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Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes

A Systematic Review and Network Meta-analysis

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Background: Several pharmacologic options for type 2 diabetes are available.

Purpose: To compare benefits and harms of glucose-lowering drugs in adults with type 2 diabetes.

Data Sources: Several databases from inception through 18 December 2019 and ClinicalTrials.gov on 10 April 2020.

Study Selection: English-language randomized trials that had at least 24 weeks of intervention and assessed the effects of glucose-lowering drugs on mortality, glycemic, and vascular outcomes.

Data Extraction: Pairs of reviewers extracted data and appraised risk of bias.

Data Synthesis: 453 trials assessing 21 antidiabetic interventions from 9 drug classes were included. Interventions included monotherapies (134 trials), add-on to metformin-based therapies (296 trials), and monotherapies versus add-on to metformin therapies (23 trials). There were no differences between treatments in drug-naive patients at low cardiovascular risk. Insulin regimens and specific glucagon-like peptide-1 receptor agonists (GLP-1 RAs) added to metformin-based background therapy produced the greatest reductions in hemoglobin A_{1c} level. In patients at low cardiovascular risk receiving metformin-based background treatment (298 trials), there were no clinically meaningful differences between treatments for mortality and vascular outcomes. In patients at increased cardiovascular risk receiving metformin-based background treatment (21 trials), oral semaglutide, empagliflozin, liraglutide, extended-release exenatide, and dapagliflozin reduced all-cause mortality. Oral semaglutide, empagliflozin, and liraglutide also reduced cardiovascular death. Odds of stroke were lower with subcutaneous semaglutide and dulaglutide. Sodium–glucose cotransporter-2 (SGLT-2) inhibitors reduced heart failure hospitalization and end-stage renal disease. Subcutaneous semaglutide and canagliflozin increased diabetic retinopathy and amputation, respectively.

Limitation: Inconsistent definitions of cardiovascular risk and low-level confidence in some estimates for patients at low cardiovascular risk.

Conclusion: In diabetic patients at low cardiovascular risk, no treatment differs from placebo for vascular outcomes. In patients at increased cardiovascular risk receiving metformin-based background therapy, specific GLP-1 RAs and SGLT-2 inhibitors have a favorable effect on certain cardiovascular outcomes.

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Several pharmacologic options for type 2 diabetes are available. Accumulating evidence shows that antidiabetic drug classes and individual agents differ not only in glycemic efficacy but also in their effect on mortality and vascular end points. Hence, pharmacologic management has shifted its focus from glycemic control to prevention of cardiovascular outcomes, and therapeutic decision making is based on patients' history of atherosclerotic disease, heart failure, or chronic renal disease (1–3).

On the basis of pairwise meta-analyses of cardiovascular outcome trials, compared with placebo, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce cardiovascular death and stroke (4), whereas sodium–glucose cotransporter-2 (SGLT-2) inhibitors reduce heart failure hospitalization (5) and end-stage renal disease (6). Both drug classes reduce the composite of cardiovascular death, myocardial infarction, and stroke (7). However, the utility of conventional pairwise meta-analysis is limited because of its inability to assess comparative effects of interventions that have not been directly compared in head-to-head trials. This is particularly relevant for type 2 diabetes given the plethora of medication options and lack of head-to-head trial comparisons for many of them. Network meta-analysis can overcome this limitation by comparing all treatments and assessing their relative merits (8). This systematic review and network meta-analysis of randomized controlled trials assessing the long-term effects of antidiabetic drugs on clinically important outcomes and in clinically relevant subpopulations aimed to inform pharmacologic management of type 2 diabetes.

Methods

We registered the protocol (PROSPERO: CRD42019122043), followed standard reporting meth-

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ods (9), and report detailed methods in section 1 of the Supplement (available at Annals.org).

Data Sources and Searches

We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception through 18 December 2019 (without language restrictions; see section 1.2 of the Supplement); conference abstracts published in journals' supplementary issues; and ClinicalTrials.gov on 10 April 2020.

Study Selection

We included randomized controlled trials, published in English, in adults with type 2 diabetes that had a duration of intervention of at least 24 weeks, reported data for at least 1 outcome of interest, and assessed glucose-lowering drugs that had been approved or had pending applications for regulatory authorization in Europe or the United States. Comparisons among the following single interventions were included: metformin, sulphonylureas, pioglitazone, dipeptidyl peptidase-4 (DPP-4) inhibitors, GLP-1 RAs, SGLT-2 inhibitors, basal insulin, basal–bolus insulin regimens (including basal-plus insulin), premixed insulins, α-glucosidase inhibitors, meglitinides, or placebo. Agents that were withdrawn, are no longer available, or are not used in clinical practice (for example, rosiglitazone, taspoglutide, albiglutide, first-generation sulphonylureas, and insulin lente) were not eligible.

We considered all eligible medications as drug classes and excluded trials that compared medications of the same drug class, except for trials with intraclass comparisons of GLP-1 RAs or SGLT-2 inhibitors, which were also eligible. This decision was made a priori and was based on findings from trials suggesting a variable effect of individual GLP-1 RAs and SGLT-2 inhibitors on cardiovascular end points (10). In each comparison, background treatment was defined as the antidiabetic medication therapy used in both the intervention and control groups after randomization. Eligible background therapy was either no background treatment (monotherapy) or metformin-based background treatment (metformin only or metformin plus any other antidiabetic medication). After deduplication, pairs of independent reviewers (I.A., T.K., K.M., A.M., or P.A.) screened the titles and abstracts of retrieved records and examined the full text of potentially eligible records. Any disagreements were resolved through discussion with another reviewer (A.T. or E.B.).

Data Extraction and Quality Assessment

Study data were extracted and risk of bias (11) was assessed by pairs of independent reviewers (I.A., K.M., A.M., or P.A.); discrepancies were resolved through consensus with another reviewer (A.T., T.K., or E.B.). For each treatment, we merged outcome data from all approved doses into a single intervention group. If a study reported results at different time points, we preferably extracted data from the report with the longest duration of intervention for each outcome.

Our initial choices of relevant outcomes to examine were guided by findings of a mixed-methods study that included patient focus groups and a survey eliciting patients' and clinicians' preferences for diabetes-related outcomes (12). We considered change from baseline in hemoglobin A_{1c} level and all-cause mortality the primary outcomes in the network meta-analysis. Secondary outcomes were severe hypoglycemia, cardiovascular death, stroke, myocardial infarction, hospitalization for heart failure, diabetic retinopathy, and amputation. As a post hoc decision, we also extracted and analyzed data for end-stage renal disease from eligible cardiovascular and renal outcome trials.

Data Synthesis and Analysis

Initially, we did pairwise meta-analyses and then explored the transitivity assumption that a network meta-analysis approach was appropriate by comparing the distribution of potential effect modifiers across treatment comparisons (duration of diabetes, age, hemoglobin A_{1c} level at baseline, and body mass index) (13). We did frequentist random-effects network meta-analyses and calculated mean differences (MDs) for the change in hemoglobin A_{1c} level and odds ratios (ORs) and 95% CIs for dichotomous outcomes, assuming a common heterogeneity variable across all comparisons (14, 15). In case of sparse networks, we used a fixed-effects model, given that the common between-study heterogeneity cannot be estimated reliably in such networks (16). We evaluated heterogeneity by comparing the magnitude of the common between-study variance (τ^2) for each outcome with empirical distributions of heterogeneity variances (17, 18). We evaluated consistency in the networks both locally by comparing direct with indirect evidence (19) and globally by using the design-by-treatment interaction model (20). The presence of small-study effects bias was assessed by means of comparison-adjusted funnel plots (21).

Medications were analyzed as drug classes except for GLP-1 RAs and SGLT-2 inhibitors, which were also analyzed as individual agents. Data were synthesized into 2 main networks on the basis of use of treatments either as monotherapy in drug-naive patients or as add-on to metformin-based therapy. We analyzed mortality and vascular outcomes in separate subnetworks based on patients' cardiovascular risk at baseline. One subnetwork included only studies exclusively recruiting patients at increased cardiovascular risk, as defined in each study, whereas the remaining studies comprised the second subnetwork. For each subnetwork, we calculated the event rate of cardiovascular deaths in the placebo group across all trials as a proxy for the underlying average cardiovascular risk to explore the external validity of our findings (22). Glycemic outcomes (change in hemoglobin A_{1c} level and incidence of severe hypoglycemia) were analyzed in the main networks regardless of cardiovascular risk at baseline. In the monotherapy network, for these 2 outcomes, we did an exploratory analysis of data from trials of drug-naive patients and trials of patients with prior antidiabetic treatment, which was discontinued at randomiza-

tion. We also did a sensitivity analysis restricted to trials at low risk of bias for the 2 primary outcomes and a subgroup analysis with studies exclusively recruiting patients older than 65 years. All statistical analyses were done in R (R Foundation) using the meta and netmeta packages (23, 24). We evaluated confidence in network meta-analysis effect estimates for all outcomes and treatment comparisons using the CINeMA (Confidence In Network Meta-Analysis) methodological framework and application (25, 26).

Role of the Funding Source

The European Foundation for the Study of Diabetes, supported by an unrestricted educational grant from AstraZeneca, funded this study but had no role in the conception, design, data collection, conduct, analysis, or reporting; review of the manuscript; or the decision to submit the manuscript for publication.

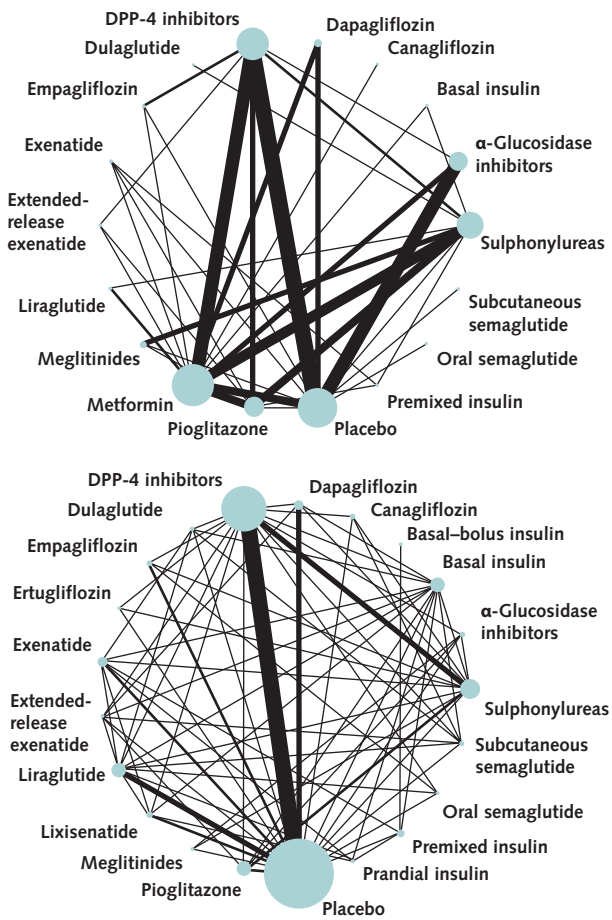
RESULTS

Overview of Trials

Electronic searches retrieved 52 374 records, of which 453 trials (320 474 patients) assessing 21 antidiabetic interventions from 9 drug classes met eligibility criteria (section 2 of the Supplement). Study and patient characteristics are presented in section 3 of the Supplement. Most studies (n = 360) were funded by the pharmaceutical industry. In 134 trials (41 862 patients), treatment interventions were used as monotherapy, of which 101 studies were in drug-naive patients, whereas the remaining studies recruited patients who had received antidiabetic treatment in the past but had all prior medication withdrawn at randomization. In 296 trials (264 087 patients), treatment interventions were used as an add-on to metformin-based therapy (metformin only or metformin plus any other antidiabetic medication). The remaining 23 studies (14 525 patients) included both groups that evaluated treatments as monotherapy and groups with patients receiving background metformin-based therapy. The median duration of trials was 26 weeks (interquartile range, 24 to 52 weeks). Three hundred studies had a double-blind design, 127 were open label, and 5 were single-blind; blinding status was unclear in the remaining studies. Mean hemoglobin A_{1c} level at baseline was 8.3% (SD, 0.76%), and mean body weight was 85.1 kg (SD, 9.17). The median hemoglobin A_{1c} level was 8.2% (interquartile range, 7.9% to 8.7%) in monotherapy trials and 8.2% (interquartile range, 8.0% to 8.5%) in trials with drugs as an add-on to metformin-based therapy. The median duration of diabetes across all trials was 6.9 years (interquartile range, 4.6 to 9.3 years). On the basis of the distribution of potential effect modifiers (duration of diabetes, age, hemoglobin A_{1c} level at baseline, and body mass index) across all treatment comparisons, eligible trials were deemed sufficiently similar to assume that a network meta-analysis was appropriate (section 4 of the Supplement).

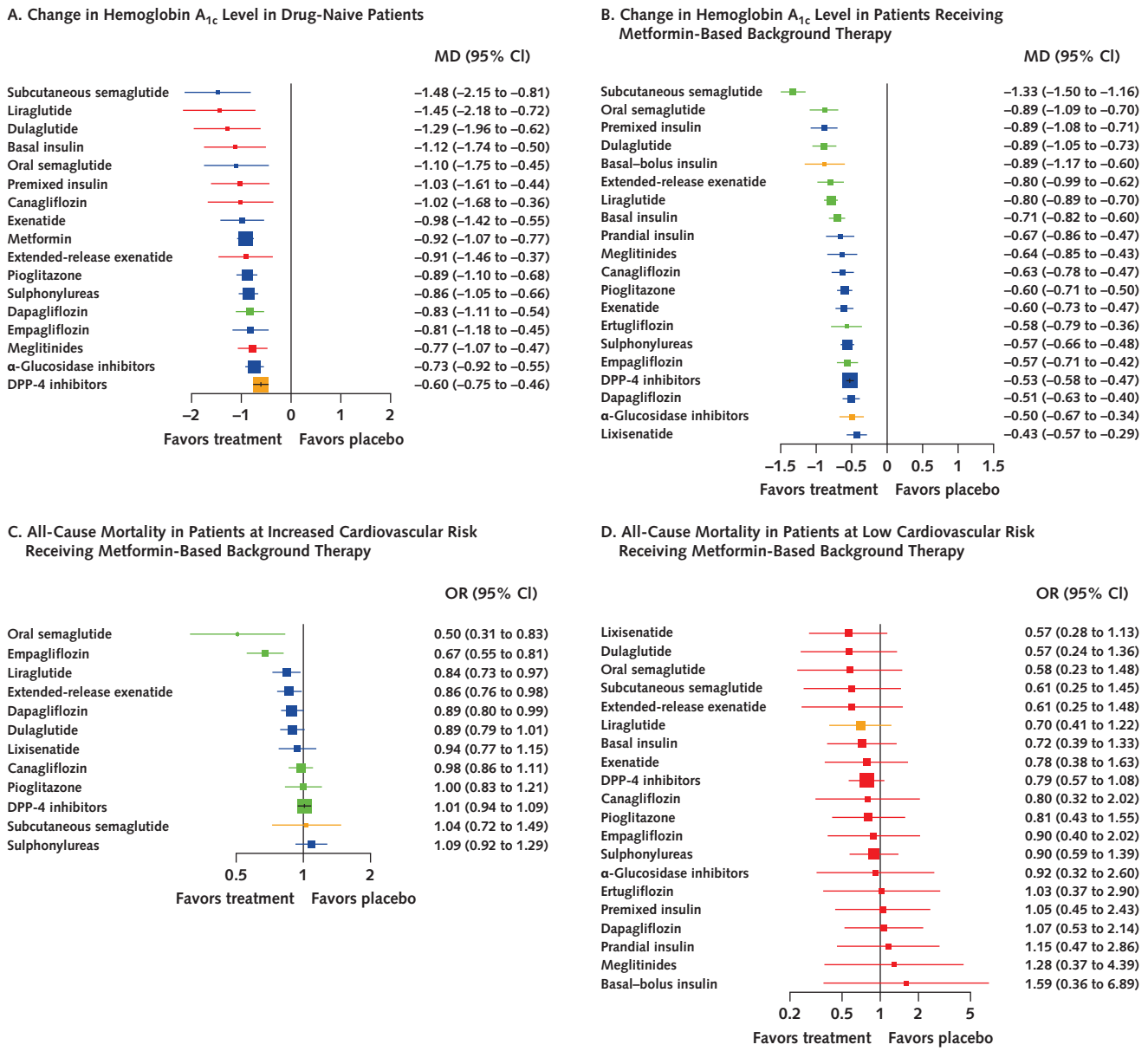
Figure 1 depicts the networks of trials used in the meta-analyses for the change in hemoglobin A_{1c} level when agents were used as monotherapy in drug-naive patients (95 trials; 26 331 patients) or as an add-on to metformin-based therapy (302 trials; 231 335 patients). The networks for all other outcomes are presented in sections 5 and 6 of the Supplement. Regarding change in hemoglobin A_{1c} level, 224 trials (58%) had low overall risk of bias (section 7 of the Supplement). For all-cause mortality, overall risk of bias was low in 80 trials (20%), whereas 292 trials (74%) had high risk of bias (section 7 of the Supplement). Comparison-adjusted funnel plots did not suggest presence of small-study effects bias (section 8 of the Supplement). There was no evidence of heterogeneity for any outcome except for change in hemoglobin A_{1c} level in both subnetworks and for diabetic retinopathy and amputation in the subnetwork of patients at increased cardiovascular risk receiving metformin-based background therapy (section 9 of the Supplement). The design-by-treatment

Figure 1. Meta-analysis networks for change in hemoglobin A_{1c} level.



Each cycle indicates a treatment node. Lines connecting 2 nodes represent direct comparisons between 2 treatments. The size of the nodes is proportional to the number of trials evaluating each treatment. The thickness of the lines is proportional to the number of trials directly comparing the 2 connected treatments. DPP-4 = dipeptidyl peptidase-4. **Top.** Monotherapy in drug-naive patients. **Bottom.** Add-on to metformin-based therapy.

Figure 2. Network meta-analysis results for the primary outcomes compared with placebo.



Treatments are presented according to their effect estimate compared with placebo. Effect sizes are presented as MDs or ORs with 95% CIs. Colors indicate the confidence in the effect estimates according to the CINeMA (Confidence In Network Meta-Analysis) framework: green = high, blue = moderate, orange = low, red = very low. DPP-4 = dipeptidyl peptidase-4; MD = mean difference; OR = odds ratio.

interaction model did not identify global inconsistency in any of the networks, except for change in hemoglobin A_{1c} level in the network of drug-naive patients. Local inconsistency in all analyses was generally low (section 10 of the Supplement).

Drug-Naive Patients

Glycemic Outcomes

Pairwise meta-analysis results for drug-naive patients are presented in section 11 of the Supplement. Network meta-analysis results are presented in section 12 of the Supplement. All treatments reduced hemoglobin A_{1c} level compared with placebo, with MDs ranging from −1.48% (95% CI, −2.15% to −0.81%) for subcutaneous semaglutide to −0.60% (CI, −0.75% to −0.46%) for DPP-4 inhibitors (Figure 2, *A*). The confidence in these effect estimates was moderate (section 13 of the Supplement). All treatments reduced hemoglobin A_{1c} level to a similar extent with metformin, except for DPP-4 inhibitors (MD, 0.32% [CI, 0.17% to 0.46%]), which were also inferior to liraglutide, subcutaneous semaglutide, pioglitazone, and sulphonylureas. For all treatments, there was no difference versus placebo or metformin in the incidence of severe hypoglycemia (59 studies; 24 479 patients).

Mortality and Vascular Outcomes

Network meta-analysis results for mortality and vascular outcomes in drug-naive patients are presented in section 14 of the Supplement. We did not identify any trials exclusively recruiting drug-naive patients at increased cardiovascular risk; hence, for mortality and vascular outcomes, all trials in drug-naive patients were analyzed in a single network. Of note, patients in these trials likely had low underlying cardiovascular risk given that no cardiovascular deaths were reported among patients in the placebo groups. All medications had a neutral effect on all-cause mortality (97 studies; 31 489 patients), cardiovascular death (91 studies; 24 212 patients), stroke (16 studies; 10 744 patients), myocardial infarction (27 studies; 15 286 patients), or hospitalization for heart failure (8 studies; 2560 patients). The confidence in these estimates was generally deemed very low (section 15 of the Supplement). We did not do meta-analyses for diabetic retinopathy and amputation because of a paucity of pertinent data.

Patients on Metformin-Based Background Therapy

Glycemic Outcomes

Pairwise meta-analysis results for patients on metformin-based background therapy are presented in section 11 of the Supplement. Network meta-analysis results for glycemic outcomes for these patients are presented in section 16 of the Supplement. The greatest placebo-subtracted reductions in hemoglobin A_{1c} level were seen with GLP-1 RAs, premixed insulin, and basal–bolus insulin regimens (Figure 2, *B*). Subcutaneous semaglutide was more efficacious in lowering hemoglobin A_{1c} level than all other treatments (MD vs. placebo, −1.33% [CI, −1.50% to −1.16%]). Sulphonylureas, premixed insulin, and basal–bolus insulin were associated with an increase in the incidence of severe hypoglycemia (252 studies; 261 559 patients). The confidence in effect estimates for change in hemoglobin A_{1c} level was high to moderate, whereas the confidence for severe hypoglycemia was generally moderate to low (section 17 of the Supplement).

Patients at Increased Cardiovascular Risk

Network meta-analysis results for mortality and vascular outcomes for patients at increased cardiovascular risk receiving metformin-based background therapy are presented in section 18 of the Supplement. This network included 18 large cardiovascular or renal outcome trials and 3 small studies that recruited patients with a history of cardiovascular disease or chronic kidney disease, totaling 145 694 patients. The mean event rate of cardiovascular deaths in the placebo group in this subnetwork of trials was 4.9%. The definition of cardiovascular risk varied among studies; in some trials all patients had a history of cardiovascular disease, whereas other trials recruited both patients with established cardiovascular disease and patients with isolated cardiovascular risk factors.

Compared with placebo, all-cause mortality (21 studies; 145 694 patients) was reduced with oral semaglutide (OR, 0.50 [CI, 0.31 to 0.83]), empagliflozin (OR, 0.67 [CI, 0.55 to 0.81]), liraglutide (OR, 0.84 [CI, 0.73 to 0.97]), extended-release exenatide (OR, 0.86 [CI, 0.76 to 0.98]), and dapagliflozin (OR, 0.89 [CI, 0.80 to 0.99]) (Figure 2, *C*). The confidence in these effect estimates was high to moderate (section 19 of the Supplement). On the basis of indirect comparisons, oral semaglutide and empagliflozin also had a favorable effect compared with canagliflozin, dapagliflozin, DPP-4 inhibitors, dulaglutide, extended-release exenatide, lixisenatide, pioglitazone, subcutaneous semaglutide, and sulphonylureas. Compared with placebo, oral semaglutide, empagliflozin, and liraglutide were associated with lower odds of cardiovascular death (21 studies; 145 694 patients) (Figure 3). The confidence in these effect estimates was high to moderate (Figure 3). Empagliflozin had a favorable effect on cardiovascular death compared with several other treatments, including canagliflozin, dapagliflozin, DPP-4 inhibitors, dulaglutide, extended-release exenatide, pioglitazone, and sulphonylureas (Figure 3).

The networks for stroke and myocardial infarction included 20 studies with 143 555 patients. Compared with placebo, GLP-1 RAs reduced the incidence of stroke (OR, 0.84 [CI, 0.75 to 0.93]). In terms of individual agents, the odds of stroke were lower with subcutaneous semaglutide (OR, 0.61 [CI, 0.37 to 0.99]) and dulaglutide (OR, 0.76 [CI, 0.62 to 0.94]). The confidence in these effect estimates was high to moderate (Figure 3). No differences were evident among any treatments for myocardial infarction. Sodium–glucose cotransporter-2 inhibitors reduced hospitalization for heart failure (19 studies; 142 149 patients) when compared with placebo (OR, 0.72 [CI, 0.65 to 0.80]). This effect was consistent for empagliflozin (OR, 0.65 [CI, 0.50 to 0.85]), canagliflozin (OR, 0.72 [CI, 0.60 to 0.87]), and dapagliflozin (OR, 0.75 [CI, 0.64 to 0.86]). The odds of hospitalization for heart failure were increased with pioglitazone compared with placebo (OR, 1.42 [CI, 1.10 to 1.83]) or other treatments (Figure 3). The confidence in effect estimates for hospitalization for heart failure was moderate (Figure 3).

The odds of diabetic retinopathy (12 studies; 95 664 patients) were similar to placebo for all treatments, except for subcutaneous semaglutide (OR, 1.75 [CI, 1.10 to 2.78]). The odds of amputation (11 studies; 93 922 patients) versus placebo were increased with canagliflozin (OR, 1.61 [CI, 1.27 to 2.05]) and reduced with liraglutide (OR, 0.65 [CI, 0.45 to 0.96]). The network for end-stage renal disease included 11 studies with 98 379 patients. Compared with placebo, SGLT-2 inhibitors reduced the odds of end-stage renal disease (OR, 0.63 [CI, 0.50 to 0.79]). This effect was consistent for dapagliflozin (OR, 0.32 [CI, 0.13 to 0.79]), empagliflozin (OR, 0.46 [CI, 0.22 to 0.98]), and canagliflozin (OR, 0.69 [CI, 0.54 to 0.88]). The confidence in effect estimates for diabetic retinopathy, amputation, and end-stage renal disease was low (section 19 of the Supplement).

Figure 3. Network meta-analysis results for cardiovascular death (*left lower half*) and hospitalization for heart failure (*right upper half*) in patients at increased cardiovascular risk receiving metformin-based background therapy.

Canagliflozin	0.97† (0.76–1.22)	*0.68† (0.55–0.84)*	0.76† (0.59–1.00)	1.10† (0.80–1.54)	*0.76† (0.58–0.98)*	0.82† (0.63–1.07)	0.75† (0.55–1.03)	*0.51† (0.37–0.69)*	0.85‡ (0.46–1.56)	0.66† (0.43–1.00)	0.83† (0.58–1.17)	*0.72* (0.60–0.87)*
1.05† (0.85–1.30)	Dapagliflozin	*0.70* (0.59–0.84)*	0.79† (0.62–1.01)	1.14† (0.84–1.56)	*0.78† (0.62–0.99)*	0.85† (0.67–1.08)	0.78† (0.58–1.04)	*0.53† (0.39–0.70)*	0.88‡ (0.48–1.60)	0.68† (0.45–1.02)	0.86† (0.61–1.19)	*0.75* (0.64–0.86)*
0.98† (0.82–1.16)	0.92† (0.78–1.10)	DPP-4 inhibitors	1.13† (0.91–1.40)	*1.63† (1.22–2.18)*	1.12† (0.90–1.38)	1.22† (0.98–1.50)	1.11† (0.84–1.46)	*0.75† (0.57–0.98)*	1.25‡ (0.70–2.26)	0.97‡ (0.66–1.43)	1.22† (0.92–1.62)	1.06† (0.96–1.17)
1.06† (0.85–1.32)	1.00‡ (0.81–1.24)	1.08† (0.90–1.30)	Dulaglutide	*1.45† (1.04–2.01)*	0.99† (0.76–1.29)	1.08† (0.82–1.41)	0.98‡ (0.71–1.35)	*0.66† (0.48–0.91)*	1.11‡ (0.60–2.05)	0.86‡ (0.56–1.31)	1.08‡ (0.76–1.54)	0.94‡ (0.78–1.14)
1.57† (1.19–2.08)	*1.49† (1.14–1.96)*	*1.62† (1.26–2.07)*	*1.49† (1.13–1.97)*	Empagliflozin	*0.68† (0.49–0.95)*	0.74† (0.54–1.03)	*0.68† (0.47–0.98)*	*0.46† (0.32–0.67)*	0.77‡ (0.41–1.46)	*0.59† (0.37–0.94)*	0.75† (0.50–1.12)	*0.65* (0.50–0.85)*
1.09† (0.88–1.34)	1.03‡ (0.83–1.27)	1.11† (0.94–1.33)	1.03‡ (0.83–1.28)	*0.69† (0.52–0.91)*	Extended-release exenatide	1.09† (0.84–1.42)	0.99‡ (0.72–1.36)	*0.67† (0.49–0.92)*	1.12‡ (0.61–2.07)	0.87‡ (0.57–1.32)	1.09‡ (0.77–1.56)	0.95‡ (0.79–1.15)
1.24† (0.98–1.57)	1.17† (0.93–1.48)	*1.27† (1.04–1.55)*	1.17† (0.92–1.49)	0.79† (0.59–1.05)	1.14† (0.90–1.44)	Liraglutide	0.91† (0.67–1.25)	*0.62† (0.45–0.84)*	1.03‡ (0.56–1.90)	0.80† (0.52–1.21)	1.00‡ (0.71–1.43)	0.87† (0.73–1.05)
0.98† (0.74–1.28)	0.93† (0.71–1.21)	1.00‡ (0.78–1.28)	0.92† (0.70–1.22)	*0.62† (0.45–0.86)*	0.90† (0.69–1.18)	0.79† (0.59–1.05)	Lixisenatide	*0.68† (0.47–0.97)*	1.13‡ (0.60–2.13)	0.87‡ (0.56–1.38)	1.10‡ (0.74–1.63)	0.96† (0.74–1.24)
0.99‡ (0.74–1.32)	0.94† (0.71–1.25)	1.01† (0.78–1.31)	0.94† (0.70–1.25)	*0.63† (0.45–0.88)*	0.91† (0.69–1.21)	0.80† (0.59–1.08)	1.01‡ (0.73–1.41)	Pioglitazone	1.68† (0.89–3.16)	1.29† (0.82–2.04)	*1.63† (1.10–2.41)*	1.42† (1.10–1.83)
1.88† (1.00–3.52)	1.78† (0.95–3.33)	*1.93† (1.04–3.57)*	1.78† (0.95–3.34)	1.19‡ (0.62–2.29)	1.73† (0.93–3.24)	1.52† (0.80–2.87)	1.93† (1.01–3.69)	1.90† (0.99–3.66)	Oral semaglutide	0.77‡ (0.39–1.54)	0.97‡ (0.51–1.87)	0.85‡ (0.47–1.51)
1.01‡ (0.64–1.57)	0.96‡ (0.61–1.49)	1.03‡ (0.67–1.59)	0.95‡ (0.61–1.49)	0.64† (0.40–1.03)	0.93‡ (0.59–1.45)	0.81† (0.52–1.29)	1.03‡ (0.64–1.66)	1.02‡ (0.63–1.65)	0.54† (0.26–1.12)	Subcutaneous semaglutide	1.26† (0.78–2.04)	1.10‡ (0.75–1.60)
1.00‡ (0.76–1.33)	0.95† (0.72–1.25)	1.03‡ (0.83–1.28)	0.95† (0.72–1.26)	*0.64† (0.46–0.88)*	0.92† (0.70–1.22)	0.81† (0.60–1.09)	1.03‡ (0.74–1.42)	1.01‡ (0.73–1.41)	0.53† (0.28–1.02)	1.00‡ (0.62–1.61)	Sulphonylureas	0.87† (0.65–1.17)
0.96† (0.83–1.12)	0.91† (0.79–1.06)	0.99* (0.90–1.08)	0.91† (0.78–1.07)	*0.61* (0.49–0.77)*	0.89† (0.76–1.03)	*0.78† (0.65–0.93)*	0.99‡ (0.79–1.24)	0.97† (0.76–1.24)	*0.51† (0.28–0.94)*	0.96‡ (0.63–1.45)	0.96† (0.76–1.21)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs of the column-defining treatment compared with the row-defining treatment for cardiovascular death. Treatment estimates are ORs and 95% CIs of the row-defining treatment compared with the column-defining treatment for hospitalization for heart failure. Odds ratios less than 1 favor the column-defining treatment for cardiovascular death and the row-defining treatment for hospitalization for heart failure. Significant results are italicized. DPP-4 = dipeptidyl peptidase-4; OR = odds ratio.
* High level of confidence in effect estimate.
† Moderate level of confidence in effect estimate.
‡ Low level of confidence in effect estimate.

Patients at Low Cardiovascular Risk

Network meta-analysis results for mortality and vascular outcomes for patients at low cardiovascular risk receiving metformin-based background therapy are presented in section 20 of the Supplement. Cardiovascular deaths in the placebo groups of studies in this subnetwork were rare (mean event rate, 0.1%). When treatments were analyzed as drug classes, GLP-1 RAs were associated with reduced odds of all-cause mortality (292 studies; 136 942 patients) versus placebo (OR, 0.64 [CI, 0.45 to 0.91]). Incidence of myocardial infarction (131 studies; 91 152 patients) was lower with GLP-1 RAs and SGLT-2 inhibitors than placebo, whereas odds of diabetic retinopathy (38 studies; 25 151 patients) were increased with sulphonylureas (OR versus placebo, 2.48 [CI, 1.02 to 6.07]). All drug classes were similar to placebo in terms of cardiovascular death (263 studies; 118 419 patients), stroke (106 studies; 76 660 patients), hospitalization for heart failure (27 studies; 12 570 patients), and amputation (16 studies; 8921 patients). When GLP-1 RAs and SGLT-2 inhibitors were analyzed as individual agents, all treatments were similar to placebo in terms of all-cause mortality (Figure 2, *D*) and cardiovascular outcomes. The confidence in most effect estimates in this subnetwork was very low because of imprecision and within-study bias (section 21 of the Supplement).

Additional Analyses

Sensitivity analyses that included only trials at low risk of bias and exploratory analyses that included all monotherapy trials regardless of patients' drug-naive status yielded results similar to those of the main analyses (section 22 of the Supplement). In the subgroup analysis of trials exclusively recruiting older patients, metformin monotherapy was more efficacious than α-glucosidase inhibitors in lowering hemoglobin A_{1c} level (7 trials; 2303 patients), whereas sulphonylureas were more efficacious than DPP-4 inhibitors when used as an add-on to metformin-based therapy (6 trials; 1754 patients) (section 23 of the Supplement). In this subgroup of patients, all treatments were similar to placebo in terms of all-cause mortality (section 23 of the Supplement).

DISCUSSION

In drug-naive patients, all medications except for DPP-4 inhibitors were as efficacious as metformin in reducing hemoglobin A_{1c} level. In drug-naive patients at low cardiovascular risk, there were no differences in mortality and vascular outcomes among medications. We did not identify any trials exclusively recruiting drug-naive patients at increased cardiovascular risk.

When used as an add-on to metformin-based therapy, insulin regimens and GLP-1 RAs were the most efficacious in reducing hemoglobin A_{1c} level, whereas sulphonylureas, basal–bolus insulin therapy, and premixed insulin increased the odds of severe hypoglycemia. In patients at low cardiovascular risk receiving metformin-based background therapy, all treatments were similar to placebo for vascular outcomes. In patients at increased cardiovascular risk receiving metformin-based background therapy, the addition of oral semaglutide, empagliflozin, or liraglutide reduced both all-cause mortality and cardiovascular death, whereas the addition of extended-release exenatide or dapagliflozin reduced only all-cause mortality. Both dulaglutide and subcutaneous semaglutide lowered the odds of stroke. Canagliflozin, dapagliflozin, and empagliflozin had a favorable effect on hospitalization for heart failure and development of end-stage renal disease. Subcutaneous semaglutide was associated with increased odds of diabetic retinopathy. Incidence of amputation was increased with canagliflozin and reduced with liraglutide.

We searched MEDLINE to April 2020 to identify other pertinent network meta-analyses. Consistent with our findings for drug-naive patients, an earlier network meta-analysis of 75 trials found that, when used as monotherapy, antidiabetic agents were similar to metformin in reducing hemoglobin A_{1c} level, except for DPP-4 inhibitors, which were less efficacious (27). A network meta-analysis of GLP-1 RAs and SGLT-2 inhibitors including 64 trials showed that semaglutide was the most efficacious agent in lowering hemoglobin A_{1c} level (28), a finding that we corroborated both for drug-naive patients and patients receiving metformin-based background therapy. In accordance with our findings for patients at increased cardiovascular risk, a meta-analysis of 14 cardiovascular outcome trials found that GLP-1 RAs and SGLT-2 inhibitors reduced all-cause mortality and cardiovascular death, whereas GLP-1 RAs lowered the risk for stroke (29). In that analysis, both drug classes reduced hospitalization for heart failure (29), whereas our analysis, which included 4 additional cardiovascular outcome trials (30–33), found that only SGLT-2 inhibitors reduced hospitalization for heart failure. A previous analysis suggested that sulphonylureas may increase the risk for diabetic retinopathy (34). Our analysis corroborated that finding in patients at low cardiovascular risk receiving metformin-based background therapy, although the level of confidence was very low. A network meta-analysis of 301 trials identified through March 2016 did not find any significant effect on all-cause mortality or cardiovascular death for 9 antidiabetic drug classes, either as monotherapy or as an add-on to metformin (35). Conversely, another network meta-analysis of 236 trials, including 9 cardiovascular outcome trials retrieved through October 2017, found that GLP-1 RAs and SGLT-2 inhibitors reduced all-cause mortality and cardiovascular death in all patients with type 2 diabetes regardless of background therapy or underlying cardiovascular risk (36). Our findings corroborated the latter meta-analysis for specific GLP-1 RAs and SGLT-2 inhibitors in patients at increased cardiovascular risk receiving metformin-based background therapy. Finally, a recently published umbrella review suggesting that specific GLP-1 RAs and SGLT-2 inhibitors have favorable cardiovascular effects was based mainly on evidence from preexisting pairwise meta-analyses; grouped patients with diabetes, prediabetes, or high risk for diabetes together; and did not analyze treatments by background therapy or history of cardiovascular disease (37).

In comparison with previous network meta-analyses, we incorporated a considerably larger number of randomized controlled trials (453 trials; 320 474 patients), including recently published cardiovascular or renal outcome trials and trials with novel agents, such as oral semaglutide. We highlighted both interclass and intraclass differences among treatments and synthesized all available evidence in clinically relevant subnetworks based on both presence of background antidiabetic therapy and patients' underlying cardiovascular risk, in accordance with current recommendations from the American Diabetes Association, the European Association for the Study of Diabetes, and the European Society of Cardiology (1–3).

Certain limitations should be acknowledged. Our subnetwork of patients at low cardiovascular risk comprised a mixed population of patients with unknown or variable cardiovascular risk. The level of confidence in the effect estimates for mortality and vascular outcomes in patients at low cardiovascular risk was very low. The definition of cardiovascular risk was not consistent among individual trials in the network of patients at increased cardiovascular risk. There were potential differences in patients' baseline renal function among individual trials that could have confounded or affected findings for end-stage renal disease. Background therapy was not identical in the network of metformin-based trials, whereas hemoglobin A_{1c} level effects may have been masked in cardiovascular outcome trials where glycemic equipoise was attempted.

Recently completed and ongoing trials are expected to strengthen the evidence base about the effects of GLP-1 RAs and SGLT-2 inhibitors on vascular end points. Our search of ClinicalTrials.gov in April 2020 retrieved 39 ongoing or recently completed but unpublished pertinent trials (section 24 of the **Supplement**). These include 2 ongoing cardiovascular outcome trials with oral semaglutide (NCT03914326) and dapagliflozin (NCT03982381), the recently completed cardiovascular outcome trial for ertugliflozin (NCT01986881), and 3 ongoing renal outcome trials with subcutaneous semaglutide (NCT03819153), dapagliflozin (NCT03036150), and empagliflozin (NCT03594110). The renal outcome trials for dapagliflozin and empagliflozin also recruit patients without type 2 diabetes, provided they have chronic kidney disease. Two ongoing trials with empagliflozin (NCT03057977 and NCT03057951) and 1 trial with dapagliflozin (NCT03619213) are evaluating the long-term effects of these agents on the composite outcome

of cardiovascular death or hospitalization for heart failure in patients with heart failure with or without type 2 diabetes (section 24 of the **Supplement**).

In conclusion, the use of metformin as first-line treatment of drug-naive patients at low cardiovascular risk seems justified. Given the lack of pertinent evidence, we could not reach a conclusion about the optimal initial treatment of drug-naive patients at increased cardiovascular risk. In patients at low cardiovascular risk receiving metformin-based background therapy, choice among available agents should be based on their effect on other efficacy and safety outcomes because of lack of difference in vascular outcomes. For patients at increased cardiovascular risk receiving metformin-based background therapy, the optimal choice between specific GLP-1 RAs and SGLT-2 inhibitors should be based on the cardiovascular profile of individual agents and guided by patients' personal preferences and therapeutic priorities.

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