Original Investigation

Comparison of Clinical Outcomes and Adverse Events Associated With Glucose-Lowering Drugs in Patients With Type 2 Diabetes
A Meta-analysis

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IMPORTANCE Numerous glucose-lowering drugs are used to treat type 2 diabetes.

OBJECTIVE To estimate the relative efficacy and safety associated with glucose-lowering drugs including insulin.

DATA SOURCES Cochrane Library Central Register of Controlled Trials, MEDLINE, and EMBASE databases through March 21, 2016.

STUDY SELECTION Randomized clinical trials of 24 weeks' or longer duration.

DATA EXTRACTION AND SYNTHESIS Random-effects network meta-analysis.

MAIN OUTCOMES AND MEASURES The primary outcome was cardiovascular mortality. Secondary outcomes included all-cause mortality, serious adverse events, myocardial infarction, stroke, hemoglobin A_{1c} (HbA_{1C}) level, treatment failure (rescue treatment or lack of efficacy), hypoglycemia, and body weight.

RESULTS A total of 301 clinical trials (1 417 367 patient-months) were included; 177 trials (56 598 patients) of drugs given as monotherapy; 109 trials (53 030 patients) of drugs added to metformin (dual therapy); and 29 trials (10 598 patients) of drugs added to metformin and sulfonylurea (triple therapy). There were no significant differences in associations between any drug class as monotherapy, dual therapy, or triple therapy with odds of cardiovascular or all-cause mortality. Compared with metformin, sulfonylurea (standardized mean difference [SMD], 0.18 [95% CI, 0.01 to 0.34]), thiazolidinedione (SMD, 0.16 [95% CI, 0.00 to 0.31]), DPP-4 inhibitor (SMD, 0.33 [95% CI, 0.13 to 0.52]), and α-glucosidase inhibitor (SMD, 0.35 [95% CI, 0.12 to 0.58]) monotherapy were associated with higher HbA_{1C} levels. Sulfonylurea (odds ratio [OR], 3.13 [95% CI, 2.39 to 4.12]; risk difference [RD], 10% [95% CI, 7% to 13%]) and basal insulin (OR, 17.9 [95% CI, 1.97 to 162]; RD, 10% [95% CI, 0.08% to 20%]) were associated with greatest odds of hypoglycemia. When added to metformin, drugs were associated with similar HbA_{1C} levels, while SGLT-2 inhibitors offered the lowest odds of hypoglycemia (OR, 0.12 [95% CI, 0.08 to 0.18]; RD, −22% [−27% to −18%]). When added to metformin and sulfonylurea, GLP-1 receptor agonists were associated with the lowest odds of hypoglycemia (OR, 0.60 [95% CI, 0.39 to 0.94]; RD, −10% [95% CI, −18% to −2%]).

CONCLUSIONS AND RELEVANCE Among adults with type 2 diabetes, there were no significant differences in the associations between any of 9 available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality. Metformin was associated with lower or no significant difference in HbA_{1C} levels compared with any other drug classes. All drugs were estimated to be effective when added to metformin. These findings are consistent with American Diabetes Association recommendations for using metformin monotherapy as initial treatment for patients with type 2 diabetes and selection of additional therapies based on patient-specific considerations.

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Diabetes was estimated to account for approximately 1.5 million deaths in 2012, with more than 80% of diabetes-related deaths occurring in low- and middle-income countries.[1] In addition, diabetes was estimated to cause disability (blindness, limb amputation, kidney failure, cardiovascular events) among 47 million people in 2010.[2] Lifestyle modification and glucose-lowering drug treatment are the mainstay of therapy to prevent and delay diabetes-related complications. A large number of glucose-lowering drug classes are approved for type 2 diabetes, including metformin, insulins, sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose–linked cotransporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, meglitinides, and α-glucosidase inhibitors.

American Diabetes Association guidelines suggest metformin as first-line drug treatment, and, if glycemic control is not achieved, the addition of a second drug (often sulfonylurea) is recommended.[3] Triple therapy with 2 drugs added to metformin is suggested when glycemic control is no longer sustained with 2 drugs. Annual drug expenditure for glucose-lowering therapy was estimated at $31.7 billion for 2012 in the United States, with most patients receiving at least dual therapy.[4] However, despite the widespread use of these drugs, the comparative effects of glucose-lowering strategies on clinical outcomes, especially mortality and cardiovascular events, are uncertain.[5,6] Emerging evidence suggests that SGLT-2 inhibitors and GLP-1 receptor agonists lower rates of a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke when the drug is added to standard care in high-risk patients.[7,8] However, randomized clinical trials of diabetes medications have been generally insufficiently powered to establish the role of drug treatment for preventing cardiovascular death, limiting the ability of single studies to inform practice and policy.

Head-to-head trials and standard meta-analysis do not allow all treatments to be compared simultaneously, constraining the comparative assessment of longer-term benefits and risks associated with available medications.[6] Therefore, a systematic review with network meta-analysis was conducted to compare and rank glucose-lowering treatments for type 2 diabetes.

Key Points

Question What are the most effective medical treatments for type 2 diabetes?

Findings In this systematic review with network meta-analysis, risks of cardiovascular and all-cause mortality were not different between any glucose-lowering drugs alone or in combination. Metformin was associated with lower or similar HbA_{1C} levels compared with all other drugs given as monotherapy. All drugs were estimated to be effective when added to metformin.

Meaning Metformin monotherapy is an appropriate initial treatment for patients with type 2 diabetes. Selection of additional therapies can be based on patient-specific considerations.

Methods

Study Design

A systematic review with network meta-analysis was conducted with a frequentist approach using a prespecified study protocol. Additional post hoc analyses and changes to the protocol are described in eMethods 1 in the Supplement. The study was reported according to the PRISMA extension statement for network meta-analysis.[9]

Search Strategy and Selection Criteria

Randomized clinical trials publicly available on March 21, 2016, comparing 2 individual glucose-lowering drug classes for treatment of type 2 diabetes were identified. The Cochrane Library Central Register of Controlled Trials, MEDLINE, and EMBASE were searched using a highly sensitive search strategy developed by an experienced trials search coordinator for each database (eTable 1 in the Supplement).

Study Selection and Data Extraction

Parallel-group randomized clinical trials in which treatment was given for 24 weeks or longer were included. Comparisons of the following drug classes were considered: metformin, sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, basal insulin, meglitinide, and α-glucosidase inhibitor. Trials in which basal-bolus and prandial insulin regimens were compared with the specified drug classes of interest or placebo or standard therapy were also included. Trials were considered within separate analytical networks based on whether drugs were given as monotherapy, added to metformin (dual therapy), or added to metformin and sulfonylurea (triple therapy). Metformin plus sulfonylurea was chosen a priori as the baseline therapy for 3-drug combinations, as this has been most widely used.[10] Studies evaluating treatments that were no longer available or withdrawn from the market (eg, phenformin and troglitazone) were excluded, as were those that did not principally act to lower blood glucose levels. Studies evaluating treatment in children (18 years or younger) and pregnant women were ineligible.

Two investigators (G.D.B., S.P.) screened the titles and abstracts of retrieved citations independently to identify potentially eligible trials. Any discrepancies were discussed between researchers until a consensus was reached. Any potentially relevant citation was then retrieved in full-text and reviewed by the same 2 investigators against the eligibility criteria, and decisions about eligibility were double-checked independently by a third author (V.G.). Information in non–English-language studies was formally translated before assessment. At least 2 investigators (S.C.P., D.W.J., J.M., V.G., G.D.B., M.R., P.N., V.S., S.B., Y.C., A.N., M.B., L.F., A.L., N.A., Y.L., and S.T.) independently reviewed the main reports and supplementary materials, including data reported in the ClinicalTrials.gov portal, and extracted study and patient characteristics and treatment strategies. All extracted data were independently checked by 2 authors (S.P., J.M.).

Outcomes

The association of drug treatment with cardiovascular mortality was the primary end point. Secondary individual effi-

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cacy end points were all-cause mortality, myocardial infarction, stroke, hemoglobin A_{1c} (HbA_{1C}) level, and treatment failure (lack of efficacy or need for rescue treatment). Secondary individual safety end points were serious adverse events, hypoglycemia, and body weight.

Quality Assessment—Risk of Bias

Two investigators (J.M., V.G.) used the Cochrane tool to assess study risks of bias.[11]

Statistical Analysis

Detailed methods for statistical analysis were described in eMethods 1 in the Supplement. The clinical setting and characteristics of the trials (considering age, proportion of men, HbA_{1C} level, body weight, duration of diagnosed diabetes, duration of follow-up, and year of publication) reporting each drug class were evaluated to consider whether the included trials were sufficiently similar that a network meta-analysis approach was appropriate. Treatment effects were then estimated by random-effects pairwise meta-analysis.[12] The association between treatment and outcomes was estimated using standardized mean differences (SMD) for HbA_{1C} level and body weight and odds ratios (ORs) for cardiovascular mortality, all-cause mortality, myocardial infarction, stroke, serious adverse events, treatment failure, and hypoglycemia, together with 95% confidence intervals. In general, an SMD of 0.2 is considered small, 0.5 medium, and 0.8 large.[13]

Frequentist network meta-analysis was then used to compare available treatment strategies within a single analytical framework.[14,15] Odds ratios were also accompanied by absolute risk differences (RDs). Network meta-analysis was performed in Stata version 13 (StataCorp) using the network command and self-programmed Stata routines.[16,17] The relative ranking probability of each treatment was estimated, and the treatment hierarchy of competing interventions was obtained using rankograms, surface under the cumulative ranking (SUCRA) curves, and mean ranks. The restricted maximum likelihood method was used to estimate heterogeneity, assuming a common estimate for heterogeneity variance across different comparisons for a single clinical outcome.[18] The extent of heterogeneity in each network analysis was evaluated by comparing the magnitude of a common heterogeneity variance for the network (tau [τ]) with an empirical distribution of heterogeneity variances, considering the range of expected treatment estimates (ORs and SMDs), in which values of τ from 0.1 to 0.5 were reasonable, 0.5 to 1.0 were considered fairly high, and greater than 1.0 represented fairly extreme heterogeneity.[19-21]

To explore for evidence of within-network inconsistency, the loop-specific approach was used. This compared the estimated treatment effects from head-to-head trials with corresponding treatment estimates derived from triangular and quadrilateral loops in the treatment network. A derived inconsistency factor was the difference between ORs or SMDs from direct and indirect evidence. An inconsistency factor with wide confidence intervals indicated the need for further investigation to identify possible sources of heterogeneity between direct and indirect evidence.[22] To check the assumption of consistency in the entire analytical network, a "design-by-treatment" approach was used.[23] A comparison-adjusted funnel plot of treatment estimates for drug classes as monotherapy on cardiovascular mortality was used to assess for evidence of small-study effects. In addition, random-effects bivariable network meta-regression analyses were conducted to assess baseline HbA_{1C} level, body weight, duration of diagnosed diabetes, and age as effect modifiers on estimates for end-of-treatment HbA_{1C} level, body weight, and hypoglycemia. Post hoc sensitivity analysis was performed to assess for intraclass variation in the effect of individual sulfonylurea drugs as monotherapy on odds of hypoglycemia. Additional post hoc sensitivity analyses were conducted restricted to studies of monotherapy in which allocation concealment was at low risk of bias.

Statistical testing was 2-sided, with $P < .05$ considered statistically significant.

Results

Electronic searching through March 21, 2016, retrieved 9819 citations (**Figure 1**). Overall, 301 randomized clinical trials involving 118 094 patients were eligible for inclusion in the review. In 177 trials (56 598 patients), drugs were given as monotherapy; in 109 trials (53 030 patients), drugs were added to metformin; and in 29 trials (10 598 patients), drugs were added to metformin and sulfonylurea therapy (eTables 2-4 in the Supplement). The number of patients allocated to each treatment in trials ranged between 8[24-26] and 1562[27] (median, 104 adults [interquartile range, 46-190]).

The mean HbA_{1C} level at randomization was 8.2% (SD, 1.1%) in monotherapy trials, 8.2% (SD, 0.6%) in dual-therapy trials, and 8.4% (SD, 0.6%) in triple-therapy trials. Mean body weight at baseline was 81.9 (SD, 8.9) kg in monotherapy trials, 83.8 (SD, 15.7) kg in dual-therapy trials, and 84.1 (SD, 9.5) kg in triple-therapy trials. The median duration of diagnosed diabetes at randomization was 5.7 (interquartile range, 3.3-7.0) years. Mean study follow-up ranged between 24 weeks and 76.8 months (median, 6 months [interquartile range, 5.5-12 months]).

The clinical trials were deemed sufficiently similar on the basis of study-level age, sex, HbA_{1C} level, body weight, duration of diagnosed diabetes, and duration of follow-up that a network analysis was appropriate, although newer drug classes (DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists) were evaluated in trials published more recently (eFigure 1 in the Supplement).

Risks of Bias

Overall, the risk of bias was high or unclear for random sequence generation in 208 trials (69.1%); concealment of treatment allocation in 232 trials (77.1%); masking of participants, masking of investigators, or both in 96 trials (31.9%); masking of outcome assessment in 281 trials (93.4%); completeness of outcome reporting in 179 trials (59.5%); and selective reporting of outcomes in 172 trials (57.5%) (eTables 5-7 in the Supplement). The trial sponsor was involved in authorship, data management, or both in 190 trials (63.1%).

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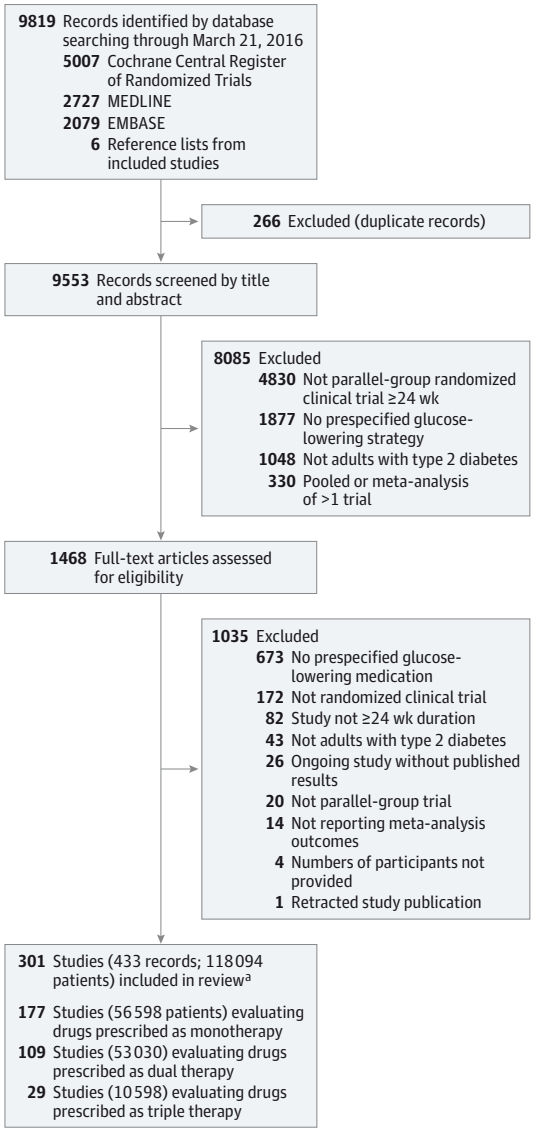
Figure 1. Summary of Study Retrieval and Identification for Network Meta-analysis



[a] Fourteen studies evaluated glucose-lowering strategies as both monotherapy and dual therapy.

Network Consistency

The networks of individual treatment end points are shown in **Figure 2** and eFigure 2 in the Supplement. Inconsistencies between direct and indirect evidence were noted for some drug comparisons (eFigures 3-5 in the Supplement), assessing dual therapy (for treatment failure, hypoglycemia, and body weight) and triple therapy (HbA_{1C} level and hypoglycemia). The design-by-treatment interaction model did not identify global inconsistency in treatment networks (except treatment failure with dual therapy and HbA_{1C} level with 3-drug therapy) (eTable 8 in the Supplement). However, the confidence intervals for inconsistency in loops of drug comparisons were often very wide, and robust conclusions about inconsistency could not be drawn. When assuming a common heterogeneity variance within treatment networks for binary outcomes, there was evidence of low levels of heterogeneity in all networks with the exception of HbA_{1C} for dual therapy, in which there was evidence of fairly high network heterogeneity (τ, 0.5-1.0) (eTable 9 in the Supplement). Definitions of treatment failure in the included studies were generally lack of efficacy or need for additional glucose-lowering therapy (eTable 10 in the Supplement). Contributions of direct evidence to network analyses were reported in eTable 11 in the Supplement.

Treatment Outcomes

Treatment effects in pairwise meta-analyses are shown in eFigures 6-8 in the Supplement.

Drugs as Monotherapy: Primary Outcome

Twenty-five studies involving 14 477 adults evaluated the association of drug classes as monotherapy with the primary outcome of cardiovascular death, including a total of 67 events during 197 763 patient-months of follow-up (Figure 2). There were no significant differences in the associations between any drug class as monotherapy with odds of cardiovascular mortality (**Table**; eTable 12 in the Supplement). Data were absent for basal insulin and GLP-1 receptor agonist monotherapy, and rankings of drug classes for cardiovascular mortality were imprecise (**Figure 3**).

Drugs as Monotherapy: Secondary Outcomes

All monotherapies had uncertain comparative associations with all-cause mortality, serious adverse events, myocardial infarction, and stroke (Table; eTable 12 in the Supplement). All drug classes as monotherapy were associated with lower HbA_{1C} levels than placebo (SMDs ranging from −0.66 [95% CI, −0.88 to −0.44] for α-glucosidase inhibitors to −1.11 [95% CI, −1.44 to −0.77] for meglitinides). Compared with metformin, sulfonylurea (SMD, 0.18 [95% CI, 0.10 to 0.34]), thiazolidinedione (SMD, 0.16 [95% CI, 0.00 to 0.31]), DPP-4 inhibitor (SMD, 0.33 [95% CI, 0.13 to 0.52]), and α-glucosidase inhibitor (SMD, 0.35 [95% CI, 0.12 to 0.58]) monotherapy were associated with higher HbA_{1C} levels, while SGLT-2 inhibitors (SMD, 0.18 [95% CI, −0.15 to 0.51]), basal insulin (SMD, 0.13 [95% CI, −0.24 to 0.51]), GLP-1 receptor agonists (SMD, −0.04 [95% CI, −0.31 to 0.23]), and meglitinides (SMD, −0.09 [95% CI, −0.42 to 0.24]) showed no significant difference in HbA_{1C} levels. There was limited confidence in hierarchical treatment rankings for HbA_{1C} levels (Figure 3).[28]

Placebo was associated with the greatest odds of treatment failure (OR vs metformin, 3.83 [95% CI, 2.88 to 5.10]; RD, 11% [95% CI, 8% to 14%]), while DPP-4 inhibitor (OR, 1.53 [95% CI, 1.16 to 2.01]; RD, 3% [95% CI, 1% to 6%]) and meglitinide (OR, 2.58 [1.43 to 4.66]; RD, 5% [1% to 9%]) monotherapies were also associated with higher odds of treatment failure compared with metformin. SGLT-2 inhibitor treatment was associated with the lowest odds of treatment failure (OR vs metformin, 0.47 [95% CI, 0.31 to 0.71]; RD, −0.3% [95% CI, −4% to 3%]).

Basal insulin (OR, 17.9 [95% CI, 1.97 to 162]; RD, 10% [95% CI, 0.08% to 20%]) or sulfonylurea (OR, 3.13 [95% CI, 2.39 to 4.12]; RD, 10% [95% CI, 7% to 13%]) monotherapy were

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hierarchically the worst for an association with hypoglycemia, while placebo (OR, 0.58 [95% CI, 0.40 to 0.83]; RD, −3% [95% CI, −5% to −0.2%), thiazolidinediones (OR, 0.67 [95% CI, 0.50 to 0.88]; RD, −4% [95% CI, −7% to −1%]), and DPP-4 inhibitors (OR, 0.69 [95% CI, 0.50 to 0.94; RD, −1% [95% CI, −4% to 1%]) were associated with a lower risk of hypoglycemia than metformin. Compared with metformin, GLP-1 receptor agonist monotherapy was associated with a lower body weight (SMD, −0.28 [95% CI, −0.52 to −0.04]), while sulfonylurea (SMD, 0.19 [95% CI, 0.04 to 0.33]) and thiazolidinedione (SMD, 0.24 [95% CI, 0.04 to 0.43]) monotherapy were associated with higher body weight.

Drugs Added to Metformin: Primary Outcome

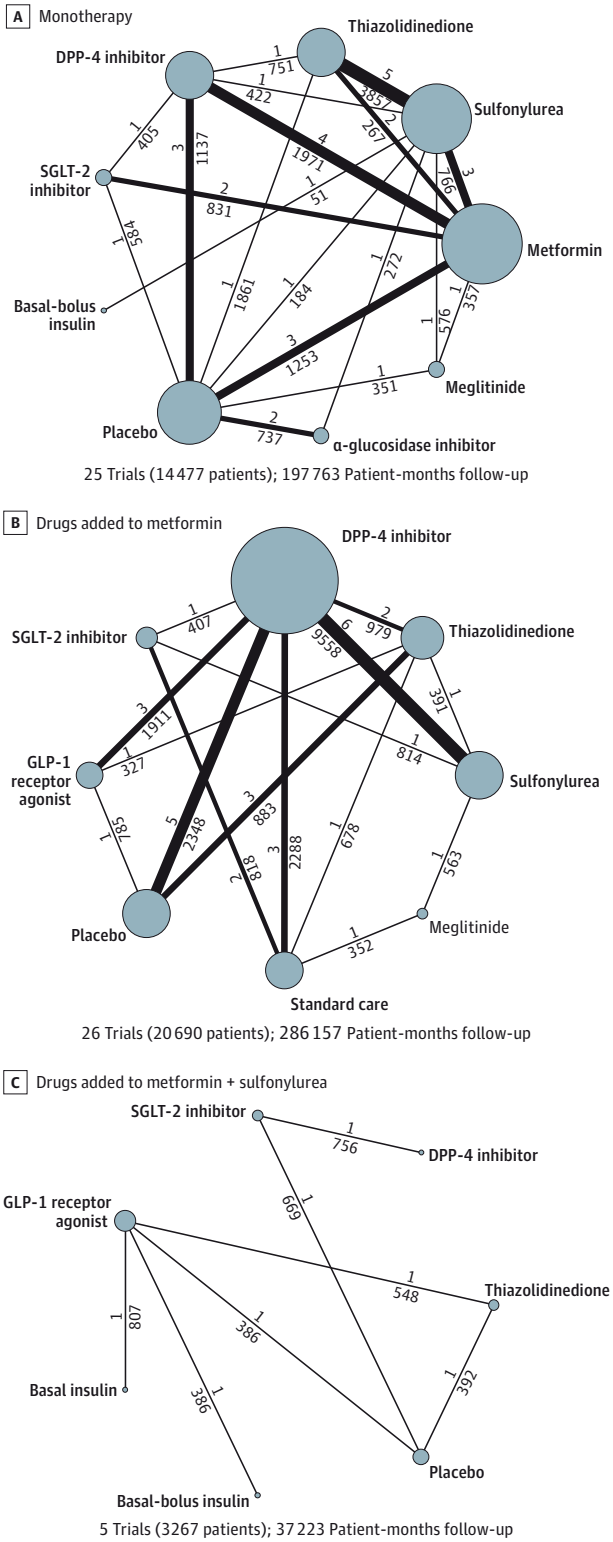
Twenty-six trials involving 20 690 adults evaluated dual therapy (drugs added to metformin) including 45 cardiovascular deaths during 286 157 patient-months of dual therapy (Figure 2). There was no significant association between any drug class and odds of cardiovascular mortality (Table; eTable 13 in the Supplement). Data for basal insulin or α-glucosidase inhibitors added to metformin were absent, and rankings of drug classes for cardiovascular mortality were very imprecise (Figure 3).

Drugs Added to Metformin: Secondary Outcomes

There were no significant differences between any drug class when added to metformin for odds of all-cause mortality, serious adverse events, myocardial infarction, or stroke (Table; eTable 13 in the Supplement), with the exception of a lower odds of stroke associated with metformin + DPP-4 inhibitor vs metformin + sulfonylurea (OR, 0.47 [95% CI, 0.23 to 0.95]; RD, −0.2% [95% CI, −0.4% to −0.04%). When considering efficacy, all drug classes as dual-therapy regimens lowered HbA_{1C} levels to a similar extent, although there was fairly high statistical heterogeneity in this network. Direct and indirect evidence tended to indicate similar results, with the exception of the comparison between sulfonylurea and placebo therapy when added to metformin (eFigure 7 in the Supplement). Compared with metformin + sulfonylurea, metformin + SGLT-2 inhibitor ranked the best for avoiding treatment failure (OR, 0.68 [95% CI, 0.48 to 0.96]; RD, −3% [95% CI, −6% to −0.8%]), while metformin + α-glucosidase inhibitor (OR, 12.4 [95% CI, 1.84 to 83.3]; RD, 9% [95% CI, 1% to 17%]) and metformin + DPP-4 inhibitor (OR, 1.37 [95% CI, 1.07 to 1.76]; RD, 1% [95% CI, −1% to 3%]) strategies were associated with higher odds of treatment failure.

All dual-therapy classes were associated with lower odds of hypoglycemia than metformin + sulfonylurea dual therapy, with mean odds of hypoglycemia ranging from 0.56 (95% CI, 0.32 to 0.98; RD, −4% [95% CI, −12% to 5%]) for metformin + basal insulin to 0.12 (95% CI, 0.08 to 0.18; RD, −22% [95% CI, −27% to −18%]) for metformin + SGLT-2 inhibitor, which was ranked as the best option to avoid hypoglycemia (Figure 3). Metformin+sulfonylurea dual therapy was ranked worst for body weight. Compared with metformin + sulfonylurea treatment, metformin + DPP-4 inhibitor (SMD, −0.58 [95% CI, −1.06 to −0.11]), metformin + SGLT-2 inhibitor (SMD, −0.96 [95% CI,

Figure 2. Graphic Representation of Available Glucose-Lowering Drugs on Cardiovascular Mortality in Clinical Trials of Type 2 Diabetes



Connecting lines represent head-to-head drug comparisons, indicated by the connected nodes (size proportional to number of trials). Numbers above and below the lines indicate studies and patients respectively. Line thickness is proportional to the number of trials comparing the 2 drug classes.

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Table. Summary Effects of Glucose-Lowering Interventions in Patients With Type 2 Diabetes[a]

Outcome	Metformin	Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 Inhibitor	Basal Insulin	GLP-1 Receptor Agonist	Meglitinide	α-Glucosidase Inhibitor	Placebo
Drugs Given as Monotherapy										
Cardiovascular mortality, OR (95% CI)	1 [Reference]	1.25 (0.59 to 2.67)	0.87 (0.30 to 2.49)	1.00 (0.37 to 2.65)	0.75 (0.14 to 3.96)	NA[b]	NA[b]	0.55 (0.07 to 4.61)	0.92 (0.13 to 6.38)	1.38 (0.41 to 4.72)
All-cause mortality, OR (95% CI)	1 [Reference]	1.19 (0.81 to 1.75)	1.09 (0.72 to 1.65)	0.73 (0.41 to 1.30)	0.84 (0.22 to 3.21)	NA[b]	0.91 (0.18 to 4.46)	1.10 (0.17 to 7.05)	0.79 (0.17 to 3.79)	1.09 (0.44 to 2.75)
Serious adverse event, OR (95% CI)	1 [Reference]	0.96 (0.83 to 1.12)	1.00 (0.86 to 1.16)	1.08 (0.87 to 1.34)	1.24 (0.81 to 1.92)	NA[b]	0.86 (0.62 to 1.20)	1.65 (0.82 to 3.30)	0.73 (0.31 to 1.71)	1.05 (0.79 to 1.39)
Myocardial infarction, OR (95% CI)	1 [Reference]	0.94 (0.58 to 1.50)	0.99 (0.62 to 1.59)	0.90 (0.36 to 2.23)	0.63 (0.06 to 6.24)	NA[b]	0.80 (0.15 to 4.17)	NA[b]	0.87 (0.03 to 26.4)	1.15 (0.35 to 3.74)
Stroke, OR (95% CI)	1 [Reference]	1.08 (0.67 to 1.76)	1.04 (0.60 to 1.80)	1.43 (0.50 to 4.09)	0.70 (0.05 to 9.71)	NA[b]	0.74 (0.17 to 3.21)	NA[b]	NA[b]	1.35 (0.33 to 5.46)
HbA_{1c}, SMD (95% CI)	1 [Reference]	0.18 (0.01 to 0.34)[c]	0.16 (0.00 to 0.31)[c]	0.33 (0.13 to 0.52)[c]	0.18 (−0.15 to 0.51)	0.13 (−0.24 to 0.51)	−0.04 (−0.31 to 0.23)	−0.09 (−0.42 to 0.24)	0.35 (0.12 to 0.58)[c]	1.01 (0.84 to 1.18)[c]
Treatment failure, OR (95% CI)	1 [Reference]	1.18 (0.86 to 1.65)	1.21 (0.87 to 1.67)	1.53 (1.16 to 2.01)[c]	0.47 (0.31 to 0.71)[c]	0.22 (0.01 to 5.51)	0.62 (0.37 to 1.04)	2.58 (1.43 to 4.66)[c]	2.54 (0.67 to 9.60)	3.83 (2.88 to 5.10)[c]
Hypoglycemia, OR (95% CI)	1 [Reference]	3.13 (2.39 to 4.12)[c]	0.67 (0.50 to 0.88)[c]	0.69 (0.50 to 0.94)[c]	0.63 (0.30 to 1.32)	17.9 (1.97 to 162)[c]	1.06 (0.74 to 1.52)	2.16 (1.49 to 3.12)	0.65 (0.37 to 1.13)	0.58 (0.40 to 0.83)[c]
Body weight, SMD (95% CI)	1 [Reference]	0.19 (0.04 to 0.33)[c]	0.24 (0.04 to 0.43)[c]	0.12 (−0.09 to 0.32)	−0.06 (−0.22 to 0.08)	0.07 (−0.45 to 0.60)	−0.28 (−0.52 to −0.04)[c]	−0.09 (−0.30 to 0.13)	0.03 (−0.18 to 0.23)	0.09 (−0.05 to 0.24)
Drugs Given as Dual Therapy (in Addition to Metformin)										
Cardiovascular mortality, OR (95% CI)		1 [Reference]	2.10 (0.48 to 9.15)	0.81 (0.36 to 1.82)	0.86 (0.14 to 5.27)	NA[b]	0.52 (0.08 to 3.43)	1.03 (0.10 to 10.9)	NA[b]	1.60 (0.35 to 7.37)
All-cause mortality, OR (95% CI)		1 [Reference]	1.29 (0.39 to 4.23)	0.75 (0.45 to 1.24)	0.83 (0.37 to 1.86)	3.76 (0.30 to 47.2)	0.87 (0.39 to 1.91)	1.20 (0.25 to 5.72)	NA[b]	1.12 (0.45 to 2.78)
Serious adverse event, OR (95% CI)		1 [Reference]	1.23 (0.92 to 1.65)	0.94 (0.82 to 1.07)	0.92 (0.73 to 1.15)	1.13 (0.66 to 1.92)	1.13 (0.91 to 1.41)	0.87 (0.46 to 1.63)	2.11 (0.73 to 6.09)	0.93 (0.73 to 1.17)
Myocardial infarction, OR (95% CI)		1 [Reference]	1.59 (0.43 to 5.91)	0.59 (0.32 to 1.09)	0.42 (0.12 to 1.48)	0.22 (0.01 to 5.70)	0.89 (0.35 to 2.22)	NA[b]	NA[b]	1.00 (0.36 to 2.79)
Stroke, OR (95% CI)		1 [Reference]	0.81 (0.20 to 3.29)	0.47 (0.23 to 0.95)[c]	2.75 (0.76 to 10.0)	1.58 (0.06 to 42.1)	0.88 (0.26 to 2.97)	NA[b]	NA[b]	1.40 (0.50 to 3.89)
HbA_{1c}, SMD (95% CI)		1 [Reference]	0.03 (−0.36 to 0.41)	−0.02 (−0.43 to 0.39)	0.17 (−0.49 to 0.82)	0.07 (−0.75 to 0.88)	0.10 (−0.41 to 0.62)	−0.83 (−1.80 to 0.14)	0.58 (−0.22 to 1.37)	1.24 (0.76 to 1.72)[c]
Treatment failure, OR (95% CI)		1 [Reference]	1.18 (0.70 to 1.98)	1.37 (1.07 to 1.76)[c]	0.68 (0.48 to 0.96)[c]	0.10 (0.01 to 1.89)	0.84 (0.54 to 1.30)	1.16 (0.59 to 2.26)	12.4 (1.84 to 83.3)[c]	3.43 (2.50 to 4.72)[c]
Hypoglycemia, OR (95% CI)		1 [Reference]	0.14 (0.09 to 0.24)[c]	0.12 (0.10 to 0.16)[c]	0.12 (0.08 to 0.18)[c]	0.56 (0.32 to 0.98)[c]	0.19 (0.13 to 0.27)[c]	0.55 (0.32 to 0.93)[c]	0.13 (0.05 to 0.40)[c]	0.14 (0.10 to 0.21)[c]
Body weight, SMD (95% CI)		1 [Reference]	−0.25 (−0.65 to 0.13)	−0.58 (−1.06 to −0.11)[c]	−0.96 (−1.46 to −0.47)[c]	−0.99 (−2.14 to 0.16)	−1.05 (−1.54 to −0.57)[c]	NA[b]	−0.63 (−1.65 to 0.40)	−0.63 (−1.05 to −0.21)[c]
Drugs Given as Triple Therapy (in Addition to Metformin and Sulfonylurea)										
Cardiovascular mortality, OR (95% CI)			1 [Reference]	0.73 (0.00 to 136)	3.69 (0.05 to 258)	2.13 (0.04 to 108)	2.13 (0.04 to 108)	NA[b]	NA[b]	2.42 (0.15 to 39.1)
All-cause mortality, OR (95% CI)			1 [Reference]	0.44 (0.02 to 11.6)	2.16 (0.10 to 45.2)	0.69 (0.02 to 19.3)	0.15 (0.01 to 2.22)	NA[b]	NA[b]	1.37 (0.27 to 6.94)
Serious adverse event, OR (95% CI)			1 [Reference]	0.62 (0.32 to 1.20)	0.53 (0.27 to 1.06)	0.73 (0.42 to 1. 27)	0.64 (0.39 to 1.07)	NA[b]	NA[b]	0.93 (0.54 to 1.62)

(continued)

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Table. Summary Effects of Glucose-Lowering Interventions in Patients With Type 2 Diabetes[a] (continued)

Outcome	Metformin	Sulfonylurea	Thiazolidinedione	DPP-4 Inhibitor	SGLT-2 Inhibitor	Basal Insulin	GLP-1 Receptor Agonist	Meglitinide	α-Glucosidase Inhibitor	Placebo
Myocardial infarction, OR (95% CI)			1 [Reference]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
Stroke, OR			1 [Reference]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
HbA_{1C}, SMD (95% CI)			1 [Reference]	0.23 (−0.62 to 1.08)	0.12 (−1.12 to 1.35)	0.00 (−0. 61 to 0.61)	0.11 (−0.55 to 0.70)	NA[b]	1.42 (0.57 to 2.26)[c]	0.86 (0.25 to 1.48)[c]
Treatment failure, OR (95% CI)			1 [Reference]	2.20 (1.32 to 3.68)[c]	0.78 (0.39 to 1.57)	0.44 (0.20 to 0.99)[c]	0.95 (0.60 to 1.50)	NA[b]	NA[b]	4.66 (3.04 to 7.17)[c]
Hypoglycemia, OR (95% CI)			1 [Reference]	0.87 (0.50 to 1.51)	0.86 (0.48 to 1.54)	0.95 (0.60 to 1.52)	0.60 (0.39 to 0.94)[c]	NA[b]	NA[b]	0.37 (0.24 to 0.57)[c]
Body weight, SMD (95% CI)			1 [Reference]	−0.23 (−0.46 to −0.00)[c]	−0.33 (−0.59 to −0.07)[c]	0.16 (−0.36 to 0.68)	−0.23 (−0.39 to −0.06)[c]	NA[b]	−0.28 (−0.48 to −0.08)[c]	−0.26 (−0.50 to −0.02)[c]

[a] An odds ratio (OR) greater than 1 indicates that the outcome is more likely with treatment than the reference intervention. A standardized mean difference (SMD) greater than 0 indicates a higher body weight or hemoglobin A_{1C} (HbA_{1C}) level at end of treatment with the drug being considered compared with the reference treatment. An SMD of 0.2 is considered to indicate a small difference between treatments, 0.5 a moderate difference, and 0.8 a large difference. For example, sulfonylurea monotherapy was associated with a small increase in mean HbA_{1C} levels (SMD, 0.18) compared with metformin monotherapy, and this difference had a 95% probability of ranging between 0.01 and 0.34. Insufficient data were available to generate networks for drug classes used as triple therapy and outcomes of myocardial infarction and stroke. Mean ORs or SMDs with wide confidence intervals should be interpreted with caution (eg, the estimated odds of hypoglycemia associated with basal insulin vs metformin was 17.9 and included a 95% CI of 1.97 to 162). The true odds of hypoglycemia associated with treatment might be considerably different than the mean estimated effect (OR, 17.9) and range from a small increase in hypoglycemia (OR, 1.97) to very high odds of hypoglycemia (OR, 162). Confidence intervals were wide for many drug comparisons and outcomes.

[b] Treatment effects were not estimable owing to an insufficient number of observations.

[c] Statistically significant at $P < .05$.

−1.46 to −0.47]), and metformin + GLP-1 receptor agonist (SMD, −1.05 [95% CI, −1.54 to −0.57]) were associated with significantly lower body weight at the end of treatment.

Drugs Added to Metformin and Sulfonylurea: Primary Outcome

Five trials involving 3267 adults evaluated triple therapy (drugs added to metformin and sulfonylurea) (Figure 2), including 6 cardiovascular deaths during 37 223 patient-months of triple therapy. There was no evidence of an association of any drug class with cardiovascular mortality (Table; eTable 14 in the Supplement). Data for meglitinides and α-glucosidase inhibitors added to metformin and sulfonylurea were absent, and rankings of drug classes for cardiovascular death were imprecise (Figure 3).

Drugs Added to Metformin and Sulfonylurea: Secondary Outcomes

There was no evidence of significantly different associations with all-cause mortality or serious adverse events between any of the drug classes given as triple therapy (Table; eTable 14 in the Supplement). Insufficient observations were available to generate evidence networks for myocardial infarction or stroke.

As add-ons to metformin and sulfonylurea, α-glucosidase inhibitors ranked worst for lowering HbA_{1C} levels, whereas thiazolidinediones or basal insulin were best (Figure 3; eTable 14 in the Supplement). α-Glucosidase inhibitors were associated with higher HbA_{1C} levels compared with thiazolidinediones (SMD, 1.42 [95% CI, 0.57 to 2.26]), GLP-1 receptor agonists (SMD, 1.34 [95% CI, 0.37 to 2.32]), and basal insulin (SMD, 1.42 [95% CI, 0. 44 to 2.39]) when added to metformin and sulfonylurea. Metformin + sulfonylurea + basal insulin ranked best for avoiding treatment failure, whereas metformin + sulfonylurea + DPP-4 inhibitor was the worst (Figure 3 and Table). Compared with thiazolidinedione given as triple therapy, basal insulin was associated with lower odds of treatment failure (OR, 0.44 [95% CI, 0.20 to 0.99]; RD, −5% [95% CI, −20% to 9%]), while metformin + sulfonylurea + DPP-4 inhibitor was associated with higher odds of treatment failure (OR, 2.20 [95% CI, 1.32 to 3.68]; RD, 21% [95% CI, 7% to 35%]).

When added to metformin and sulfonylurea, GLP-1 receptor agonists were ranked best for avoiding hypoglycemia, while thiazolidinediones ranked worst (**Figure 4**). GLP-1 receptor agonists were associated with lower odds of hypoglycemia than thiazolidinediones (OR, 0.60 [95% CI, 0.39 to 0.94]; RD, −10% [95% CI, −18% to 2%]) in triple therapy. When added to metformin and sulfonylurea, SGLT-2 inhibitors were ranked best for minimizing weight gain, while thiazolidinediones and basal insulin ranked worst (Figure 4). All other drug classes except basal insulin were associated with a lower body weight than thiazolidinediones when added to metformin and sulfonylurea (SMDs ranging from −0.23 [95% CI, −0.46 to −0.00] for DPP-4 inhibitors and −0.23 [95% CI, −0.39 to −0.06] for GLP-1 receptor agonists to −0.33 [95% CI, −0.59 to −0.07] for SGLT-2 inhibitors).

Meta-regression and Sensitivity Analysis

Network meta-regression analyses were used to assess whether treatment effects for HbA_{1C} level, hypoglycemia, and body

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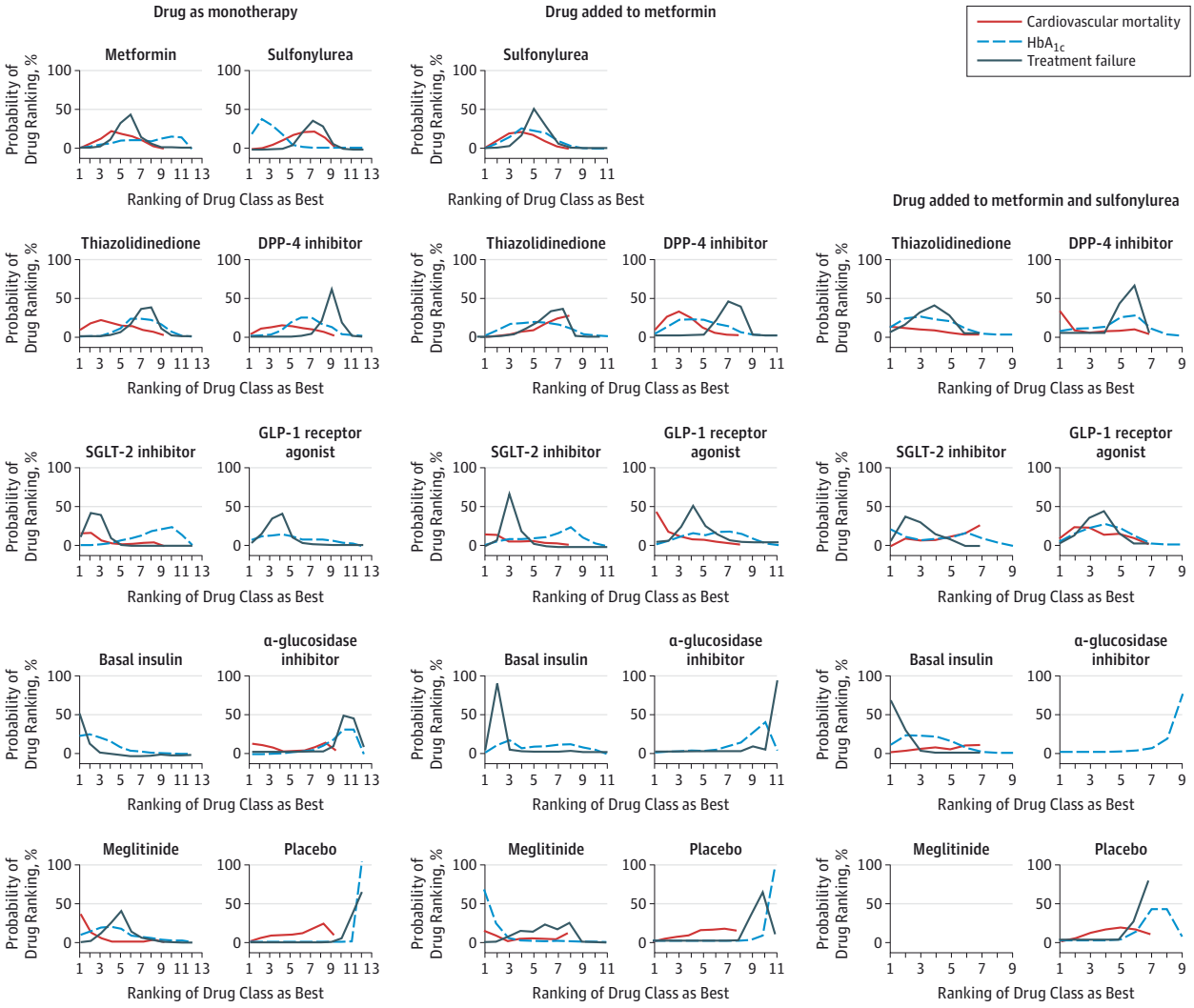
Figure 3. Efficacy Rankings of Available Glucose-Lowering Drugs for Treatment of Type 2 Diabetes



Drug rankings for efficacy (cardiovascular mortality, treatment failure, and hemoglobin A_{1c} [HbA_{1C}] levels). Drug classes are stratified according to administration as monotherapy, as dual therapy in addition to metformin, or as triple therapy in addition to metformin and sulfonylurea. The lines show the probability of the drug ranking for each outcome between best and worst (ranking first, second, third, etc), and the peak indicates the ranking with the highest probability for the corresponding drug class. For example, for treatment failure, sodium-glucose–linked transporter 2 (SGLT-2) inhibitor monotherapy demonstrates a higher probability of ranking best than thiazolidinedione monotherapy. Basal insulin monotherapy has a 50% probability of ranking as the best drug for avoiding treatment failure and a 100% probability of ranking the worst (13th best) for hypoglycemia (see Figure 4). Rankogram lines without marked peaks (for example, for all drug classes as monotherapy and their association with odds of cardiovascular mortality) indicate similar probabilities of all rankings and lower confidence in comparative ranking of the relevant drug class for that outcome. Rankograms showing no data indicate observations were insufficient to generate a rankogram for the drug class for the corresponding outcome. For example, there were insufficient data for meglitinides as triple therapy to infer drug rankings for any outcome. Similarly, there were insufficient data to infer drug rankings for α-glucosidase inhibitor treatment in triple therapy for the outcome of cardiovascular mortality. The peak of the rankogram curve can be used to assess probabilities of drug classes between best and worst (for example, for treatment failure, SGLT-2 inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists were most likely to be among the best treatments and had similar ranking). DPP-4 indicates dipeptidyl peptidase 4.

weight were modified by study-level age, HbA_{1C} level, body weight, duration of diagnosed diabetes, and duration of treatment. Generally, regression analyses were nonsignificant or had limited associations with estimated treatment effects (eTable 15 in the Supplement). There was no evidence of different associations between drug classes as monotherapy between small and large trials for the primary outcome of cardiovascular mortality (**Figure 5**). In additional analyses, all sulfonylureas as monotherapy ranked similarly and among the worst treatments for odds of hypoglycemia (eTable 16 and eFigure 9 in the Supplement). There were no substantive differences in the findings for drug classes as monotherapy when analyses were restricted to trials at low risk of bias from allocation concealment (eTable 17 in the Supplement). Compared with metformin, DPP-4 inhibitors were associated with moderately higher HbA_{1C} levels and higher odds of treatment failure and with lower risks of hypoglycemia. Sulfonylurea monotherapy was associated with higher odds of hypoglycemia compared with

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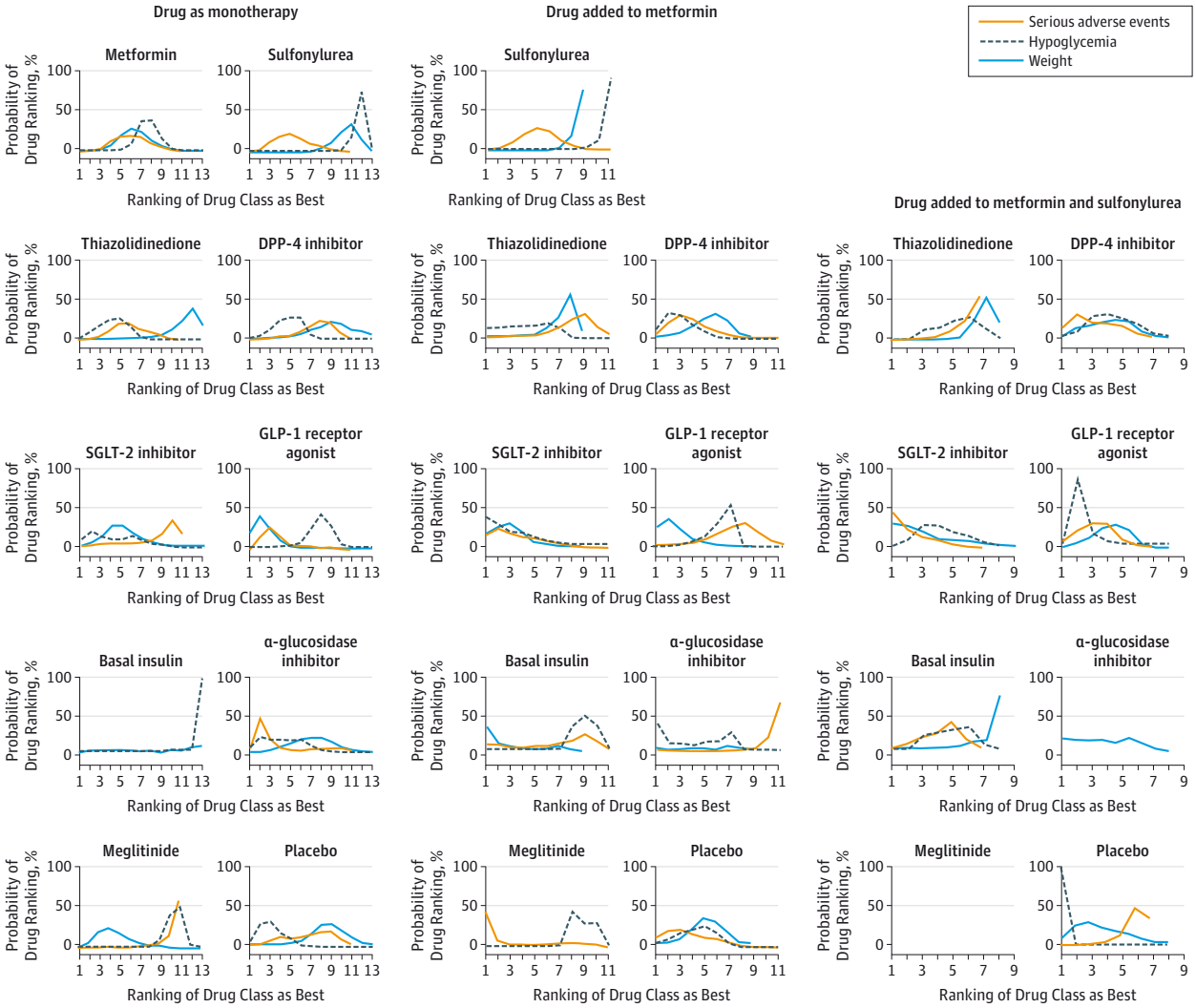
Figure 4. Adverse Effects Rankings of Available Glucose-Lowering Drugs for Treatment of Type 2 Diabetes



Drug rankings for adverse effects (serious adverse effects, hypoglycemia, and weight gain). See Figure 3 legend for additional information.

metformin. Treatment estimates for mortality and cardiovascular events in high-quality trials were uninterpretable owing to wide confidence intervals.

Discussion

Considering cumulative trial data from 118 094 adults with type 2 diabetes, there was no evidence of differences in the associations between glucose-lowering drugs alone or in combination with odds of cardiovascular mortality, all-cause mortality, serious adverse events, myocardial infarction, or stroke. Considerable uncertainty about the association of drug treatment with cardiovascular mortality existed within trial evidence, largely because of few events in most available studies.

Drugs as monotherapy were associated with large proportional reductions in HbA_{1C} levels compared with placebo, while metformin was associated with moderately lower HbA_{1C} levels compared with other drugs including sulfonylureas, thiazolidinediones, and DPP-4 inhibitors. Basal insulin and sulfonylureas were associated with greatest odds of hypoglycemia, with an absolute risk difference of 10% compared with metformin. Metformin was associated with small reductions in body weight relative to sulfonylurea or thiazolidinedione treatment. Considering these results, with metformin showing favorable associations with HbA_{1C} levels compared with sulfonylureas, thiazolidinediones, and DPP-4 inhibitors, and without adverse signals for hypoglycemia or weight gain, metformin might be considered a reasonable first-line agent for type 2 diabetes, consistent with the American Diabetes Association recommendations.[3] However, the recommendations also suggested a patient-centered approach—considering efficacy, weight gain, hypoglycemia, and comorbidities—when selecting treatment. Therefore, based on this review, clinicians and patients may prefer to avoid sulfonylureas or basal insulin for patients who wish to minimize hypoglycemia,

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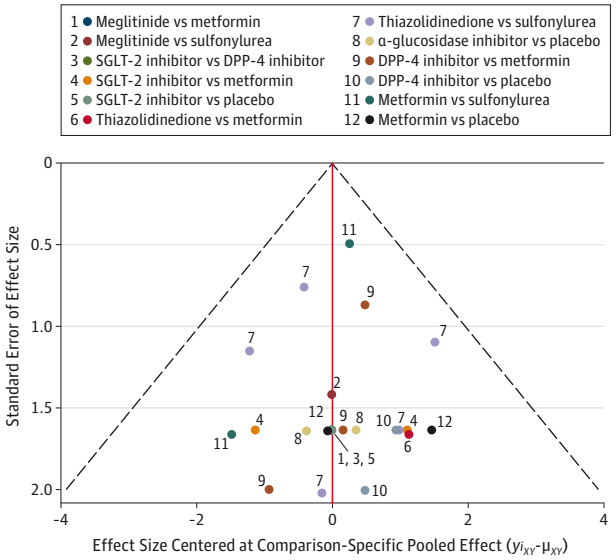
Figure 5. Funnel Plot for Cardiovascular Mortality When Glucose-Lowering Drugs Were Used as Monotherapy



A funnel plot is a scatterplot of the study effect size vs some measure of its precision, in this instance the standard error. A funnel plot that is asymmetrical with respect to the line of the summary effect (vertical red line) implies there are differences between the estimates derived from small and large studies. The studies are ordered from best to worst according to effects on cardiovascular mortality. Missing (small) studies lying on the right side of the zero line suggest that small studies tend to exaggerate the effectiveness of higher-ranked treatments compared with lower-ranked treatments. The cause of any small study effects is explored by meta-regression and is not necessarily attributable to publication bias (the absence of small, negative studies in the available literature). Red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The 2 black dashed lines represent a 95% confidence interval for the difference between study-specific effect sizes and comparison-specific summary estimates. yi_{xy} is the noted effect size in study i that compares x with y. μ_{xy} is the comparison-specific summary estimate for x vs y. Treatments are ordered by the surface under the cumulative ranking (SUCRA) curve.

choose GLP-1 receptor agonists when weight management is a priority, or consider SGLT-2 inhibitors based on their favorable combined safety and efficacy profile.

When drug classes were added to metformin, all were associated with large reductions in HbA_{1C} levels, although network heterogeneity lowered confidence in the results. SGLT-2 inhibitors were associated with less treatment failure compared with sulfonylureas, while sulfonylurea therapy was associated with more frequent hypoglycemia and SGLT-2 inhibitors ranked the best. SGLT-2 inhibitors and GLP-1 receptor agonists were associated with less weight gain. When considering the addition of a second agent to metformin, the present findings suggested a potential treatment hierarchy, with sulfonylurea therapy least preferred; SGLT-2 inhibitors suggested for patients wishing to avoid hypoglycemia and minimize treatment failure; and SGLT-2 inhibitors or GLP-1 receptor agonists suggested for those for whom weight gain is a higher priority. Given the lack of evidence that any regimen was superior for hard clinical outcomes, decision makers (especially those in lower-resource settings) may consider whether the advantages of SGLT-2 inhibitors outweigh their higher costs.

When added to metformin plus sulfonylurea, drugs had similar associations with HbA_{1C} levels. Basal insulin ranked best for avoiding treatment failure. GLP-1 receptor agonists posed the lowest risks of hypoglycemia, while SGLT-2 inhibitors were ranked best for weight gain. Considering these results, SGLT-2 inhibitors, GLP-1 receptor agonists, or basal insulin might all be considered when adding a third agent to treatment. In addition, based on analysis of 2-drug combinations, metformin plus sulfonylurea as the basis for adding a third agent appeared to be least favorable, and 3-drug combinations that include other oral agents (particularly metformin plus SGLT-2 inhibitor) warrant further evaluation.

A central finding in this meta-analysis was that despite more than 300 available clinical trials involving nearly 120 000 adults and 1.4 million patient-months of treatment, there was limited evidence that any glucose-lowering drug stratified by coexisting treatment prolonged life expectancy or prevented cardiovascular disease. Similarly, a trial in 14 671 individuals adding sitagliptin to existing therapy showed no effect on cardiovascular mortality over 3 years,[29] while saxagliptin as add-on treatment had no effect on mortality among 17 000 individuals at high cardiovascular risk.[30] By contrast, the EMPA-REG OUTCOME trial[7] demonstrated proportional reductions in cardiovascular and all-cause mortality with empagliflozin added to existing care, while liraglutide added to standard care in the LEADER trial prevented cardiovascular and all-cause death among patients at high cardiovascular risk.[8] Although these trials represent emerging evidence of glucose-lowering drug effects on mortality outcomes, none of these trials analyzed treatment as monotherapy or added to metformin. Future trials might prioritize comparisons of SGLT-2 inhibitors against metformin or added to metformin to compare specific dual-therapy regimens.

The present systematic review and network analysis extended findings from a 2011 pairwise meta-analysis of 166 randomized clinical trials and observational studies examining medications for type 2 diabetes that included assessments of 1- and 2-drug combinations.[6] The network approach allowed greater statistical power to compare all single- and 2-drug treatments with each other, confirmed the hazards of sulfonylureas alone and when combined with metformin for hypoglycemia, and indicated the beneficial associations of GLP-1 receptor agonists on body weight. The network analysis extended understanding about comparative effectiveness and safety for all other treatment options and combinations, based on metformin as initial treatment, even though these have not been directly evaluated in head-to-head trials. The consistency of many findings between the 2 reviews despite the differing analytical methods strengthened the conclusions of both studies.

Thiazolidinediones (including rosiglitazone and pioglitazone) have been linked to increased edema and heart failure without evidence of a corresponding excess in cardiovascular mortality in previous meta-analyses.[31,32] This increased risk is recommended as being considered when patients make treatment decisions about dual therapy for type 2 diabetes.[3] Because of limited trial data, heart failure was not included as an outcome in this analysis, and network analysis did not demonstrate different comparative effects between thiazolidin-

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ediones and other drug classes on other cardiovascular complications such as myocardial infarction and stroke.

The strengths of this review included the comprehensive systematic search that considered trials published in languages other than English and those published only as conference proceedings, the use of a prespecified protocol, and double-checking of data extraction. However, there were several limitations. First, analyses were limited by the amount of data in the included studies. Although cardiovascular mortality was included as an outcome because of its central clinical importance and the ongoing uncertainty about drug effectiveness for this end point, only a minority of studies reported this outcome, and most had few or zero events. In the network analysis for cardiovascular mortality with monotherapy, the mortality rate was considerably lower than that in a recent pragmatic trial among adults with previously undetected diabetes,[33] suggesting that investigators in future trials need to consider drug evaluations in real-world settings in individuals with higher morbidity and mortality risks. Randomized trials of sufficient duration and with adequate statistical power are needed to detect treatment effects of diabetes drugs on mortality[5] and include consideration of disruptive trial designs such as registry-based trials to maximize trial efficiency and feasibility. In addition, statistical inconsistency between direct and indirect comparisons in some networks, including dual-therapy associations with HbA_{1C} levels, diminished the ability to draw confident conclusions for some treatment effects. Second, triple-therapy regimens evaluated in this study were limited to individual drugs added to metformin and sulfonylurea therapy, and the comparative effectiveness of other 3-drug combinations was not assessed. Third, analyses have not been adjusted for baseline kidney function; thus, findings may not have been applicable to patients who have chronic kidney disease. A recent trial of empagliflozin added to standard therapy (EMPA-REG OUTCOME)[7] that included a subgroup of nearly 2000 adults who had chronic kidney disease found no evidence of different risks of cardiovascular death with treatment among people with kidney failure.[7] Fourth, many of the trials were conducted in higher-income countries. Medication use in lower-resource settings may be limited by cost and drug availability. Fifth, most studies were short-term, and the longer-term safety of the available drugs alone and in combination was incompletely understood.

Conclusions

Among adults with type 2 diabetes, there were no significant differences in the associations between any of 9 available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality. Metformin was associated with lower or no significant difference in HbA_{1C} levels compared with any of the other drug classes. All drugs were estimated to be effective when added to metformin. These findings are consistent with American Diabetes Association recommendations for using metformin monotherapy as initial treatment for patients with type 2 diabetes and selection of additional therapies based on patient-specific considerations.

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Author Contributions: Dr Strippoli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Critical revision of the manuscript for important intellectual content: Mavridis, Nicolucci, Johnson, Tonelli, Craig, Maggo, Gray, De Berardis, Ruospo, Saglimbene, Badve, Cho, Nadeau-Fredette, Burke, Faruque, Lloyd, Ahmad, Liu, Tiv, Wiebe, Strippoli.
Statistical analysis: Palmer, Mavridis, Ruospo, Badve, Burke.
Obtained funding: Strippoli.
Administrative, technical, or material support: Palmer, Craig, Maggo, Gray, De Berardis, Natale, Saglimbene, Cho, Faruque.
Study supervision: Nicolucci, Johnson, Craig, Ahmad, Wiebe, Strippoli.

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