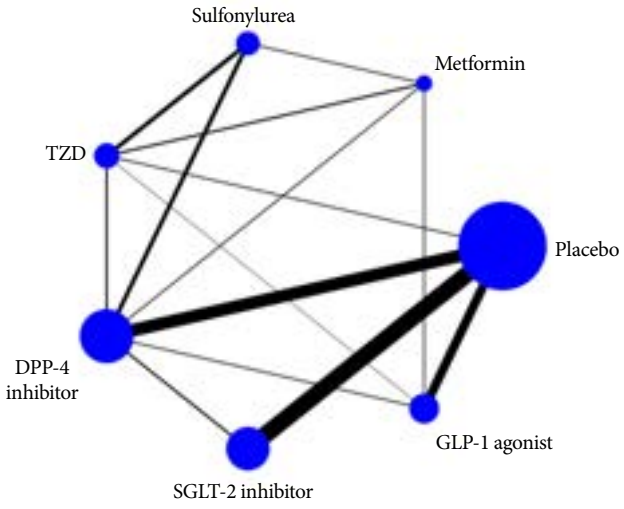

Fig. 2. Network geometry for total stroke in the network meta-analysis. Each circle node represents a drug included in the analysis and the size of circle is proportional to the number of patients randomly assigned to the drug. Each line corresponds to direct comparison between drugs and the width of line is proportional to the number of trials comparing each pair of treatments. The global test for inconsistency gives a *P* value of 0.953, giving no evidence of inconsistency. TZD, thiazolidinedione; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose cotransporter-2; GLP-1, glucagon-like peptide-1.

The results of the subgroup analyses stratified by stroke subtype (ischemic stroke [44 trials], hemorrhagic stroke [20 trials], unspecified stroke [37 trials], and TIA [26 trials]), and publication type (published [44 trials] and unpublished [35 trials] stud-

Table 1. Network and pairwise meta-analyses for total stroke of antihyperglycemic drugs

	Placebo	Metformin	Sulfonylurea	TZD	DPP-4 inhibitor	SGLT-2 inhibitor	GLP-1 agonist
Placebo		-	-	2 Studies I^2=0.0% −0.22 (−0.51 to 0.07)	19 Studies I^2=0.0% −0.04 (−0.17 to 0.08)	24 Studies I^2=64.3% −0.22 (−0.50 to 0.06)	13 Studies I^2=0.00% −0.17 (−0.27 to −0.07)[a]
Metformin	1.01 (0.55 to 1.85)		2 Studies I^2=19.0% 0.14 (−0.44 to 0.72)	3 Studies I^2=0.0% −0.23 (−0.88 to 0.41)	2 Studies I^2=0.0% −1.23 (−3.49 to 1.04)	-	2 Studies I^2=0.0% −0.40 (−2.33 to 1.52)
Sulfonylurea	1.05 (0.70 to 1.60)	1.04 (0.61 to 1.78)		6 Studies I^2=0.0% −0.02 (−0.53 to 0.49)	6 Studies I^2=0.0% −0.15 (−0.41 to 0.11)	-	-
TZD	0.86 (0.57 to 1.30)	0.85 (0.48 to 1.52)	0.82 (0.53 to 1.26)		3 Studies I^2=0.0% 0.27 (−1.65 to 2.20)	-	1 Study −0.42 (−4.34 to 3.51)
DPP-4 inhibitor	0.93 (0.74 to 1.16)	0.92 (0.50 to 1.66)	0.88 (0.60 to 1.30)	1.08 (0.70 to 1.65)		3 Studies I^2=0.0% −1.03 (−2.85 to 0.79)	2 Studies I^2=0.0% −1.25 (−3.73 to 1.24)
SGLT-2 inhibitor	0.81 (0.67 to 0.98)[a]	0.80 (0.42 to 1.51)	0.77 (0.48 to 1.21)	0.94 (0.60 to 1.48)	0.87 (0.65 to 1.16)		-
GLP-1 agonist	0.83 (0.68 to 1.02)	0.82 (0.44 to 1.54)	0.79 (0.50 to 1.25)	0.97 (0.61 to 1.52)	0.90 (0.67 to 1.20)	1.03 (0.78 to 1.35)	

Traditional pairwise (upper right side) and network (lower left side) meta-analytic results are depicted for total stroke. Outcome of meta-analysis is expressed as effect size with 95% confidence intervals in the case of pairwise meta-analysis and 95% credible intervals in the case of network meta-analysis. For the pairwise meta-analysis, effect size of less than 0 indicate that the drug located in the column is safer. For the network meta-analysis, relative risks of less than 1 indicate that the drug located in the row is safer.
TZD, thiazolidinedione; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose cotransporter-2; GLP-1, glucagon-like peptide-1.
[a]It results indicate statistical significance. The total number of traditional pairwise studies was 83 trials due to two three arms studies and one four arms study.

ies) are shown in Supplementary Figs. 2-7. There were no significant differences between antidiabetic drugs and placebo in these analyses. The results of the subgroup analyses stratified by age, baseline HbA1c, duration of diabetes, and cardiovascular risk status are shown in Supplementary Figs. 8-15. The subgroup analysis of subjects with baseline HbA1c ≥8.0% (51 trials) was in line with the full analysis, in which SGLT-2 inhibitor was associated with a lower risk than placebo (RR, 0.78; 95% CI, 0.62 to 0.97) (Supplementary Fig. 11). In the subgroup analysis of low cardiovascular disease risk (40 trials), GLP-1 agonist was associated with a lower risk of total stroke compared to placebo (RR, 0.82; 95% CI, 0.73 to 0.93) (Supplementary Fig. 14).

DISCUSSION

In this network meta-analysis, we identified 79 RCTs that reported cerebrovascular outcomes for antidiabetic drugs. Our study showed that SGLT-2 inhibitors and GLP-1 agonists, among glucose-lowering treatments, had benefits for total stroke compared to placebo, in patients with T2DM.

In a previous network meta-analysis comparing cardiovascular outcomes among new antidiabetic drug classes, SGLT-2 inhibitors did not reduce nonfatal stroke [5]. In a meta-analysis of five RCTs which directly compared SGLT-2 inhibitors to placebo, there was no significant effect on total stroke; a pooled analysis of three trials showed that SGLT-2 inhibitors were associated with a substantial reduction in hemorrhagic stroke alone [22]. However, in the present study, the network meta-analysis showed that SGLT-2 inhibitors had a significant preventive effect on total stroke, while the traditional pairwise meta-analysis of 24 RCTs comparing the effect of SGLT-2 inhibitors and placebo was not significant. Our study included more recent RCTs on SGLT-2 inhibitors, such as the Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) and Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trials, which may have contributed to this mixed result. In the SCORED trial, which enrolled 10,584 diabetic patients with chronic kidney disease, sotagliflozin showed a stroke-protective effect [23]. On the other hand, in the SOLOIST-WHF trial consisting of 1,222 diabetic patients with recent worsening health failure, there was a greater number of stroke events in the sotagliflozin group than in the placebo group [24]. Sotagliflozin is a SGLT-1 and SGLT-2 co-inhibitor, so the additive effects might affect cardiovascular outcome [25]. In the network meta-analysis after exclusion of studies on sotagliflozin, the association for SGLT-2 inhibitors remained statistically significant (Supplementary Table 5). Nevertheless, SGLT-1 versus SGLT-2 selectivity might have had an impact on the results of stroke prevention, and this effect may have contributed to the discrepancy between pairwise meta-analysis and network meta-analysis.

GLP-1 agonist use was associated with a lower risk of total stroke based on the pairwise meta-analysis in our study. This coincides with results from previous meta-analyses in which GLP-1 agonists were associated with a 15% lower risk of nonfatal stroke and a 16% lower risk of total stroke [26,27]. Our study also comprised newer trials such as the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) and SUSTAIN-6 trials, which focused on liraglutide and semaglutide, respectively [13,14]. These studies reported the superiority of GLP-1 agonists in terms of the cardiovascular composite outcome but not regarding stroke. In addition, the exploratory subanalysis of the Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND) trial which investigated the effect of dulaglutide on stroke were included in our study. In this trial, weekly dulaglutide reduced ischemic stroke (hazard ratio [HR], 0.75; 95% CI, 0.59 to 0.94; P=0.012), nonfatal stroke (HR, 0.76; 95% CI, 0.61 to 0.95; P=0.017), and disabling stroke (HR, 0.74; 95% CI, 0.56 to 0.99; P=0.042) [28].

The difference among glucose-lowering medications regarding the effect on stroke may be attributed to various drug mechanisms in terms of glucose variability [13] and hemodynamics. Diabetic patients are known to suffer from episodes of asymptomatic and symptomatic hypoglycemia, and one of the most common causes is intensive glycemic control [29]. Severe hypoglycemia can lead to brain injury via neuroinflammatory pathways and has been shown to increase stroke risk even in prediabetic patients [30]. Drugs with greater glucose variability may mechanistically increase the risk of stroke. Studies have shown that long-term glucose variability in T2DM is correlated with an increased risk of macrovascular complications; the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial substantiates this effect [31,32]. A meta-analysis by Lee et al. [33] showed the correlation between SGLT-2 inhibitors and GLP-1 agonists, and glucose variability. Both SGLT-2 inhibitors and GLP-1 agonists were significantly associated with a

reduction in the mean amplitude of glucose excursion and mean blood glucose levels and an increase in the percentage of time with euglycemic levels [33]. DPP-4 inhibitors also reduced glucose variability compared to other antidiabetic agents. However, comparison groups mostly included sulfonylureas [34]. In addition, the effects on neuroinflammation or endothelial dysfunction associated with atherosclerosis may also cause differences between drugs [8].

Subgroup analyses showed the SGLT-2 inhibitors use was associated with a reduced risk of total stroke in patients with HbA1c ≥8.0% [35,36]. In a trial consisting of diabetic and hypertensive patients with a mean HbA1c of 8.59, empagliflozin, compared to placebo, showed a lower number of cerebrovascular events [37]. SGLT-2 inhibitors are known to have a pleiotropic effect on hemodynamics. Possible mechanisms by which SGLT-2 inhibitors exert their cardiorenal benefits include reductions in insulin resistance, inflammation, oxidative stress [38], and the risk of albuminuria [39,40]. The high HbA1c group is more vulnerable in these respects, and for this reason, SGLT-2 inhibitor may have shown a more protective effect in this group [21]. Further investigation is warranted to explore the impact of SGLT-2 inhibitors on stroke in patients with relatively high HbA1c.

Our study also showed GLP-1 agonists were associated with a lower risk of total stroke in patients without cardiovascular disease risk such as renal impairment, heart failure, or old age. Compared to previous meta-analyses [25,26] our meta-analysis included more recent studies on semaglutide (Peptide Innovation for Early Diabetes Treatment [PIONEER] 1 and PIONEER 5) [41,42]. In the PIONEER 5 trial, in which patients had moderate renal impairment, there were two cerebrovascular events in the semaglutide group and none in the placebo group. However, the PIONEER 1 trial, which did not consist of a high cardiovascular disease risk population, showed no cerebrovascular events in the semaglutide group and three in the placebo group. Collectively, these results may have influenced the association observed in the low-risk subgroup. GLP-1 agonists have a positive effect on the reduction of weight, blood pressure, and serum lipids; in a meta-analysis that included longer duration studies, GLP-1 agonists showed neuroprotective effects [43]. However, in high-risk patients with advanced complications, these positive effects may not be sufficiently exhibited. Additionally, the issue of the differing effects of GLP-1 agonists on stroke based on the type of GLP-1 agonist (intravenous exenatide, oral semaglutide, etc.), partly owing to different half-lives, has been noted [5,44]. Therefore, future studies comparing stroke outcomes based on risk stratification and among drugs pertaining to the same class are necessary.

Several limitations should be considered when interpreting our results. First, the study included both prespecified cerebrovascular outcomes and cerebrovascular events reported as SAEs. This aspect added value in terms of the comprehensiveness of our study. However, it may have also contributed to study heterogeneity. Although there was no inconsistency in our study, the difference between SGLT-2 inhibitor and placebo became non-significant in the subgroup analysis of published trials only. Second, our study only included monotherapy without differentiating background and/or add-on therapy. Therefore, it is difficult to apply the results of this study when two or more drugs are used in combination.

In conclusion, the present meta-analysis demonstrates the benefits of SGLT-2 inhibitors and GLP-1 agonists for stroke prevention. Further studies with outcomes for different stroke subtypes, in varying clinical conditions, would provide more evidence to compare the effects of antidiabetic drugs on cerebrovascular outcomes.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2022.0421.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article, including the Esther Formula Medical Food R&D Center, was reported.

AUTHOR CONTRIBUTIONS

Conception or design: S.W.O.
Acquisition, analysis, or interpretation of data: J.S.K., G.L.
Drafting the work or revising: J.S.K., S.W.O.
Final approval of the manuscript: J.S.K., G.L., K.I.P., S.W.O.

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None

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Supplementary Table 1. Search strategy on MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL)

	Search strategy
MEDLINE	
#1	exp diabetes mellitus type 2/
#2	exp non insulin dependent diabetes mellitus/
#3	(NIDDM or T2DM or T2D or MODY).tw,ot
#4	((diabetes or diabetes mellitus or diabetic*) adj1 (type 2 or type II or type ii or noninsulin dependent or noninsulin dependent or adult onset or mature onset or late onset)).tw.
#5	or/1-4
#6	exp insulin, long acting/ or exp insulin detemir/ or exp insulin glargine/ or exp insulin aspart/ or exp insulin lispro/ or exp isophane insulin/
#7	((long acting or longer acting or intermediate acting) adj insulin*).tw,ot
#8	insulin adj1 (degludec or determir or glagine or zinc or aspart or lispro or isophane or lente or ultralente).tw
#9	exp biguanides/ or exp metformin/
#10	(biganid* or metformin*).tw,ot
#11	exp sulfonylurea compounds/ or exp acetohexamide/ or exp carbutamide/ or exp chlorpropamide/ or exp glibenclamide/ or exp gliclazide/ or exp glipizide/ or exp glyburide/ or exp tolazamide/ or exp tolbutamide/
#12	(sulfonylurea* or acetohexamide* or carbutamide* or chlorpropamide* or glibornuride* or glibenclamide* or gliclazide* or glimepiride* or glipizide* or gliquidone* or glyburide* or glycopyramide* or tolazamide* or tolbutamide*).tw,ot
#13	exp thiazolidinediones/
#14	(thiazolidinedion* or glitazone* or pioglitazon* or rosiglitazon* or rivoglitazone* or lobeglitazone*).tw,ot
#15	exp acarbose/
#16	(alpha-glucosidase inhibitor* or acarbose* or voglibose* or miglitol*).tw,ot
#17	exp dipeptidyl peptidase 4 inhibitors/
#18	(dipeptidyl-peptidase IV Inhibitor* or dipeptidyl-peptidase 4 Inhibitor* or ((DPP4 or DPP 4 or DPP IV) adj inhibitor*)).tw,ot
#19	(dipeptidyl peptidase 4 inhibitor* or alogliptin* or anagliptin* or gemigliptin* or omarigliptin* or sitagliptin* or vildagliptin* or saxagliptin* or tenegliptin* or vildagiptin* or linagliptin*).tw,ot
#20	(amylin analogue* or amylin derivative* or pramlintide).tw,ot
#21	(meglitinide* or repaglinide* or nateglinide* or mitiglinide*).tw,ot
#22	(sodium glucose cotransporter inhibitor* or sodium glucose co transporter inhibitor*).tw,ot
#23	(atigliflozin* or bexagliflozin* or canagliflozin* or dapagliflozin* or empagliflozin* or ertugliflozin* or ipragliflozin* or luseogliflozin* or sergliflozin* or remogliflozin* or sotagliflozin* or tofogliflozin*).tw,ot
#24	exp Glucagon-Like Peptide 1/
#25	(glucagon-like peptide 1 receptor inhibitor* or glucagon-like peptide 1 receptor agonist* or glucagon-like peptide 1 inhibitor* or glucagon-like peptide 1 agonist* or GLP-1 receptor inhibitor* or GLP-1 receptor agonist* or GLP-1 inhibitor* or GLP-1 agonist*).tw,ot
#26	(exenatide* or exendin 4 or liraglutide* or albiglutide* or lixisenatide* or dulaglutide* or semaglutide* or taspoglutide*).tw,ot
#27	or/6-26
#28	cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or vertebral artery dissection/
#29	(stroke or poststroke or post-stroke or cerebrovasc* or brain vasc* or cerebral vasc* or cva* or apoplex* or SAH).tw,ot
#30	((brain* or cerebr* or cerebell* or intracran* or intracerebral) adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus*)).tw,ot
#31	((brain* or cerebr* or cerebell* or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage* or hemorrhage* or haematoma* or hematoma* or bleed*)).tw,ot

(*Continued to the next page*)

Supplementary Table 1. Continued

	Search strategy
#32	exp hemiplegia/ or exp paresis/
#33	(hemipleg* or hemipar* or paresis or paretic).tw,ot
#34	exp Gait Disorders, Neurologic/
#35	or/28-34
#36	randomized controlled trial.pt.
#37	controlled clinical trial.pt.
#38	randomized.ab.
#39	placebo.ab.
#40	drug therapy.fs.
#41	randomly.ab.
#42	trial.ab.
#43	groups.ab.
#44	or/36-43
#45	exp animals/ not humans.sh.
#46	44 not 45
#47	5 and 27 and 35 and 46
EMBASE	
#1	('non insulin dependent diabetes mellitus'/exp OR 't2dm' OR 'adult onset diabetes' OR 'adult onset diabetes mellitus' OR 'diabetes mellitus type 2' OR 'diabetes mellitus type ii' OR 'diabetes mellitus, maturity onset' OR 'diabetes mellitus, non insulin dependent' OR 'diabetes mellitus, non-insulin-dependent' OR 'diabetes mellitus, type 2' OR 'diabetes mellitus, type ii' OR 'diabetes type 2' OR 'diabetes type ii' OR 'diabetes, adult onset' OR 'dm 2' OR 'insulin independent diabetes' OR 'insulin independent diabetes mellitus' OR 'ketosis resistant diabetes mellitus' OR 'maturity onset diabetes' OR 'maturity onset diabetes mellitus' OR 'maturity onset diabetes of the young' OR 'niddm' OR 'non insulin dependent diabetes' OR 'non insulin dependent diabetes mellitus' OR 'noninsulin dependent diabetes' OR 'noninsulin dependent diabetes mellitus' OR 'type 2 diabetes' OR 'type 2 diabetes mellitus' OR 'type ii diabetes') AND ('insulin derivative'/exp OR 'carbamoylinsulin' OR 'carbamylinsulin' OR 'carbonyl bis methionyl insulin' OR 'diacetoacetyl insulin' OR 'diacetylinsulin' OR 'diaminosuberoyl insulin' OR 'insulin analog' OR 'insulin analogue' OR 'insulin derivative' OR 'insulins' OR 'methylthiocarbamoylinsulin' OR 'methylthiocarbamylinsulin' OR 'mononitroinsulin' OR 'polyalanyl-insulin series' OR 'suberoyl insulin' OR 'succinyl insulin' OR 'triacetylinsulin' OR 'tricarbamylinsulin' OR 'metformin'/exp OR '1, 1 dimethylbiguanide' OR 'apophage' OR 'aron' OR 'benofomin' OR 'dabex' OR 'denkaform' OR 'deson' OR 'dextin' OR 'diabetase' OR 'diabetase s' OR 'diabetformin' OR 'diabetmin' OR 'diabetmin retard' OR 'diabetosan' OR 'diabex' OR 'diafat' OR 'diaformin' OR 'diaformina' OR 'diaformina lp' OR 'diametin' OR 'diamin' OR 'dianben' OR 'diformin' OR 'diformin retard' OR 'dimefor' OR 'dimethylbiguanide' OR 'dimethyldiguanide' OR 'dmgg' OR 'dybis' OR 'eraphage' OR 'espa-formin' OR 'euform retard' OR 'fluamine' OR 'flumamine' OR 'fornidd' OR 'fortamet' OR 'glafornil' OR 'glibudon' OR 'glifage' OR 'gliguanid' OR 'glucaminol' OR 'glucofage' OR 'glucofago' OR 'glucoform' OR 'glucoformin' OR 'glucohexal' OR 'glucoless' OR 'glucomet' OR 'glucomin' OR 'glucomine' OR 'gluconil' OR 'glucophage' OR 'glucophage forte' OR 'glucophage retard' OR 'glucophage sr' OR 'glucophage xr' OR 'glucophage xr extended release' OR 'glucophage-mite' OR 'glucostop' OR 'glucotika' OR 'gludepatic' OR 'glufor' OR 'gluformin' OR 'glukophage' OR 'glumeformin' OR 'glumet' OR 'glumetza' OR 'glupa' OR 'glustress' OR 'glyciphage' OR 'glycomet' OR 'glycon' OR 'glycoran' OR 'glyformin' OR 'glymet' OR 'haurymellin' OR 'hipoglucin' OR 'i-max' OR 'islotin' OR 'juformin' OR 'la 6023' OR 'la6023' OR 'lyomet (drug)' OR 'maformin' OR 'meglucon' OR 'meguan' OR 'melbin' OR 'melformin' OR 'mellittin' OR 'merckformin' OR 'mescorit' OR 'metaformin' OR 'metfogamma' OR 'metfoliquid geriasan' OR 'metforal' OR 'metformax' OR 'metformin' OR 'metformin hydrochloride' OR 'metformina' OR 'metformine' OR 'metformine hcl' OR 'methformin' OR 'metiguanide' OR 'metomin' OR 'metphormin' OR 'miformin' OR 'n` dimethylguanylguanide' OR 'n` dimethylguanylguanidine' OR 'n`, n` dimethyldiguanide' OR 'n, n dimethyl biguanidine' OR 'n, n dimethylbiguanide' OR 'n, n dimethylbiguanide retard' OR 'n, n dimethylbiguanidine' OR 'n, n dimethyldiguanide' OR 'n, n dimethylguanylguanidine' OR 'neoform' OR 'nndg' OR 'reglus-500' OR 'riomet' OR 'risidon' OR 'siamformet' OR 'siofor' OR 'thiabet' OR 'vimetrol' OR 'walaphage' OR 'sulfonylurea derivative'/exp OR 'sulfonurea derivative' OR 'sulfonylurea compounds' OR 'sulfonylurea derivative' OR 'sulfonylurea series' OR 'sulfonylureas, first generation' OR 'sulfonylureas, second generation' OR 'sulphonylurea derivative' OR

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Supplementary Table 1. Continued

	Search strategy
	'glitazone derivative'/exp OR 'glitazone' OR 'glitazone compound' OR 'glitazone derivative' OR 'glitazones' OR 'thiazolidinedione antidiabetic' OR 'thiazolidinedione antidiabetic agent' OR 'thiazolidinedione antidiabetic drug' OR 'acarbose'/exp OR 'acarbosa' OR 'acarbose' OR 'acarbosio' OR 'acarphage' OR 'adeksa' OR 'ag 5421' OR 'ag5421' OR 'aglucose' OR 'alpha ghi' OR 'bay g 5421' OR 'bay g5421' OR 'eclid' OR 'glibose' OR 'glicobase' OR 'glucar' OR 'glucarb' OR 'glucobay' OR 'gluconase' OR 'glucor' OR 'glumida' OR 'prandase' OR 'precose' OR 'rebose' OR 'symrose' OR 'dipeptidyl peptidase iv inhibitor'/exp OR 'dpp 4 inhibitor' OR 'dpp iv inhibitor' OR 'dipeptidyl peptidase 4 inhibitor' OR 'dipeptidyl peptidase iv inhibitor' OR 'dipeptidyl peptidase iv inhibitors' OR 'dipeptidyl-peptidase iv inhibitors' OR 'dipeptidylpeptidase 4 inhibitor' OR 'dipeptidylpeptidase iv inhibitor' OR 'gliptin' OR 'gliptins' OR 'meglitinide'/exp OR '4 [2 (5 chloro 2 methoxybenzamido) ethyl] benzoic acid' OR 'hb 699' OR 'hb699' OR 'meglitinide' OR 'n (4 carboxyphenethyl) 5 chloro 2 methoxybenzamide' OR 'sodium glucose cotransporter 2 inhibitor'/exp OR 'sglt2 inhibitor' OR 'sglt2 inhibitors' OR 'gliflozin' OR 'gliflozin derivative' OR 'gliflozins' OR 'sodium dependent glucose cotransporter 2 inhibitor' OR 'sodium glucose co-transporter 2 inhibitor' OR 'sodium glucose cotransporter 2 inhibitor' OR 'sodium-glucose transporter 2 inhibitors' OR 'glucagon like peptide 1 receptor agonist'/exp OR 'glp 1 agonist' OR 'glp 1 receptor agonist' OR 'glucagon like peptide 1 agonist' OR 'glucagon like peptide 1 receptor agonist' OR 'glucagon like peptide 1 receptor stimulating agent' OR 'long acting glp 1 agonist' OR 'long acting glp 1 receptor agonist' OR 'long acting glucagon like peptide 1 agonist' OR 'long acting glucagon like peptide 1 receptor agonist' OR 'amylin derivative'/exp OR 'amylin analog' OR 'amylin derivative' OR 'amylinomimetic agent' OR 'amylinomimetic agents') AND ('cerebrovascular disease'/exp OR 'brain angiopathy' OR 'brain circulation failure' OR 'brain vascular disease' OR 'brain vasculopathy' OR 'cerebral small vessel disease' OR 'cerebral small vessel diseases' OR 'cerebral vascular disease' OR 'cerebral vascular disorder' OR 'cerebral vascular disturbance' OR 'cerebral vascular lesion' OR 'cerebral vasculopathy' OR 'cerebrovascular damage' OR 'cerebrovascular disease' OR 'cerebrovascular disorder' OR 'cerebrovascular disorders' OR 'cerebrovascular lesion' OR 'cerebrovascular pathology' OR 'cerebrovascular syndrome') AND ('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled')
CENTRAL	
#1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#2	NIDDM or T2DM or T2D or MODY:ti,ab,kw (Word variations have been searched)
#3	non insulin* depend* or noninsulin* depend* or noninsulin?depend* or noninsulin?depend*:ti,ab,kw (Word variations have been searched)
#4	#1 or #2 or #3
#5	MeSH descriptor: [Metformin] explode all trees
#6	MeSH descriptor: [Insulins] explode all trees
#7	MeSH descriptor: [Sulfonylurea Compounds] explode all trees
#8	MeSH descriptor: [Thiazolidinediones] explode all trees
#9	MeSH descriptor: [Acarbose] explode all trees
#10	MeSH descriptor: [Dipeptidyl-Peptidase IV Inhibitors] explode all trees
#11	MeSH descriptor: [Sodium-Glucose Transporter 2] explode all trees
#12	MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees
#13	MeSH descriptor: [Islet Amyloid Polypeptide] explode all trees
#14	(insulin degludec or insulin determir or insulin glagine or insulin aspart or insulin zinc or insulin lispro or insulin isophane or insulin lente or insulin ultralente):ti,ab,kw (Word variations have been searched)
#15	long acting insulin or longer acting insulin or intermediate acting insulin:ti,ab,kw (Word variations have been searched)
#16	biganid* or metformin*:ti,ab,kw (Word variations have been searched)
#17	sulfonylurea* or acetohexamide* or carbutamide* or chlorpropamide* or glibenclamide* or gliclazide* or glimepiride* or glipizide* or gliquidone* or glyburide* or tolazamide* or tolbutamide*:ti,ab,kw (Word variations have been searched)
#18	thiazolidinedion* or glitazone* or pioglitazon* or rosiglitazon* or lobeglitazone*:ti,ab,kw (Word variations have been searched)
#19	alpha-glucosidase inhibitor* or acarbose* or miglitol*:ti,ab,kw (Word variations have been searched)

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Supplementary Table 1. Continued

	Search strategy
#20	dipeptidyl peptidase 4 inhibitor* or sitagliptin* or vildagliptin* or saxagliptin* or linagliptin* or gemigliptin* or DPP-4 or DPP-IV or DPP4 or DPPIV:ti,ab,kw (Word variations have been searched)
#21	meglitinide* or repaglinide* or nateglinide* or mitiglinide*:ti,ab,kw (Word variations have been searched)
#22	sodium glucose cotransporter inhibitor* or sodium glucose co transporter inhibitor* or atigliflozin* or bexagliflozin* or canagliflozin* or dapagliflozin* or empagliflozin* or ertugliflozin* or ipragliflozin* or luseogliflozin* or sergliflozin* or remogliflozin* or sotagliflozin$ or tofogliflozin*:ti,ab,kw (Word variations have been searched)
#23	exenatide* or liraglutide* or albiglutide* or taspoglutide* or lixisenatide* or dulaglutide* or semaglutide*:ti,ab,kw (Word variations have been searched)
#24	or/#5-#23
#25	MeSH descriptor: [Stroke] explode all trees
#26	MeSH descriptor: [Ischemic Attack, Transient] explode all trees
#27	MeSH descriptor: [Brain Infarction] explode all trees
#28	MeSH descriptor: [Intracranial Hemorrhages] explode all trees
#29	stroke* or infarction* or hemorrhage* or cerebrovasc* or SAH:ti,ab,kw (Word variations have been searched)
#30	or/#25-#29
#31	#4 and #24 and #30
#32	#31 and trials

Supplementary Table 2. Main characteristics of included trials

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM
NCT01032629	Zhou et al. (2019) [1]	III	CANVAS of the CANVAS Program)	4,330	52	Canagliflozin 100 or 300 mg	PLB	Variable	Multinational	62.4±8.0	66.1%	8.2±0.9	13.4±7.5
NCT01989754	Zhou et al. (2019) [1]	IV	CANVAS-R of the CANVAS Program	5,813	78	Canagliflozin up to 300 mg	PLB	Variable	Multinational	64.0±8.4	62.8%	8.3±1.0	13.7±7.9
NCT01730534	Wiviott et al. (2019) [2]	III	DECLARE–TIMI 58	17,160	Median 4.2 yr	Dapagliflozin 10 mg qd	PLB	Variable	Multinational	DAPA: 63.9±6.8 PLB: 64.0±6.8	DAPA: 63.1% PLB: 3,251 (62.1)	DAPA: 8.3±1.2 PLB: 8.3±1.2	eGFR ≥90 10.9±7.2
NCT01897532	Rosenstock et al. (2019) [3]	IV	CARMELINA	6,991	Median 2.2 yr	Linagliptin 5 mg	PLB	Except DPP-4, GLP-1, and SGLT-2	Multinational	LINA: 66.1±9.1 PLB: 65.6±9.1	LINA: 2,148 (61.5) PLB: 2,242 (64.3)	LINA: 7.9±1.0 PLB: 8.0±1.0	LINA: 15.0±9.6 PLB: 14.5±9.3
NCT01243424	Rosenstock et al. (2019) [4]	III	CAROLINA	6,042	Median 6.3 yr	Linagliptin 5 mg qd	Glimepiride 1–4 mg qd	Naïve, SU, or -glinide as monotherapy or in a dual combination with MET or α-glucosidase inhibitor	Multinational	LINA: 63.9±9.5 GLIME: 64.2±9.5	LINA: 1,838 (60.8) GLIME: 1,781 (59.2)	LINA: 7.2±0.6 GLIME: 7.2±0.6	Median LINA: 6.3 GLIME: 6.2
NCT02065791	Mahaffey et al. (2019) [5]		CREDENCE	4,401	Median 2.62 yr	Canagliflozin 100 mg qd	PLB	Variable	Multinational	CANA: 62.9±9.2 PLB: 63.2±9.2	CANA: 65.4% PLB: 66.7%	CANA: 8.3±1.3 PLB: 8.3±1.3	CANA: 15.5±8.7 PLB: 16.0±8.6
NCT02692716	Husain et al. (2019) [6]	III	PIONEER 6	3,183	Median 15.9 mo	Semaglutide up to 14 mg qd	PLB	Variable	Multinational	SEMA: 66±7 PLB: 66±7	SEMA: 68.1% PLB: 500 68.6%	SEMA: 8.2±1.6 PLB: 8.2±1.6	SEMA: 14.7±8.5 PLB: 15.1±8.5
NCT00894868	McMurray et al. (2018) [7]	IV	VIVIDD	254	52	Vildagliptin 50 mg bid (qd if concomitant use of SU)	PLB	Variable	Multinational	VILDA: 62.9±8.5 PLB: 63.4±10.2	VILDA: 77.3% PLB: 76.2%	VILDA: 7.8±0.95 PLB: 7.8±1.07	VILDA: 9.5±8.1 PLB: 9.1±7.8
NCT02465515	Hernandez et al. (2018) [8]		Harmony	9,463	Median 1.6 yr	Albiglutide 30–50 mg qw	PLB		Multinational	ALBI: 64.1±8.7 PLB: 64.2±8.7	ALBI: 3,304 (70) PLB: 3,265 (69)	ALBI: 8.76±1.5 PLB: 8.72±1.5	ALBI: 14.1±8.6 PLB: 14.2±8.9
NCT01144338	Holman et al. (2017) [9]	III	EXSCEL	14,752	Median 3.2 yr	Exenatide 2 mg qw	PLB	Variable	Multinational	EXEN: 62.0 PLB: 62.0	EXEN: 62.0% PLB: 62.0%	EXEN: 8.0 PLB: 8.0	EXEN: 12.0 PLB: 12.0
NCT01703208	Gantz et al. (2017) [10]	III		4,202	Median 96	Omarigliptin 25 mg qw	PLB	Variable	Multicenter	OMARI: 63.7±8.5 PLB: 63.6±8.5	OMARI: 1,461 (69.6) PLB: 1,487 (70.7)	OMARI: 8.0±0.9 PLB: 8.0±0.9	OMARI: 12.0±7.6 PLB: 12.1±8.0
NCT01179048	Marso et al. (2016) [11]	III	LEADER	9,340	Median 3.8 yr	Liraglutide	PLB	Variable	Multinational	≥60 yr LIRA: 46.8±13.5 PLB: 52.8±14.9	LIRA: 425 (14.1) PLB: 485 (16.2)	>8.3 LIRA: 319±13.7 PLB: 361±16.1	>11 yr LIRA: 340±13.9 PLB: 376±15.3

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM
NCT01720446	Marso et al. (2016) [12]	III	SUSTAIN-6	3,297	109 (median 2.1 yr)	Semaglutide 0.5 or 1.0 mg qw	PLB	Variable	Multinational	SEMA 0.5 mg: 64.6±7.3 SEMA 1.0 mg: 64.7±7.1 PLB 0.5 mg: 64.8±7.6 PLB 1.0 mg: 64.4±7.5	SEMA: 1,013 PLB: 989	SEMA 0.5 mg: 8.7±1.4 SEMA 1.0 mg: 8.7±1.5 PLB: 8.7±1.5	SEMA 0.5 mg: 14.3±8.2 SEMA 1.0 mg: 14.1±8.2 PLB 0.5 mg: 14.0±8.5 PLB 1.0 mg: 13.2±7.4
NCT01131676	Zinman et al. (2015) [13]	III	EMPA-REG OUTCOME	7,028	Median 3.1 yr	Empagliflozin 10 or 25 mg qd	PLB	Variable	Multinational	EMPA: 63.1±8.6 PLB: 63.2±8.8	EMPA: 3,336 (71.2) PLB: 1,680 (72.0)	EMPA: 8.07±0.85 PLB: 8.08±0.84	>10 yr EMPA: 2,672±57.0 PLB: 1,339±57.4
NCT01147250	Pfeffer et al. (2015) [14]	III	ELIXA	6,068	Median 25 mo	Lixisenatide upto 20 μg	PLB		Multinational	LIXI: 59.9±9.7 PLB: 60.6±9.6	LIXI: 69.6% PLB: 69.1%	LIXI: 7.7±1.3 PLB: 7.6±1.3	LIXI: 9.2±8.2 PLB: 9.4±8.3
NCT00790205	Green et al. (2015) [15]	III	TECOS	14,735	Median 3.0 yr	Sitagliptin 100 mg qd	PLB	Variable	Multinational	SITA: 65.4±7.9 PLB: 65.5±8.0	SITA: 70.9% PLB: 70.5%	SITA: 7.2±0.5 PLB: 7.2±0.5	Mean SITA: 11.6±8.1 PLB: 11.6±8.1
NCT01042977	Leiter et al. (2014) [16]	III		964	24	Dapagliflozin 10 mg qd	PLB	Variable	Multinational	DAPA: 63.9±7.6 PLB: 63.6±7.0	DAPA: 66.9% PLB: 67.0%	DAPA: 8.0±0.8 PLB: 8.1±0.8	DAPA: 13.5±8.2 PLB: 13.0±8.4
NCT01294423	Kaku et al. (2014) [17]	III		261	24	Dapagliflozin 5 or 10 mg	PLB		Multicenter	DAPA5: 58.6±10.4 DAPA10: 57.5±9.3 PLB: 60.4±9.7	DAPA5: 50 (58.1) DAPA10: 53 (60.2) PLB: 52 (59.8)	DAPA5: 7.50±0.72 DAPA10: 7.46±0.61 PLB: 7.50±0.63	DAPA5: 4.59±5.56 DAPA10: 4.93±4.52 PLB: 5.29±6.17
NCT00968708	White et al. (2013) [18]	III	EXAMINE	5,380	Median 18 mo	Alogliptin 6.25, 12.5, or 25 mg	PLB	Variable	Multinational	Median ALO: 61.0 PLB: 61.0	ALO: 1,828 (67.7) PLB: 1,823 (68.0)	ALO: 8.0±1.1 PLB: 8.0±1.1	ALO: 7.1 PLB: 7.3
NCT01107886	Scirica et al. (2013) [19]	IV	SAVOR-TIMI 53	16,492	Median 2.1 yr	Saxagliptin 2.5 or 5.0 mg	PLB	Variable	Multinational	SAXA: 65.1±8.5 PLB: 65.0±8.6	SAXA: 66.6% PLB: 67.3%	SAXA: 8.0±1.4 PLB: 8.0±1.4	SAXA: 10.3 PLB: 10.3
NCT00513630	Hong et al. (2013) [20]	IV	SPREAD-DIMCAD	304	Median 5 yr	Glipizide (mean dose 28.3±3.9 mg)	Metformin (mean dose 1.4±0.2 mg)		Multicenter	GLIP: 63.8±9.4 MET: 62.8±8.5	GLIP: 114 (77.0) MET: 122 (78.2)	GLIP: 7.6±1.7 MET: 7.6±1.7	GLIP: 3.0±5.1 MET: 2.9±4.8
NCT00744926	Raz et al. (2012) [21]	III	T-emerge 1	373	24	Taspoglutide 10 or 20 mg qw	PLB		Multinational	TASPO10: 53.4±9.6 TASPO20: 55.0±10.4 PLB: 55.8±8.5	TASPO10: 41 (37) TASPO20: 46 (36) PLB: 43 (37)	TASPO10: 7.5±1.0 TASPO20: 7.7±1.0 PLB: 7.6±1.0	TASPO10: 2.8±2.9 TASPO20: 2.1±2.4 PLB: 2.3±1.9
NCT00116831	Gerstein et al. (2010) [22]	III	APPROACH	672	18 mo	Rosiglitazone upto 8 mg qd	Glipizide upto 15 mg qd		Multinational	ROSI: 61.8±8.4 GLIP: 60.2±9.0	ROSI: 233 (70.0) GLIP: 223 (65.8)	ROSI: 7.1±0.8 GLIP: 7.2±0.9	Median ROSI: 5.0 GLIP: 4.6

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM
NCT00484198	Chou et al. (2012) [23]	III		1,912	26	Rivoglitazone 1.0 or 1.5 mg or pioglitazone 45 mg qd	PLB		Multinational	RIVO1.0: 55.0±10.51 RIVO1.5: 55.1±10.59 PIO45: 55.0±10.84 PLB: 55.4±12.32	RIVO1.0: 132 (48.2) RIVO1.5: 382 (50.9) PIO45: 398 (53.0) PLB: 67 (48.9)	RIVO1.0: 7.7±0.53 RIVO1.5: 7.7±0.57 PIO45: 7.7±0.58 PLB: 7.7±0.54	RIVO1.0: 5.0±5.26 RIVO1.5: 4.3±4.40 PIO45: 4.4±4.99 PLB: 4.9±6.13
NCT00740051	Barnett et al. (2012) [24]	III		227	52	Linagliptin 5 mg qd	PLB/ Glimepiride 1–4 mg qd		Multinational	LINA: 56.4±10.6 PLBGLIME: 56.7±9.7	LINA: 55 (36.4) PLBGLIME: 33 (43.4)	LINA: 8.1±1.0 PLBGLIME: 8.1±0.9	>1–5 yr LINA: 75±51.0 PLBGLIME: 40±54.8
NCT00521742	Giles et al. (2010) [25]	III		300	52	Pioglitazone 15 mg	Glyburide 2.5 mg	With or without MET	Multicenter	64	56%	PIO: 8.6±1.5 GLYB: 8.3±1.4	
NCT00494312	Tolman et al. (2009) [26]	IV		2,120	3 yr	Pioglitazone upto 45 mg	Glibenclamide upto 15 mg	With or without MET	Multicenter	Median PIO: 54 GLIBE: 55	PIO: 601 (57.2) GLIBE: 581 (55.5)	PIO: 9.5±2.0 GLIBE: 9.5±2.0	PIO: 305±301 wk GLIBE: 292±280 wk
NCT00174993	Wilcox et al. (2007) [27]	III	PROactive	5,238	Mean 34.5 mo	Pioglitazone 15–45 mg	PLB	Variable	Multinational	No previous stroke: 61.6±7.7 Previous stroke: 62.3±7.5	No previous stroke: 2,867 (67) Previous stroke: 596 (61)	No previous stroke: 8.1±1.4 Previous stroke: 8.1±1.4	Median no previous stroke: 8.0 Previous stroke: 9.0
NCT00279045	Kahn et al. (2006) [28]	III	ADOPT	4,360	Median 4.0 yr	Rosiglitazone upto 4 mg bid	Metformin upto 1 g bid; Glyburide upto 7.5 mg bid		Multinational	ROSI: 56.3±10.0 MET: 57.9±9.9 GLYB: 56.4±10.2	ROSI: 811 (55.7) MET: 864 (59.4) GLYB: 836 (58.0)	ROSI: 7.36±0.93 MET: 7.36±0.93 GLYB: 7.35±0.92	<1 yr ROSI: 651±44.6 MET: 673±46.3 GLYB: 637±44.2
NCT00087516	Aschner et al. (2006) [29]	III		741	24 (+80)[a]	Sitagliptin 100 or 200 mg qd	PLB		Multinational	SITA100: 53.4±9.5 SITA200: 54.9±10.1 PLB: 54.3±10.1	SITA100: 136 (57.1) SITA200: 117 (46.8) PLB: 130 (51.4)	SITA100: 8.01±0.88 SITA200: 8.08±0.94 PLB: 8.03±0.82	4.4
NCT00707993		III		441	52	Glipizide 5 mg qd	Alogliptin 25 mg qd		Multicenter	GLIP: 69.8±4.07 ALO: 70.1±4.42	GLIP: 198 (44.9) ALO: 102 (45.9)		GLIP: 5.94±6.276 ALO: 6.25±6.285
NCT01164501	Barnett et al. (2014) [30]	III		741	52	Empagliflozin 10 or 20 mg	PLB		Multinational	CKD III: EMPA25: 64.6±8.9 PLB: 65.1±8.2	CKD III EMPA25: 107 (57.2) PLB: 106 (56.7)	CKD III EMPA25: 8.02±0.84 PLB: 8.09±0.80	CKD III >10 yr EMPA25: 129±69.0 PLB: 123±65.8
NCT00800683		III		133	52	Linagliptin 5 mg	PLB	Insulin with or without SU	Multinational	LINA: 64.0±10.9 PLB: 64.9±9.6	LINA: 45 (66.2) PLB: 35 (53.8)	LINA: 8.2±1.1 PLB: 8.2±0.9	

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM
NCT01106651	Bode et al. (2015) [31]	III		716	104	Canagliflozin 100 or 300 mg	PLB	Variable	Multicenter	CANA100: 64.3±6.46 CANA300: 63.4±5.99 PLB: 63.2±.21	CANA100: 124 (51.5) CANA300: 129 (54.7) PLB: 143 (60.3)	CANA100: 7.8±0.8 CANA300: 7.7±0.8 PLB: 7.8±0.8	CANA100: 12.3±7.8 CANA300: 11.3±7.2 PLB: 11.4±7.3
NCT02025907		IV		218	26	Canagliflozin 100–300 mg	PLB	MET and sitagliptin	Multicenter	CANA: 57.4±9.28 PLB: 57.5±10.14	CANA: 66 (61.7) PLB: 55 (51.9)	8.5±0.8	9.9±5.7
NCT01064414		III		272	52	Canagliflozin 100 or 300 mg	PLB		Multicenter	CANA100: 69.5±8.2 CANA300: 67.9±8.24 PLB: 68.2±8.4	CANA100: 58 (64.4) CANA300: 48 (53.9) PLB: 57 (63.3)		
NCT01106625		III	CANTATA-MSU	469	52	Canagliflozin 100 or 300 mg	PLB	MET and SU	Multicenter	CANA100: 57.3±10.47 CANA300: 56±8.95 PLB: 56.7±8.36	CANA100: 76 (48.4) CANA300: 87 (55.8) PLB: 76 (48.7)		
NCT01081834	Stenlof et al. (2013) [32]	III	CANTATA-M	678	52	Canagliflozin 100 or 300 mg	PLB/Sitagliptin 100 mg		Multicenter	CANA100: 55.1±10.83 CANA300: 55.3±10.17 PLBSITA: 55.7±10.88	CANA100: 81 (41.5) CANA300: 89 (45.2) PLBSITA: 88 (45.8)	CANA100: 8.1±1.0 CANA300: 8.0±1.0 PLBSITA: 8.0±1.0	CANA100: 4.5±4.4 CANA300: 4.3±4.7 PLBSITA: 4.2±4.1
NCT00094757		III		521	54	Sitagliptin 100 or 200 mg	PLB/Pioglitazone 30 mg qd		Multicenter	SITA100: 54.5±10.0 SITA300: 55.4±9.2 PLBPIO: 55.5±10.1	SITA100: 110 (53.7) SITA300: 104 (50.5) PLBPIO: 69 (62.7)	SITA100: 8.0±0.8 SITA300: 8.1±0.9 PLBPIO: 8.0±0.9	
NCT02413398	Fioretto et al. (2018) [33]	III	DERIVE	321	24	Dapagliflozin 10 mg	PLB	Variable	Multinational	DAPA: 65.3 PLB: 66.2	DAPA: 91 (56.9) PLB: 91 (56.5)	DAPA: 8.33±1.08 PLB: 8.03±1.08	DAPA: 14.3±8.1 PLB: 14.5±8.3
NCT01095653	Ji et al. (2014) [34]	III		393	24	Dapagliflozin 5 or 10 mg	PLB		Multinational	DAPA5: 53.0±11.07 DAPA10: 51.2±9.89 PLB: 49.9±10.87	DAPA5: 84 (65.6) DAPA10: 86 (64.7) PLB: 87 (65.9)	DAPA5: 8.14±0.74 DAPA10: 8.28±0.95 PLB: 8.35±0.95	DAPA5: 1.15±2.3 DAPA10: 1.67±2.8 PLB: 1.30±2.0
NCT00663260	Kohan et al. (2014) [35]	II/III		252	104	Dapagliflozin 5 or 10 mg	PLB	Variable	Multinational	DAPA5: 66±8.9 DAPA10: 68±7.7 PLB: 67±8.6	DAPA5: 55 (66.3) DAPA10: 56 (65.9) PLB: 53 (63.1)	DAPA5: 8.30±1.04 DAPA10: 8.22±0.98 PLB: 8.53±1.28	DAPA5: 16.9±9.0 DAPA10: 18.2±10.1 PLB: 15.7±9.5

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM
NCT01031680	Cefalu et al. (2015) [36]	III		922	52	Dapagliflozin 10 mg	PLB	Variable excluding rosiglitazone	Multinational	DAPA: 62.8±7.0 PLB: 63.0±7.7	DAPA: 67.9% PLB: 68.6%	DAPA: 8.18±0.84 PLB: 8.08±0.80	DAPA: 12.6±8.7 PLB: 12.3±8.2
NCT02182830	Ferdinand et al. (2019) [37]	III		166	24	Empagliflozin 10–25 mg qd	PLB	Variable	Multicenter	EMPA: 56.5±9.3 PLB: 57.2±9.3	EMPA: 43 (55.1) PLB: 36 (50.0)	EMPA: 8.66±0.11 PLB: 8.51±0.13	EMPA: 9.3±6.2 PLB: 9.3±7.9
NCT01986855	Grunberger et al. (2018) [38]	III	VERTIS RENAL	468	52	Ertugliflozin 5 or 15 mg qd	PLB	Variable (except MET, rosiglitazone, and other SGLT-2)	Multinational	ERTU5: 66.7±8.3 ERTU15: 67.5±8.5 PLB: 67.5±8.9	ERTU5: 84 (53.2) ERTU15: 75 (48.4) PLB: 72 (46.8)	ERTU5: 8.2±1.0 ERTU15: 8.2±0.9 PLB: 8.1±0.9	ERTU5: 14.9±9.0 ERTU15: 14.5±8.5 PLB: 13.1±8.1
NCT00676338	Russell-Jones et al. (2012) [39]	III	DURATION-4	820	26	Exenatide 2 mg qw	Metformin 2,000 mg qd; Pioglitazone 45 mg qd; Sitagliptin 100 mg qd		Multinational	EXEN: 54±11 MET: 54±11 PIO: 55±11 SITA: 52±11	EXEN: 139 (56.0) MET: 154 (62.6) PIO: 97 (59.5) SITA: 94 (57.7)	EXEN: 8.5±1.2 MET: 8.6±1.2 PIO: 8.5±1.2 SITA: 8.5±1.3	EXEN: 2.7±3.2 MET: 2.6±3.6 PIO: 2.7±3.7 SITA: 2.7±3.7
NCT01087502	Laakso et al. (2015) [40]	III		235	52	Linagliptin 5 mg qd	PLB/ Glimepiride 1–4 mg qd		Multinational	LINA: 67.3±9.2 PLBGLIME: 65.9±9.4	LINA: 70 (61.9) PLBGLIME: 79 (64.8)	LINA: 8.08±0.89 PLBGLIME: 8.03±0.94	
NCT00601250		III		701	24	Linagliptin 5 mg qd	PLB		Multinational	LINA: 56.5±10.1 PLB: 56.6±10.9	LINA: 278 (53.2) PLB: 101 (57.1)	LINA: 8.09±0.86 PLB: 8.02±0.88	
NCT01084005	Barnett et al. (2013) [41]	III		241	24	Linagliptin 5 mg qd	PLB	Variable	Multinational	LINA: 74.9±4.4 PLB: 74.9±4.2	LINA: 116 (71.6) PLB: 49 (62.0)	LINA: 7.8±0.8 PLB: 7.7±0.7	>10 yr LINA: 89±55.6 PLB: 42±53.8
NCT01620489	Davies et al. (2016) [42]	III	LIRA-RENAL	279	26	Liraglutide 1.8 mg qd	PLB	Variable	Multinational	LIRA: 68.0±8.3 PLB: 66.3±8.0	LIRA: 75 (53.6) PLB: 65 (47.4)	LIRA: 8.08±0.792 PLB: 8.00±0.853	LIRA: 15.9±8.9 PLB: 14.2±7.5
NCT01798706	Meneilly et al. (2017) [43]	III	GetGoal-O	350	24	Lixisenatide 20 μg	PLB	Variable	Multinational	LIXI: 74.0±4.0 PLB: 74.4±3.8	LIXI: 92 (52.3) PLB: 90 (51.7)	LIXI: 8.1±0.7 PLB: 8.1±0.7	LIXI: 13.6±7.3 PLB: 14.6±7.9
NCT01126580	Umpierrez et al. (2014) [44]	III	AWARD-3	807	52	Dulaglutide 0.75 or 1.5 mg qw	Metformin upto 2,000 mg qd		Multinational	DULA0.75: 56±11 DULA1.5: 56±10 MET: 55±10	DULA0.75: 118 (44) DULA1.5: 114 (42) MET: 121 (45)	DULA0.75: 7.6±0.9 DULA1.5: 7.6±0.9 MET: 7.6±0.8	DULA0.75: 3±2 DULA1.5: 3±2 MET: 3±2
NCT01704261	Lee et al. (2017) [45]	III		307	24	Omarigliptin 25 mg qw	PLB	MET ≥1,500 mg qd and glimepiride or another SU	Multinational	OMARI: 57.2±8.4 PLB: 58.4±9.4	OMARI: (47.4) PLB: (48.4)	OMARI: 8.5±0.8 PLB: 8.6±0.8	OMARI: 9.8±5.3 PLB: 10.4±5.5

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM
NCT01698775	Chacra et al. (2017) [46]	III		213	24	Omarigliptin 12.5 or 25 mg	PLB/Glipizide 20 mg qd		Multinational	OMARI: 65.9±9.4 PLBGLIP: 64.5±9.7	OMARI: 68 (63.6) PLBGLIP: 63 (59.4)	OMARI: 8.3±0.8 PLBGLIP: 8.3±0.8	OMARI: 14.9±8.2 PLBGLIP: 15.1±8.7
NCT00225277	Nissen et al. (2008) [47]	III	PERISCOPE	547	72	Glimepiride 1–4 mg	Pioglitazone 15–45 mg		Multinational	GLIME: 59.7±9.1 PIO: 60.0±9.4	GLIME: 180 (65.9) PIO: 186 (68.9)	GLIME: 7.4±1.0 PIO: 7.4±1.0	Median GLIME: 71.0±30.0–131.0 m PIO: 70.0±27.0–129.0 m
NCT01177813	Roden et al. (2013) [48]	III		899	24	Empagliflozin 10 or 25 mg qd	PLB/Sitagliptin 100 mg qd		Multinational	EMPA10: 56.2±11.6 EMPA25: 53.8±11.6 SITA: 55.1±9.9 PLB: 54.9±10.9	EMPA10: 142 (63) EMPA25: 145 (65) SITA: 141 (63) PLB: 123 (54)	EMPA10: 7.87±0.88 EMPA25: 7.86±0.85 SITA: 7.85±0.79 PLB: 7.91±0.78	>1–5 yr EMPA10: 92±41 EMPA25: 83±37 SITA: 86±39 PLB: 104±46
NCT01210001	Kovacs et al. (2015) [49]	III	EMPA-REG EXTEND PIO	499	76	Empagliflozin 10 or 25 mg	PLB	Pioglitazone with or without MET	Multinational	EMPA10: 54.7±9.9 EMPA25: 54.2±8.9 PLB: 54.6±10.5	EMPA10: 83 (50.3) EMPA25: 85 (50.6) PLB: 73 (44.2)	EMPA10: 8.07±0.89 EMPA25: 8.06±0.82 PLB: 8.16±0.92	>1–5 yr EMPA10: 60±36.4 EMPA25: 76±45.2 PLB: 78±47.3
NCT02240680	Araki et al. (2019) [50]	IV		102	52	Linagliptin 5 mg qd	PLB	Variable	Multinational	LINA: 71.1±5.5 PLB: 71.5±5.6	LINA: 34 (65.4) PLB: 36 (72.0)	LINA: 8.1±0.8 PLB: 8.0±0.7	>15 yr LINA: 24±47.1 PLB: 22±44.0
NCT01792518	Groop et al. (2017) [51]	III	MARLINA-T2D	360	24	Linagliptin 5 mg qd	PLB	Variable	Multinational	LINA: 61.0±10.0 PLB: 60.1±9.3	LINA: 116 (63.7) PLB: 113 (63.5)	LINA: 7.82±0.87 PLB: 7.86±0.89	>10 yr LINA: 97±53.9 PLB: 71±40.8
NCT00679939	Bilezikian et al. (2013) [52]	IV		226	52	Rosiglitazone 8 mg minimum	Metformin 2,000 mg minimum		Multicenter	ROSI: 63.6±6.61 MET: 64.0±6.46	0.00%	ROSI: 6.8±0.73 MET: 6.8±0.74	ROSI: 3.9 MET: 3.3
NCT00698932		III		568	24	Saxagliptin 5 mg qd	PLB		Multinational	SAXA: 51.23±10.04 PLB: 51.57±10.34	SAXA: 160 (56.3) PLB: 155 (54.6)	SAXA: 9.15±0.125 PLB: 9.05±0.141	
NCT00614939	Nowicki et al. (2011) [53]	III		170	52	Saxagliptin 2.5 mg qd	PLB	Variable	Multicenter	SAXA: 66.8±8.3 PLB: 66.2±9.1	SAXA: 32 (37.6) PLB: 41 (48.2)	SAXA: 8.5±1.2 PLB: 8.1±1.1	SAXA: 15.1±7.5 PLB: 18.2±8.5
NCT00121641	Rosenstock et al. (2009) [54]	III		403	24 (+42 mo)[a]	Saxagliptin 2.5, 5, or 10 mg	PLB		Multicenter	SAXA2.5: 53.27±10.06 SAXA5: 53.91±11.57 SAXA10: 52.72±11.27 PLB: 53.91±12.32	SAXA2.5: 58 (56.9) SAXA5: 54 (50.9) SAXA10: 45 (45.9) PLB: 47 (49.5)	SAXA2.5: 7.9±0.9 SAXA5: 8.0±1.1 SAXA10: 7.8±0.9 PLB: 7.9±0.9	SAXA2.5: 3.1±3.5 SAXA5: 2.5±3.3 SAXA10: 2.3±3.1 PLB: 2.3±2.7

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Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM
NCT00316082	Frederich et al. (2012) [55]	III		366	76	Saxagliptin 2.5 mg AM, 5 mg AM, 2.5–5 mg AM, or 5 mg PM	PLB		Multinational	SAXA2.5: 55.2±10.44 SAXA5: 54.7±9.71 SAXA2.5-5: 54.3±10.93 SAXA5P: 55.1±10.35 PLB: 55.6±10.32	SAXA2.5: 25 (33.8) SAXA5: 38 (51.4) SAXA2.5-5: 37 (52.1) SAXA5P: 33 (45.8) PLB: 35 (47.3)	SAXA2.5: 8.0±0.8 SAXA5: 8.0±0.9 SAXA2.5-5: 8.0±1.1 SAXA5P: 79±0.9 PLB: 7.8±1.0	SAXA2.5: 1.2±1.6 SAXA5: 1.7±2.4 SAXA2.5-5: 2.0±2.9 SAXA5P: 2.0±5.2 PLB: 1.7±2.8
NCT02054897	Sorli et al. (2017) [56]	III	SUSTAIN-1	388	30	Semaglutide 0.5 or 1.0 mg	PLB		Multinational	SEMA0.5: 54.6±11.1 SEMA1.0: 52.7±11.9 PLB: 53.9±11.0	SEMA0.5: 60 (47) SEMA1.0: 80 (62) PLB: 70 (54)	SEMA0.5: 8.09±0.89 SEMA1.0: 8.12±0.81 PLB: 7.95±0.85	SEMA0.5: 4.81±6.10 SEMA1.0: 3.62±4.88 PLB: 4.06±5.48
NCT01930188	Ahren et al. (2017) [57]	III	SUSTAIN-2	1,231	56	Semaglutide 0.5 or 1.0 mg	Sitagliptin 100 mg	MET, TZD, or both	Multinational	SEMA0.5: 54.8±10.2 SEMA1.0: 56.0±9.4 SITA: 54.6±10.4	SEMA0.5: 207 (51) SEMA1.0: 205 (50) SITA: 208 (51)	SEMA0.5: 8.0±0.9 SEMA1.0: 8.0±0.9 SITA: 8.2±0.9	SEMA0.5: 6.4±4.7 SEMA1.0: 6.7±5.6 SITA: 6.6±5.1
NCT02532855	Scott et al. (2018) [58]	III	CompoSIT-R	614	24	Sitagliptin 100 mg qd	Dapagliflozin upto 10 mg	MET with or without SU	Multinational	SITA: 67.7±8.5 DAPA: 66.6±8.6	SITA: (55.0) DAPA: (60.8)	SITA: 7.7±0.7 DAPA: 7.8±0.7	SITA: 10.5±7.0 DAPA: 10.7±7.4
NCT00509262	Arjona Ferreira et al. (2013) [59]	III		426	54	Sitagliptin 25 or 50 mg qd	Glipizide upto 20 mg qd		Multinational	SITA: 64.8±10.6 GLIP: 64.3±9.2	SITA: 80 (59.3) GLIP: 78 (54.9)	SITA: 7.8±0.7 GLIP: 7.8±0.7	SITA: 10.7±7.5 GLIP: 10.1±7.8
NCT00225264	Mazzone et al. (2006) [60]	III	CHICAGO	462	72	Pioglitazone 15–45 mg qd	Glimepiride 1–4 mg qd	Variable	Multicenter	PIO: 59.3±8.0 GLIME: 59.9±8.2	PIO: 146 (63.5) GLIME: 143 (62.7)	PIO: 7.43±0.99 GLIME: 7.40±0.97	PIO: 8.0±7.6 GLIME: 7.5±6.8
NCT02827708	Mosenzon et al. (2019) [61]	III	PIONEER 5	324	26	Semaglutide 14 mg	PLB	Variable	Multinational	SEMA: 71±8 PLB: 70±8	SEMA: 83 (51) PLB: 73 (45)	SEMA: 8.0±0.7 PLB: 7.9±0.7	SEMA: 14.1±8.6 PLB: 13.9±7.4
NCT02906930	Aroda et al. (2019) [62]	III	PIONEER 1	703	26	Oral semaglutide 3, 7, or 14 mg	PLB		Multinational	SEMA3: 55±11 SEMA7: 56±11 SEMA14: 54±11 PLB: 54±11	SEMA3: 89 (50.9) SEMA7: 93 (53.1) SEMA14: 86 (49.1) PLB: 89 (50.0)	SEMA3: 7.9±0.7 SEMA7: 8.0±0.6 SEMA14: 8.0±0.7 PLB: 7.9±0.7	SEMA3: 3.8±5.3 SEMA7: 3.6±5.1 SEMA14: 3.4±4.4 PLB: 3.4±4.6
NCT00138619	Rosenstock et al. (2009) [63]	III		598	80	Vildagliptin 50 mg bid	Rosiglitazone 8 mg qd		Multinational	VILDA: 54.41±11.56 ROSI: 54.18±10.87	VILDA: 228 (57.6) ROSI: 110 (54.5)	VILDA: 8.58±1.10 ROSI: 8.63±1.17	VILDA: 1.98±2.88 ROSI: 2.60±4.19

(*Continued to the next page*)

Supplementary Table 2. Continued

NCT number	Study	Trial phase	Acronym	No. of randomized patients	Study duration, wk	Target	Comparator(s)	Background medication	Population	Age, yr	Male gender	Baseline HbA1c, %	Mean duration of T2DM
NCT00138567	Goke et al. (2008) [64]	III		780	52	Vildagliptin 100 mg qd	Metformin 2,000 mg qd		Multinational	VILDA: 52.8±11.7 MET: 53.6±10.2	VILDA: 278 (52.9) MET: 146 (57.5)	VILDA: 8.7±1.1 MET: 8.7±1.1	Median VILDA: 1.05 MET: 1.03
NCT01986881	Cannon et al. (2020) [65]		VERTIS CV	8,250	3.5 yr	Ertugliflozin 5 or 15 mg	PLB	Variable	Multicenter	ERTU: 64.4±8.1 PLB: 64.4±8.0	ERTU: 3,866 (70.3) PLB: 1,903 (69.3)	ERTU: 8.2±1.0 PLB: 8.2±0.9	ERTU: 12.9±8.3 PLB: 13.1±8.4
NCT01394952	Gerstein et al. (2020) [66]		REWIND	9,901	Median 5.4 yr	Dulaglutide 1.5 mg qw	PLB	Variable	Multinational	DULA: 66.2±6.5 PLB: 66.2±6.5	DULA: 2,643 (53.4) PLB: 2,669 (53.9)	DULA: 7.3±1.1 PLB: 7.4±1.1	DULA: 10.5±7.3 PLB: 10.6±7.2
NCT03315143	Bhatt et al. (2021) [67]		SCORED	10,584	Median 16 mo	Sotagliflozin 200 mg	PLB	Variable	Multinational	SOTA: 69 PLB: 69	SOTA: 55.7% PLB: 54.5%	Median SOTA: 8.3 PLB: 8.3	
NCT02924064	Ji et al. (2021) [68]			247	24	Teneligliptin 20 mg	PLB	MET	Multicenter	TENE: 56.0±9.8, PLB: 54.7±10.1	TENE: 81 (66.4) PLB: 67 (54.0)	TENE: 7.9±0.68, PLB: 7.87±0.72	TENE: 5.05±3.90, PLB: 5.41±4.22
NCT03521934	Bhatt et al. (2021) [69]		SOLOIST-WHF	1,222	Median 9 mo	Sotagliflozin 200 mg	PLB	Variable	Multinational	Median SOTA: 69 PLB: 70	SOTA: 67.4% PLB: 65.1%	Median SOTA: 7.1 PLB: 7.2	

Values are presented as mean±standard deviation or number (%).

HbA1c, glycosylated hemoglobin; T2DM, type 2 diabetes mellitus; CANVAS, CANagliflozin cardioVascular Assessment Study; PLB, placebo; CANVAS-R, CANagliflozin cardioVascular Assessment Study-Renal; DECLARE–TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; qd, once a day; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; CARMELINA, CArdiovascular safety and Renal Microvascular outcomE study with LINAgliptin; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium-glucose cotransporter-2; LINA, linagliptin; CAROLINA, Cardiovascular Outcome Study of Linagliptin vs Glimepiride in Type 2 Diabetes; SU, sulfonylurea; MET, metformin; GLIME, glimepiride; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CANA, canagliflozin; PIONEER, Peptide Innovation for Early Diabetes Treatment; SEMA, semaglutide; VIVIDD, Vildagliptin in Ventricular Dysfunction Diabetes; bid, two times a day; VILDA, vildagliptin; ALBI, albiglutide; qw, once a week; EXSCEL, Exenatide Study of Cardiovascular Event Lowering Trial; EXEN, exenatide; OMARI, omarigliptin; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; LIRA, liraglutide; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus Patients; EMPA, empagliflozin; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; LIXI, lixisenatide; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; SITA, sitagliptin; DAPA, dapagliflozin; EXAMINE, Cardiovascular Outcomes Study of Alogliptin in Patients With Type 2 Diabetes and Acute Coronary Syndrome; ALO, alogliptin; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; SAXA, saxagliptin; SPREAD-DIMCAD, Study on the Prognosis and Effect of Anti-diabetic Drugs on Type-2 Diabetes Mellitus With Coronary Artery Disease; GLIP, glipizide; TASPO, taspoglutide; APPROACH, Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in diabetes patients with Cardiovascular History; ROSI, rosiglitazone; RIVO, rivoglitazone; PIO, pioglitazone; LINA, linagliptin; PLBGLIME, placebo and glimepiride; GLIBE, glibenclamide; PROactive, PROspective pioglitAzone Clinical Trial In macroVascular Events; ADOPT, A diabetes outcome progression trial; GLYB, glyburide; CKD, chronic kidney disease; EMPA, empagliflozin; CANA, canagliflozin; CANTATA-MSU, CANagliflozin Treatment And Trial Analysis - Metformin and SUlphonylurea; CANTATA-M, CANagliflozin Treatment and Trial Analysis – Monotherapy; PLBSITA, placebo and sitagliptin; PLBPIO, placebo and pioglitazone; DERIVE, Dapagliflozin on Blood Glucose Level and Renal Safety in Patients With Type 2 Diabetes; VERTIS RENAL, eValuation of ERTugliflozin effIcacy and Safety in Patients with Stage 3 Chronic Kidney Disease and Type 2 Diabetes Mellitus; ERTU, ertugliflozin; LIRA-RENAL, Liraglutide Versus Placebo as Add-on to Glucose-Lowering Therapy in Patients With Type 2 Diabetes and Moderate Renal Impairment; GetGoal-O, Lixisenatide Therapy in Older Patients With Type 2 Diabetes Inadequately Controlled on Their Current Antidiabetic Treatment; AWARD-3, Dulaglutide Monotherapy Versus Metformin in Type 2 Diabetes; DULA, dulaglutide; PERISCOPE, Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; EMPA-REG EXTEND PIO, Extension of Empagliflozin as Add-on Therapy to Pioglitazone With or Without Metformin in Patients With Type 2 Diabetes Mellitus; MARLINA-T2D, Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects with Renal. Disease with LINAgliptin; CompoSIT-R, comparison of sitagliptin with dapagliflozin in mild renal impairment; CHICAGO, Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone; VERTIS CV, eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes trial; REWIND, Dulaglutide and cardiovascular outcomes in type 2 diabetes; SCORED, Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SOTA, sotagliflozin; TENE, teneligliptin; SOLOIST-WHF, Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure.

[a]Clinical trials with more than one phase, with the latter phase in parenthesis.

Supplementary Table 3. Risk of bias assessment

NCT number	Study	R	A	B1	B2	I	S
NCT01032629	Zhou et al. (2019) [1]	L	L	U	U	L	L
NCT01989754	Zhou et al. (2019) [1]	L	L	U	U	L	L
NCT01730534	Wiviott et al. (2019) [2]	U	U	L	U	L	L
NCT01897532	Rosenstock et al. (2019) [3]	L	L	L	L	L	L
NCT01243424	Rosenstock et al. (2019) [4]	L	L	L	L	L	L
NCT02065791	Mahaffey et al. (2019) [5]	U	U	L	L	U	L
NCT02692716	Husain et al. (2019) [6]	U	U	L	L	L	L
NCT01394952	Gerstein et al. (2020) [66]	L	L	L	L	L	L
NCT00894868	McMurray et al. (2018) [7]	L	L	L	U	L	L
NCT02465515	Hernandez et al. (2018) [8]	L	L	L	L	L	L
NCT01144338	Holman et al. (2017) [9]	L	L	L	L	L	L
NCT01703208	Gantz et al. (2017) [10]	L	L	L	L	L	L
NCT01179048	Marso et al. (2016) [11]	U	U	L	L	L	L
NCT01720446	Marso et al. (2016) [12]	U	U	L	L	L	L
NCT01131676	Zinman et al. (2015) [13]	L	L	L	L	L	L
NCT01147250	Pfeffer et al. (2015) [14]	L	U	L	L	L	L
NCT00790205	Green et al. (2015) [15]	L	L	L	L	L	L
NCT01042977	Leiter et al. (2014) [16]	U	U	L	U	L	L
NCT01294423	Kaku et al. (2014) [17]	U	U	L	U	L	L
NCT00968708	White et al. (2013) [18]	U	U	L	L	L	L
NCT01107886	Scirica et al. (2013) [19]	L	L	L	L	L	L
NCT00513630	Hong et al. (2013) [20]	L	U	L	U	L	L
NCT00744926	Raz et al. (2012) [21]	U	U	L	U	L	L
NCT00116831	Gerstein et al. (2010) [22]	U	U	L	L	L	L
NCT00484198	Chou et al. (2012) [23]	U	U	L	L	L	L
NCT00740051	Barnett et al. (2012) [24]	L	L	L	L	L	L
NCT00521742	Giles et al. (2010) [25]	U	U	L	L	L	L
NCT00494312	Tolman et al. (2009) [26]	L	L	L	L	L	L
NCT00174993	Wilcox et al. (2007) [27]	U	U	L	L	L	L
NCT00279045	Kahn et al. (2006) [28]	L	U	L	L	L	L
NCT00087516	Aschner et al. (2006) [29]	U	U	L	L	L	L
NCT00707993		U	U	L	U	L	L
NCT01164501	Barnett et al. (2014) [30]	L	L	L	L	L	L
NCT00800683		U	U	L	U	L	L
NCT01106651	Bode et al. (2015) [31]	L	L	L	L	L	L
NCT02025907		U	U	L	U	L	L
NCT01064414		U	U	L	U	L	L
NCT01106625		U	U	L	U	L	L
NCT01081834	Stenlof et al. (2013) [32]	U	U	L	U	L	L
NCT00094757		U	U	L	U	L	L

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Supplementary Table 3. Continued

NCT number	Study	R	A	B1	B2	I	S
NCT02413398	Fioretto et al. (2018) [33]	L	L	L	U	L	L
NCT01095653	Ji et al. (2014) [34]	L	L	L	L	L	L
NCT00663260	Kohan et al. (2014) [35]	U	U	L	L	L	L
NCT01031680	Cefalu et al. (2015) [36]	L	L	L	U	L	L
NCT02182830	Ferdinand et al. (2019) [37]	U	U	L	U	L	L
NCT01986855	Grunberger et al. (2018) [38]	L	L	L	L	L	L
NCT00676338	Russell-Jones et al. (2012) [39]	L	L	L	U	L	L
NCT01087502	Laakso et al. (2015) [40]	U	U	L	U	L	L
NCT00601250		U	U	L	U	L	L
NCT01084005	Barnett et al. (2013) [41]	L	L	L	L	L	L
NCT01620489	Davies et al. (2016) [42]	L	L	L	U	U	L
NCT01798706	Meneilly et al. (2017) [43]	L	L	L	U	L	L
NCT01126580	Umpierrez et al. (2014) [44]	L	L	L	L	L	L
NCT01704261	Lee et al. (2017) [45]	L	L	L	L	L	L
NCT01698775	Chacra et al. (2017) [46]	L	L	L	L	L	L
NCT00225277	Nissen et al. (2008) [47]	L	L	L	L	L	L
NCT01177813	Roden et al. (2013) [48]	L	L	L	L	U	L
NCT01210001	Kovacs et al. (2015) [49]	L	L	L	U	L	L
NCT02240680	Araki et al. (2019) [50]	L	L	L	U	U	L
NCT01792518	Groop et al. (2017) [51]	L	L	L	L	L	L
NCT00679939	Bilezikian et al. (2013) [52]	L	U	L	L	L	L
NCT00698932		U	U	L	U	L	L
NCT00614939	Nowicki et al. (2011) [53]	L	L	L	L	L	L
NCT00121641	Rosenstock et al. (2009) [54]	L	U	L	U	L	L
NCT00316082	Frederich et al. (2012) [55]	L	U	L	U	L	L
NCT02054897	Sorli et al. (2017) [56]	L	L	L	L	L	L
NCT01930188	Ahren et al. (2017) [57]	L	L	L	L	L	L
NCT02532855	Scott et al. (2018) [58]	L	L	L	L	L	L
NCT00509262	Arjona Ferreira et al. (2013) [59]	L	U	L	L	L	L
NCT00225264	Mazzone et al. (2006) [60]	L	U	L	L	L	L
NCT02827708	Mosenzon et al. (2019) [61]	L	L	L	U	L	L
NCT02906930	Aroda et al. (2019) [62]	L	L	L	L	L	L
NCT00138619	Rosenstock et al. (2009) [63]	L	L	L	L	L	L
NCT00138567	Goke et al. (2008) [64]	L	U	L	U	L	L
NCT01986881	Cannon et al. (2020) [65]	L	L	L	L	L	L
NCT03315143	Bhatt et al. (2021) [67]	L	L	L	L	L	L
NCT02924064	Ji et al. (2021) [68]	L	L	L	L	L	L
NCT03521934	Bhatt et al. (2021) [69]	L	L	U	L	L	L

R, random sequence generation; A, allocation concealment; B1, blinding of participants and personnel; B2, blinding of outcome assessment; I, incomplete outcome data; S, selective reporting; L, low; U, unclear.

Supplementary Table 4. Inconsistency test between direct and indirect treatment comparisons in mixed treatment comparison

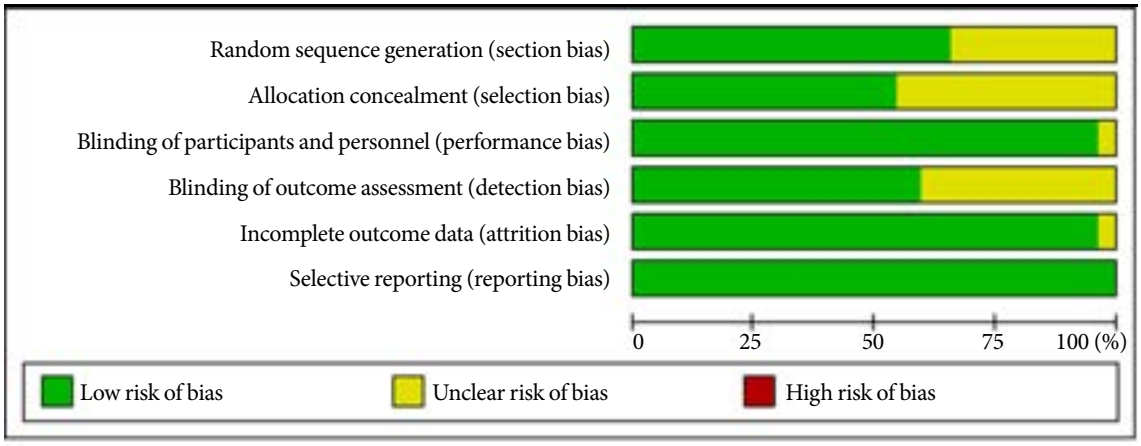
Side	Direct		Indirect		Difference		*P*>z
	Coef.	SE	Coef.	SE	Coef.	SE	
A D	–0.22742	0.263733	–0.00563	0.354818	–0.2218	0.442077	0.616
A E	–0.08632	0.121177	0.023866	0.381763	–0.11018	0.402115	0.784
A F	–0.19943	0.096979	–1.54108	1.077686	1.341647	1.08238	0.215
A G	–0.17626	0.102743	–0.76746	0.865877	0.591197	0.871929	0.498
B C	0.147713	0.308949	–0.37067	0.604587	0.518378	0.681431	0.447
B D	–0.27619	0.383634	0.015143	0.48034	–0.29133	0.619431	0.638
B E	–1.29241	1.137664	0.011656	0.31801	–1.30407	1.187081	0.272
B G	–0.45147	0.976189	–0.1654	0.342818	–0.28607	1.039023	0.783
C D	–0.01673	0.294042	–0.45136	0.343184	0.434629	0.451609	0.336
C E	–0.15462	0.236767	–0.06368	0.375574	–0.09094	0.443806	0.838
D E	0.273908	0.990021	0.063434	0.224279	0.210474	1.015104	0.836
D G	–0.41902	2.014404	–0.03029	0.233036	–0.38872	2.027839	0.848
E F	–0.96967	0.9261	–0.11407	0.148867	–0.85559	0.937835	0.362
E G	–1.24516	1.275837	–0.09309	0.152138	–1.15207	1.284871	0.37

SE, standard error; A, placebo; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; B, metformin; C, sulfonylurea.

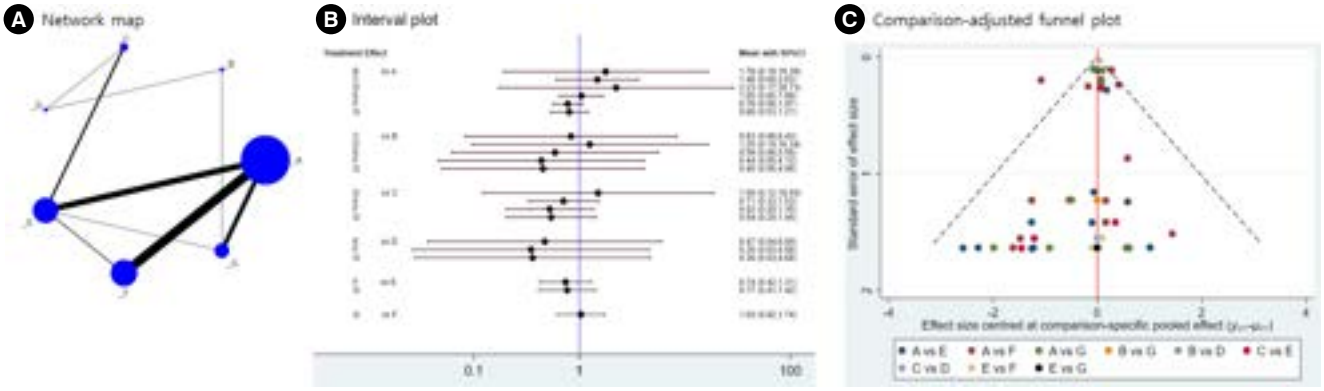
Supplementary Table 5. Network and pairwise meta-analyses for total stroke of antihyperglycemic drugs excluding sotagliflozin

	Placebo	Metformin	Sulfonylurea	TZD	DPP-4 inhibitor	SGLT-2 inhibitor	GLP-1 agonist
Placebo		-	-	2 Studies I^2=0.0% –0.22 (–0.51 to 0.07)	19 Studies I^2=0.0% –0.04 (–0.17 to 0.08)	22 Studies I^2=66.2% –0.23 (–0.55 to 0.08)	13 Studies I^2=0.00% –0.17 (–0.27 to –0.07)
Metformin	1.01 (0.55 to 1.86)		2 Studies I^2=19.0% 0.14 (–0.44 to 0.72)	3 Studies I^2=0.0% –0.23 (–0.88 to 0.41)	2 Studies I^2=0.0% –1.23 (–3.49 to 1.04)	-	2 Studies I^2=0.0% –0.40 (–2.33 to 1.52)
Sulfonylurea	1.05 (0.69 to 1.60)	1.04 (0.61 to 1.78)		6 Studies I^2=0.0% –0.02 (–0.53 to 0.49)	6 Studies I^2=0.0% –0.15 (–0.41 to 0.11)	-	-
TZD	0.86 (0.57 to 1.30)	0.85 (0.47 to 1.52)	0.82 (0.53 to 1.27)		3 Studies I^2=0.0% 0.27 (–1.65 to 2.20)	-	1 Study –0.42 (–4.34 to 3.51)
DPP-4 inhibitor	0.93 (0.74 to 1.16)	0.91 (0.50 to 1.67)	0.88 (0.59 to 1.30)	1.08 (0.70 to 1.66)		3 Studies I^2=0.0% –1.03 (–2.85 to 0.79)	2 Studies I^2=0.0% –1.25 (–3.73 to 1.24)
SGLT-2 inhibitor	0.81 (0.65 to 0.99)	0.80 (0.42 to 1.51)	0.76 (0.48 to 1.22)	0.94 (0.59 to 1.49)	0.87 (0.64 to 1.18)		-
GLP-1 agonist	0.83 (0.68 to 1.02)	0.82 (0.43 to 1.55)	0.79 (0.50 to 1.25)	0.96 (0.61 to 1.53)	0.90 (0.66 to 1.21)	1.03 (0.77 to 1.38)	

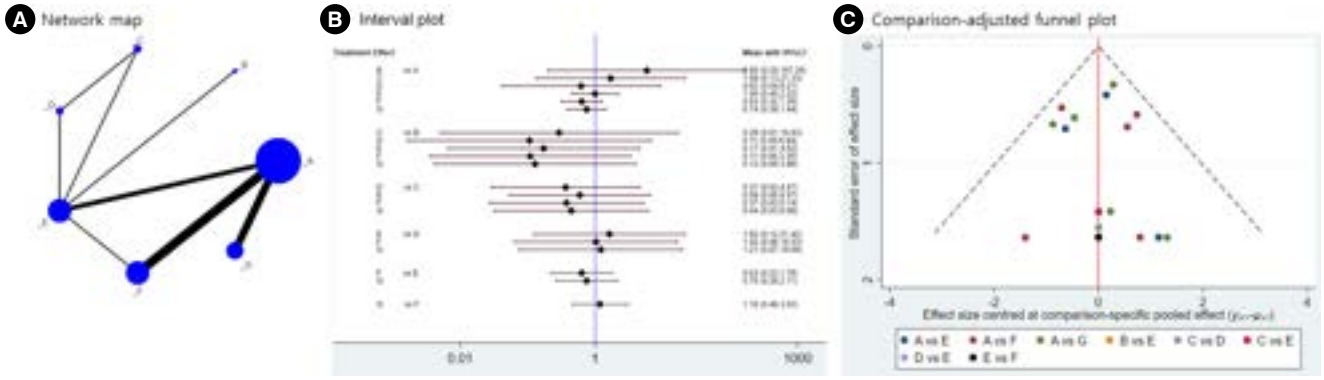
TZD, thiazolidinedione; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose cotransporter-2; GLP-1, glucagon-like peptide-1.



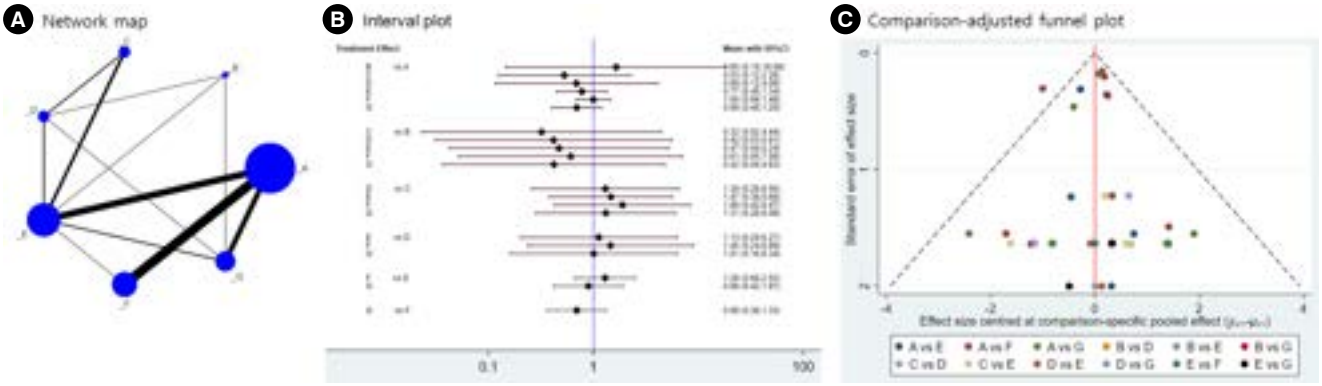
Supplementary Fig. 1. Risk of bias assessment (summary graph).



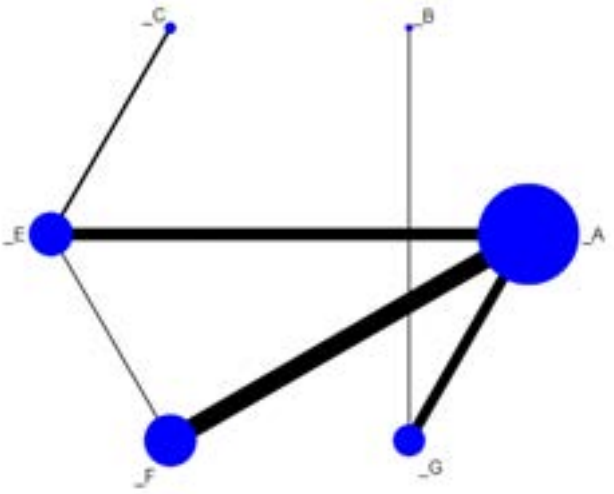
Supplementary Fig. 2. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on ischemic stroke ($n=44$ trials). Ischemic stroke includes ischemia, ischemic stroke, vertebrobasilar insufficiency, cerebrovascular insufficiency, and lacunar infarction. The global test for inconsistency gives a *P* value of 0.520, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitors; F, sodium glucose cotransporter-2 inhibitors; G, glucagon-like peptide-1 agonist; CI, confidence interval.



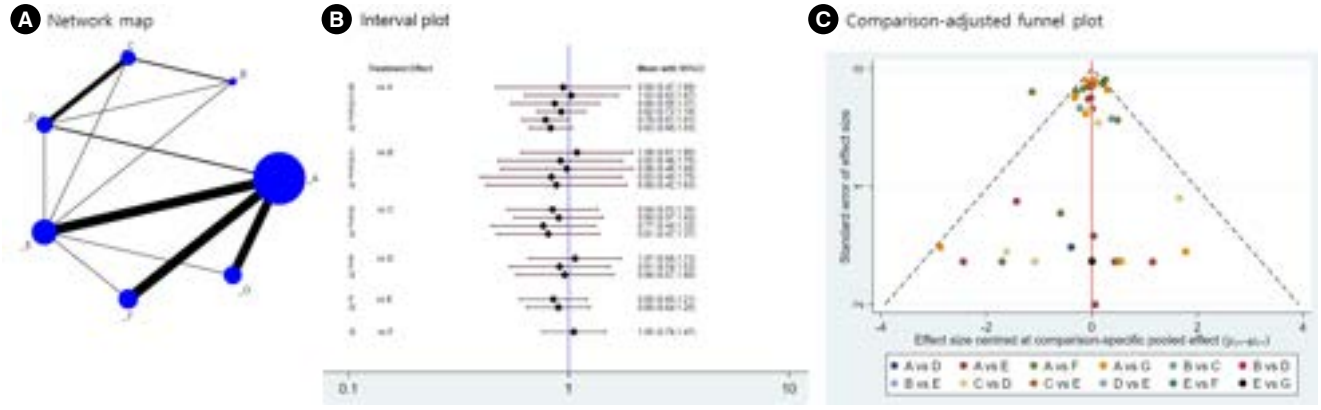
Supplementary Fig. 3. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on hemorrhagic stroke ($n=20$ trials). Hemorrhagic stroke includes hemorrhage and cerebral hematoma. The global test for inconsistency gives a *P* value of 0.550, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitors; F, sodium glucose cotransporter-2 inhibitors; G, glucagon-like peptide-1 agonist; CI, confidence interval.



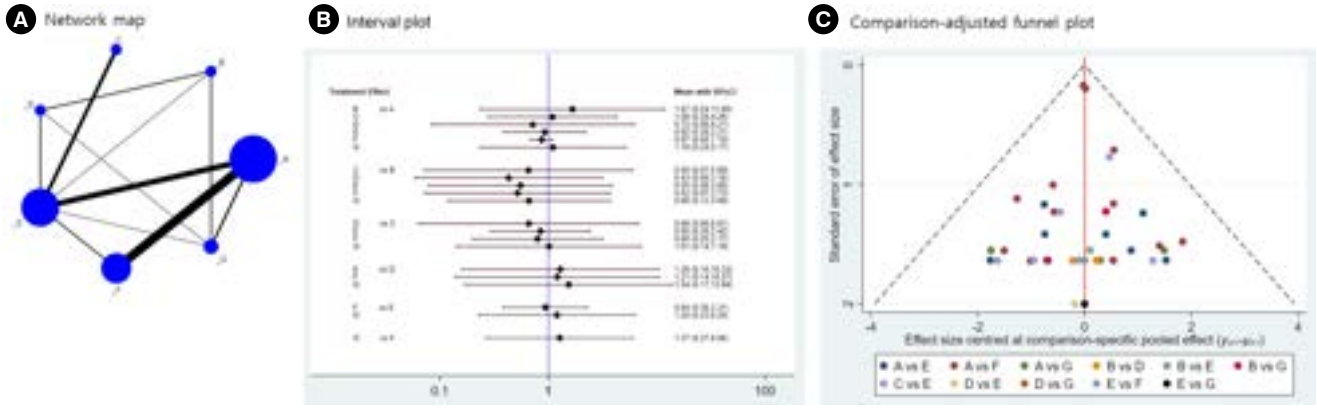
Supplementary Fig. 4. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on unspecified stroke ($n=37$ trials). Unspecified stroke includes cerebrovascular accident, cerebrovascular disorder, hemiplegia, and hemiparesis. The global test for inconsistency gives a P value of 0.999, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



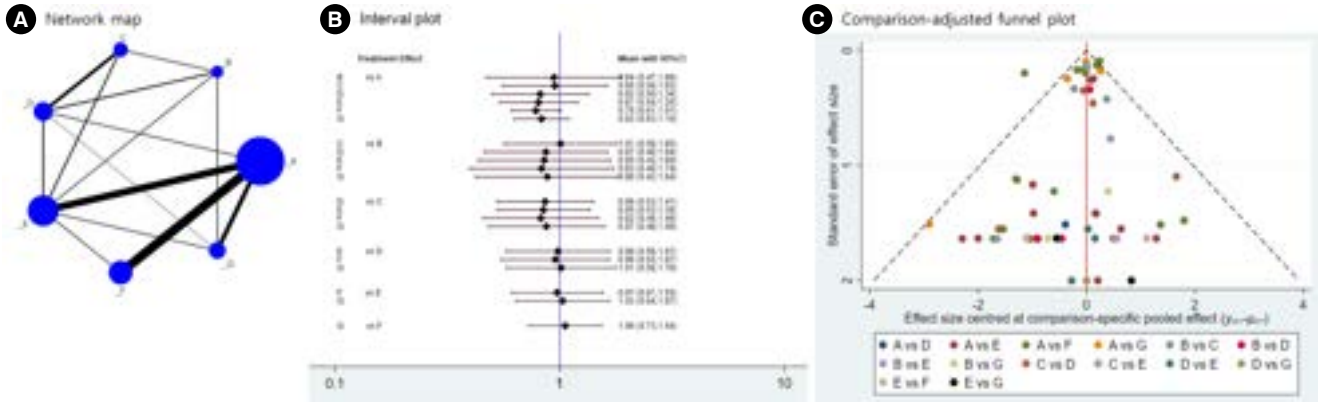
Supplementary Fig. 5. Network map for network meta-analysis of antidiabetic drugs on transient ischemic attack (n=26 trials). Transient ischemic attack including reversible ischemic neurologic deficit. Further analysis was impossible due to its disconnected network. A, placebo; B, metformin; C, sulfonylurea; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist.



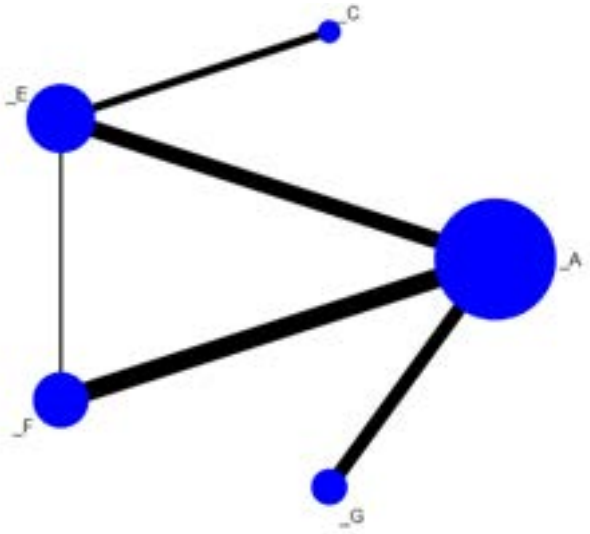
Supplementary Fig. 6. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke in published studies by peer reviewed journal (n=44 trials). The global test for inconsistency gives a P value of 0.890, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



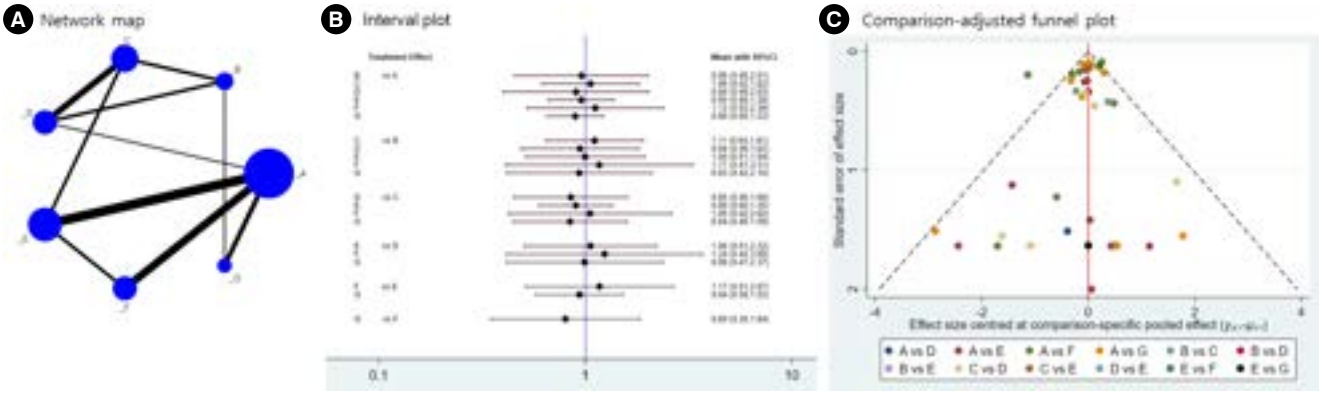
Supplementary Fig. 7. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke in unpublished studies ($n=35$ trials). The global test for inconsistency gives a *P* value of 0.702, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



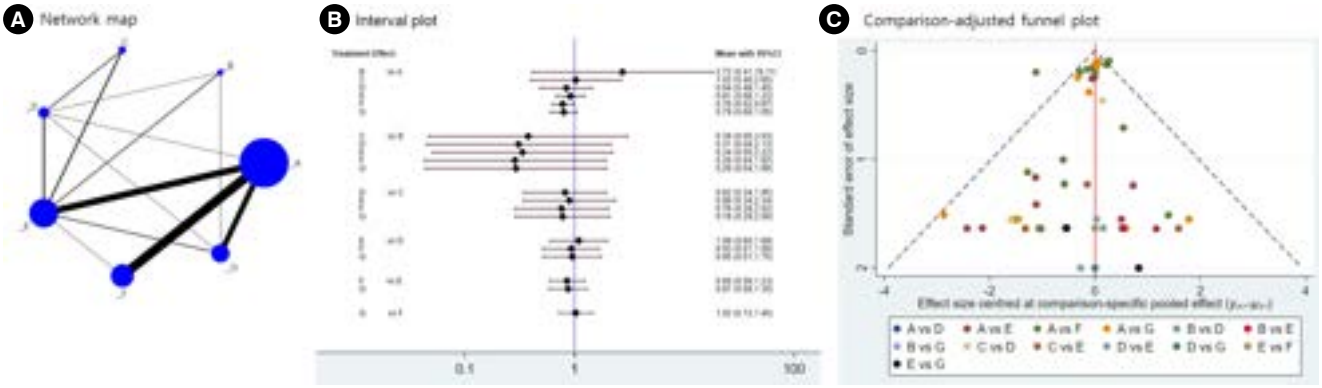
Supplementary Fig. 8. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke among subjects aged <average 65 years ($n=57$ trials). The global test for inconsistency gives a P value of 0.977, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



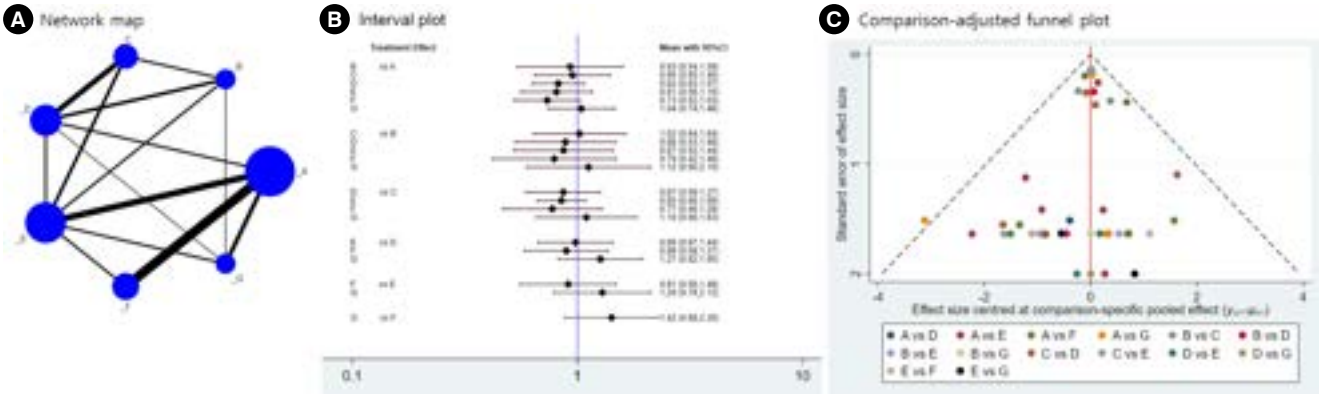
Supplementary Fig. 9. Network map for network meta-analysis of antidiabetic drugs on total stroke among subjects aged ≥average 65 years (n=22 trials). Further analysis was impossible due to its disconnected network. A, placebo; C, sulfonylurea; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist.



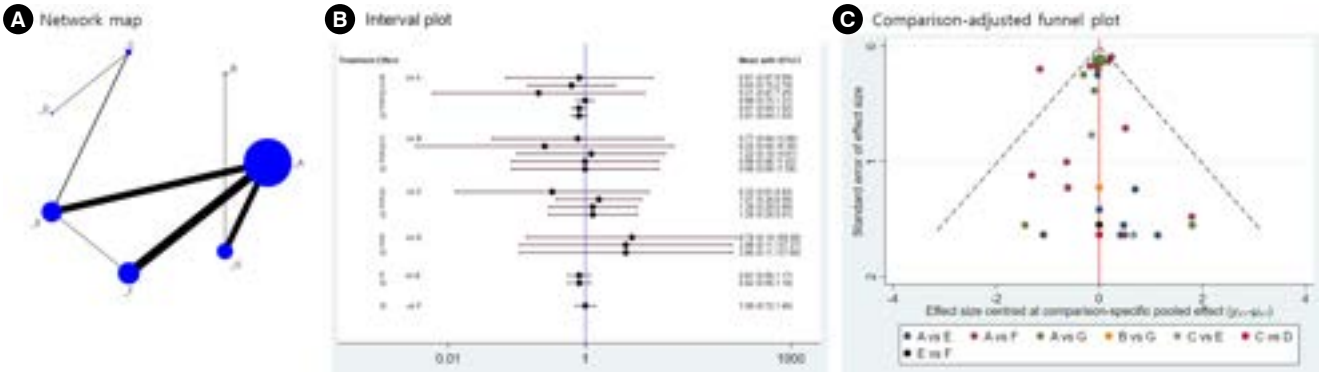
Supplementary Fig. 10. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke among subjects with baseline glycosylated hemoglobin <average 8.0% (n=24 trials). The global test for inconsistency gives a P value of 0.915, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



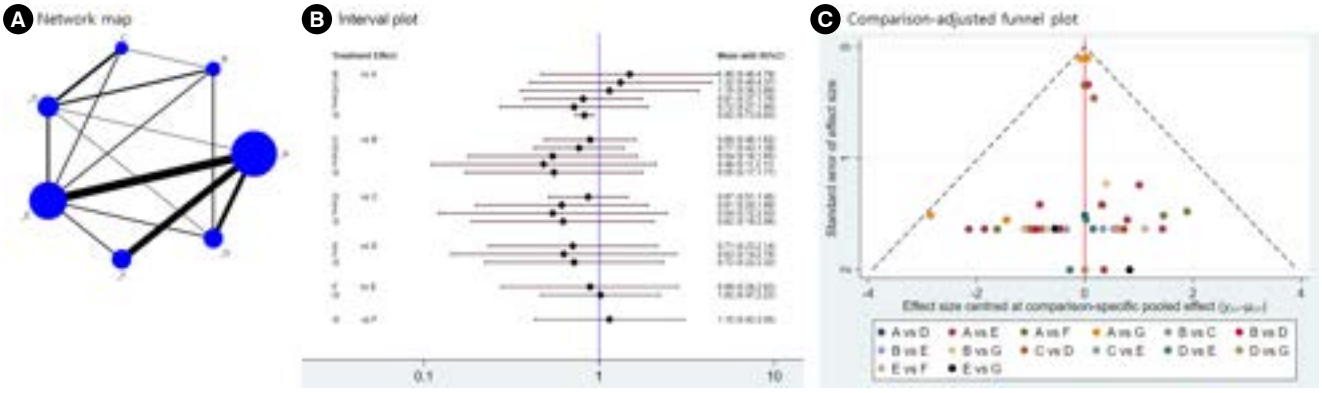
Supplementary Fig. 11. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke among subjects with baseline glycosylated hemoglobin ≥average 8.0% (n=51 trials). The global test for inconsistency gives a P value of 0.918, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



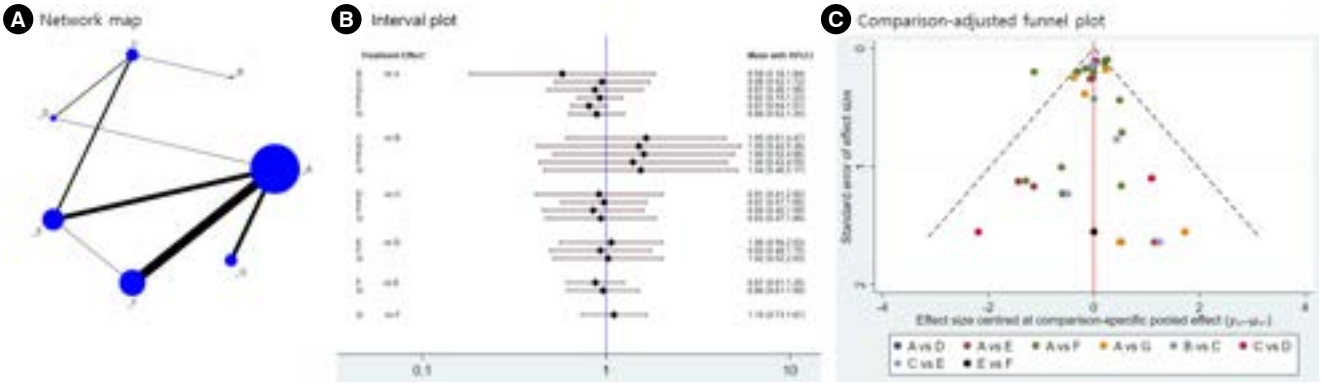
Supplementary Fig. 12. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke among subjects with type 2 diabetes mellitus duration <10 years (n=35 trials). The global test for inconsistency gives a P value of 0.946, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



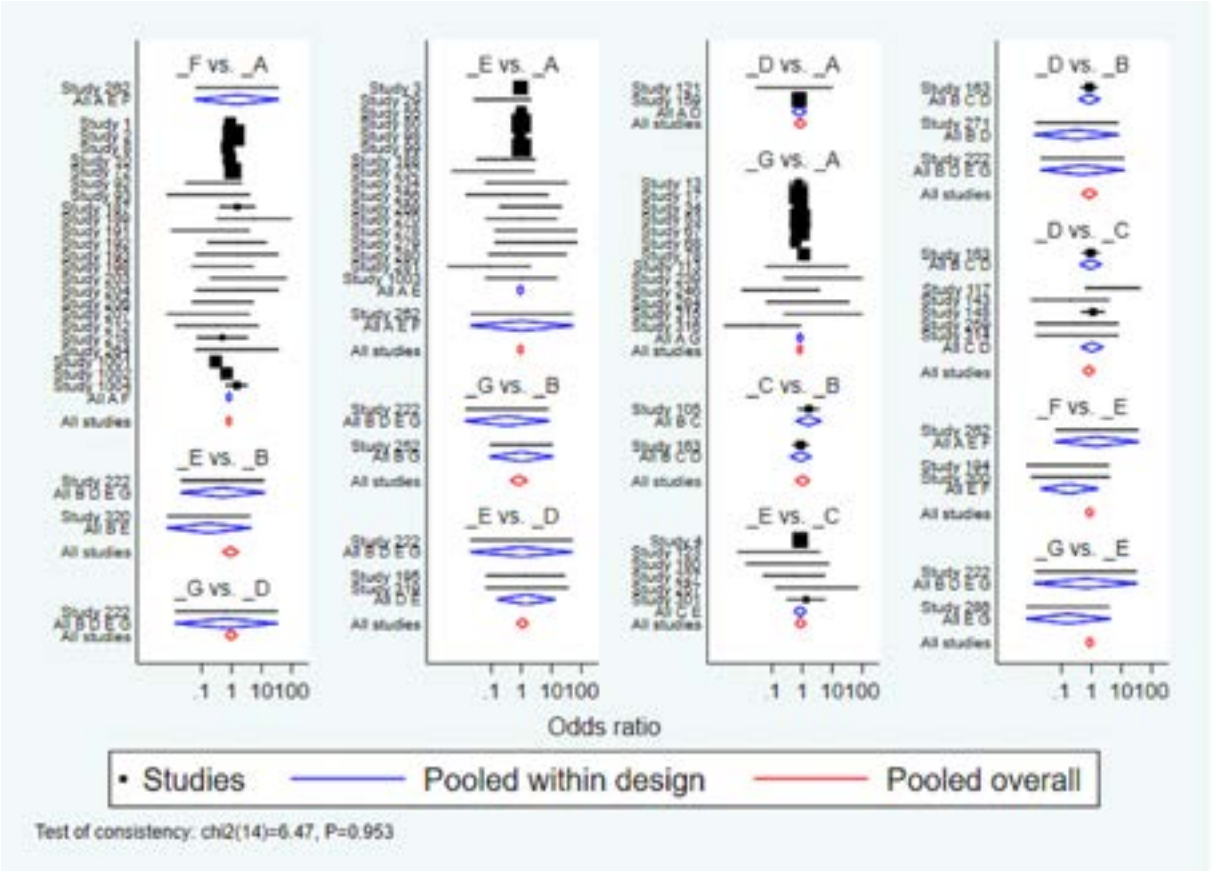
Supplementary Fig. 13. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke among subjects with type 2 diabetes mellitus duration ≥10 years (n=37 trials). The global test for inconsistency gives a P value of 0.367, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



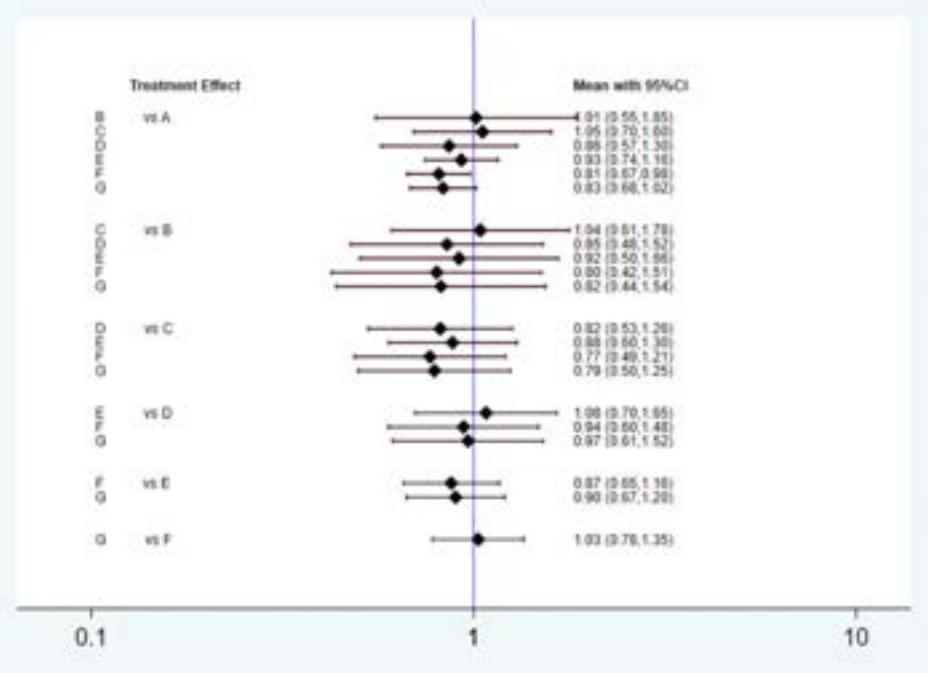
Supplementary Fig. 14. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke among subjects with low cardiovascular disease risk (n=40 trials). The global test for inconsistency gives a P value of 0.969, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



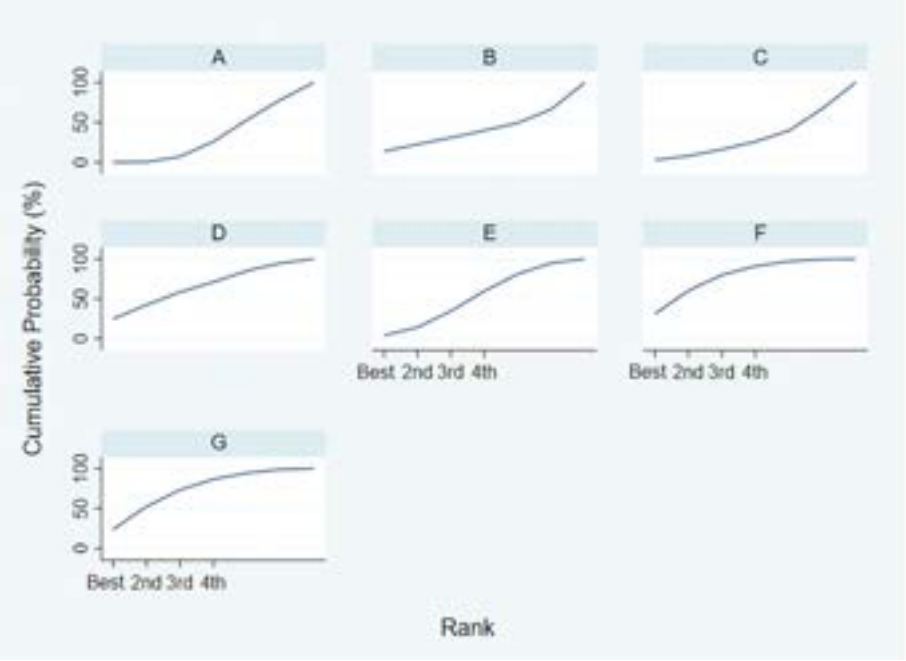
Supplementary Fig. 15. (A) Network map, (B) interval plot, and (C) comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke among subjects with high cardiovascular disease risk ($n=39$ trials). The global test for inconsistency gives a *P* value of 0.491, giving no evidence of inconsistency. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



Supplementary Fig. 16. Network forest plot for total stroke. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist.

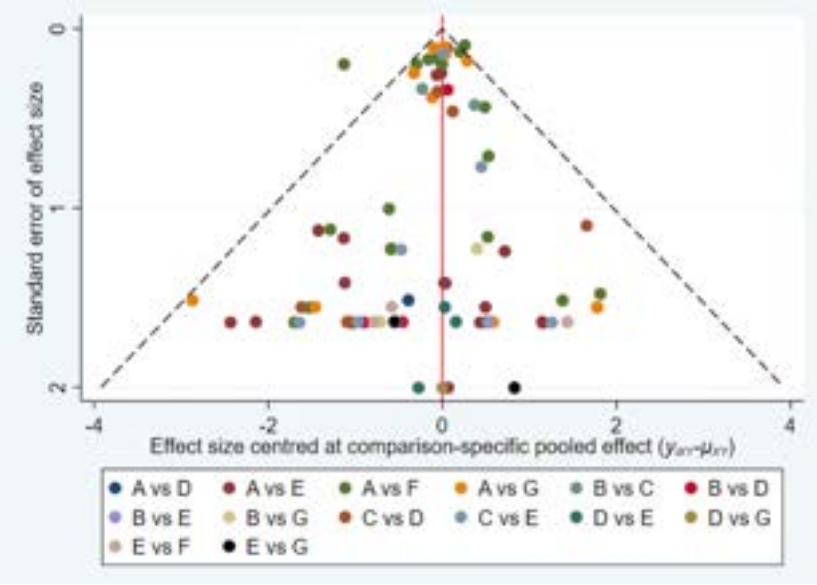


Supplementary Fig. 17. Interval plot for total stroke. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; CI, confidence interval.



Study and rank	Treatment						
	A	B	C	D	E	F	G
Best	0.0	13.7	2.8	24.8	4.0	31.0	23.7
2nd	0.3	8.9	5.1	17.6	10.1	29.2	28.8
3rd	6.7	8.2	8.0	16.0	20.5	19.7	20.8
4th	19.0	9.0	9.8	12.7	25.0	11.2	13.4
5th	27.2	9.6	13.8	14.2	21.5	5.9	7.9
6th	25.2	17.2	27.5	9.4	13.6	2.6	4.4
Worst	21.6	33.5	32.9	5.3	5.2	0.4	1.0
Mean rank	5.4	4.8	5.4	3.2	4.1	2.4	2.7
SUCRA	27.5	37.1	26.5	62.8	48.1	76.4	71.7

Supplementary Fig. 18. Results of network rank test. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist; SUCRA, surface under the cumulative ranking curve.



Supplementary Fig. 19. Comparison-adjusted funnel plot for network meta-analysis of antidiabetic drugs on total stroke. A, placebo; B, metformin; C, sulfonylurea; D, thiazolidinedione; E, dipeptidyl peptidase-4 inhibitor; F, sodium glucose cotransporter-2 inhibitor; G, glucagon-like peptide-1 agonist.

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