Effects of glucose-lowering agents on cardiovascular and renal outcomes in subjects with type 2 diabetes: An updated meta-analysis of randomized controlled trials with external adjudication of events

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Abstract

Aims: To investigate the effects of glucose-lowering agents on all-cause mortality, and cardiovascular and renal outcomes in adults with type 2 diabetes.

Methods: A MEDLINE and EMBASE search was performed to identify randomized controlled trials, published up to 28 February 2022, with a follow-up ≥52 weeks, in which glucose-lowering drugs were compared with either placebo or active comparators. We included only trials reporting formal external adjudication of events. All-cause mortality, 3-point MACE (major cardiovascular events), and hospitalization for heart failure (HHF) were considered as principal outcomes. Doubling of serum creatinine, worsening albuminuria, and renal death were considered as secondary endpoints.

Results: We included randomized controlled trials performed on metformin (n = 17), pioglitazone (n = 20), alpha-glucosidase inhibitors (n = 9), insulin secretagogues (n = 42), dipeptidyl-peptidase-4 inhibitors (n = 67), glucagon-like peptide-1 receptor agonists (n = 45) or sodium-glucose co-transporter-2 inhibitors (SGLT-2i; n = 42) and insulin (n = 18). Glucagon-like peptide-1 receptor agonist and SGLT-2i were associated with a significant reduction in all-cause mortality [Mantel-Haenszel odds ratio (MH-OR), 95% confidence interval: 0.88 (0.83; 0.95) and 0.85 (0.79; 0.91), respectively] and MACE [MH-OR, 95% confidence interval: 0.89 (0.84; 0.94) and 0.90 (0.84; 0.96), respectively]. SGLT-2i was associated with a reduced risk of HHF [MH-OR 0.68 (0.62; 0.75)], worsening albuminuria [MH-OR 0.67 (0.55; 0.80)] and doubling of serum creatinine [MH-OR 0.58 (0.44; 0.79)]. Metformin and pioglitazone were associated with a significantly lower risk of MACE [MH-OR 0.60 (0.47; 0.80) and 0.85 (0.74; 0.97), respectively] and pioglitazone with a higher risk of HHF [MH-OR 1.30 (1.04; 1.62)]. Insulin secretagogues were associated with increased risk of all-cause mortality [MH-OR 1.12 (1.01; 1.24)] and MACE [MH-OR 1.19 (1.02; 1.39)].

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Conclusions: The results of this updated meta-analysis need to be considered in the choice of drug treatment for type 2 diabetes mellitus, which cannot be merely based on the effect of glucose-lowering drugs on long-term glycaemic control.

KEYWORDS
all-cause mortality, glucose-lowering agents, major cardiovascular adverse events, meta-analysis, renal adverse outcomes

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cardiovascular disease,[1] microvascular complications[2] and mortality.[3] Increasing evidence from randomized controlled trials (RCTs) suggests that intensive glycaemic control in patients with T2DM is capable of reducing the risk of developing major adverse cardiovascular events (MACE)[4,5] and microvascular complications,[6] but not all-cause mortality.[7] In addition, several glucose-lowering agents, such as metformin, pioglitazone, glucagon-like peptide-1 receptor agonists (GLP-1 RA) or sodium-glucose co-transporter-2 inhibitors (SGLT-2i), could exert some extra-glycaemic beneficial effects on all-cause mortality and/or cardiovascular morbidity.[8-17] SGLT-2i have also been shown to exert beneficial effects on hospitalization for heart failure (HHF)18 and renal outcomes,[19,20] which appear to be independent of glycaemic control.[21-24] Conversely, other classes of glucose-lowering drugs seem to be neutral[25-27] or even detrimental[16,28] with respect to some of the cardiovascular and kidney outcomes.

The present comprehensive and updated meta-analysis was performed in the process of developing and updating the Italian guidelines for the treatment of T2DM.[17,29] These national guidelines, which have been promoted by the Italian Diabetes Society (Società Italiana di Diabetologia, SID) and the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD), are being developed for the inclusion in the Italian National Guideline System (INGS), designed as a standard reference for diabetes clinical practice in Italy, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method.[30] The panel considered all-cause mortality and cardiovascular and renal outcomes as critical outcomes, and were investigated in the present meta-analysis. In contrast with other previous meta-analyses,[14,15,25,26,28,31-33] the present analysis includes only results from RCTs with formal adjudication of cardiovascular and renal events allowing the inclusion of a wider data set and providing more homogeneous and consistent results.

2 | METHODS

2.1 | Search strategy and selection criteria

The present meta-analysis is part of a wider and currently ongoing systematic review, which has been registered on the PROSPERO website CRD42022310017; https://www.crd.york.ac.uk/prospero). This meta-analysis is reported following the criteria of PRISMA (https://www.equator-network.org/reporting-guidelines/prisma/) statement[16] (Table S1).

A MEDLINE and EMBASE search was performed to identify all RCTs (English only), published up to 28 February 2022, with a duration of follow-up of at least 52 weeks, in which any glucose-lowering drug approved in Europe (see a complete list in Table S2) was compared with either placebo or active comparators in adults with established T2DM. Detailed information on the search string is reported in Table S3. We included all RCT reporting data on all-cause mortality; conversely, for RCTs with cardiovascular (MACE and HHF) and renal outcomes, we included only those reporting the formal external adjudication of events. For trials that included both diabetic and non-diabetic subjects, only data from subgroups with diabetes were extracted and analysed. We excluded RCTs performed on patients with type 1 diabetes, patients with gestational diabetes or subjects without T2DM, as well as RCTs performed with glucose-lowering drugs not currently approved in Europe for the treatment of T2DM or using drug doses different from those approved. RCTs comparing two different molecules of the same class were also excluded from the meta-analysis.

2.2 | Data retrieval

Identification of relevant abstracts, selection of studies, and data extraction were performed independently by two of the authors (MM and BN), and conflicts were resolved by a third investigator (EM). For all eligible RCTs, results reported in published papers were used as the primary source of information; when data on the outcomes considered were not available in the primary publication, an attempt of retrieving information was made on clinicaltrials.gov.

The following variables/information were extracted from each eligible RCT: first author, year of publication, name of the investigational drug, comparator(s), duration of follow-up, number of patients, mean age, mean duration of diabetes, mean haemoglobin A1c and mean body mass index, as well as information on the adjudication of cardiovascular and renal events.

The risk of bias of the eligible RCTs was assessed using the parameters proposed by the Cochrane Collaboration (Cochrane Handbook version 5.1.0; https://handbook-5-1.cochrane.org/).

2.3 | Outcomes of interest

The principal outcomes of interest for each eligible RCTs were the rates of all-cause mortality, 3-point MACE (defined as a composite endpoint of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death), and HHF. For trials not reporting MACE as the composite endpoint, the number of MACE was assumed as the sum of events of its individual components.

Secondary kidney endpoints were doubling of creatinine from baseline, renal death and worsening albuminuria (incident microalbuminuria in normoalbuminuric subjects or incident macroalbuminuria in microalbuminuric subjects) in each treatment arm of the RCT.

2.4 | Statistical analysis

Mantel-Haenszel odds ratio (MH-OR) with 95% confidence interval was calculated for all outcomes of interest, on an intention-to-treat basis. MH-OR, which is the typical measure of outcome in meta-analyses, approaches relative risk, considering the relatively low incidence of events in treatment groups. Heterogeneity was assessed by using I^2-statistics. A random-effects model was applied for all analyses.

Funnel plots were examined to estimate possible publication/disclosure bias.[34]

Subgroup analyses were performed, whenever possible, for different drugs of the class and different classes of comparators. Post-hoc analyses for RCTs with duration ≥104 weeks were also performed, whenever possible, for all outcomes of interest. A post-hoc subgroup analysis was performed to assess the effects of sulphonylureas on all-cause mortality and MACE, after excluding trials comparing sulphonylureas with drugs with proven beneficial effects on either one of those outcomes (i.e. SGLT-2i, GLP-1 RA, metformin and pioglitazone). The GRADE methodology[30] was used to assess the quality of the body of retrieved evidence, using the GRADEpro GDT software (GRADEpro Guideline Development Tool, McMaster University, 2015; available from gradepro.org).

All statistical analyses specified above were performed using Review Manager 5.3 (the Nordic Cochrane Centre, Copenhagen; The Cochrane Collaboration, 2014).

3 | RESULTS

3.1 | Randomized controlled trial characteristics

Of 15 031 records initially identified, 3255 were excluded by examining titles and abstracts and 2206 were excluded various reasons (see Figure S1). Initially, because of these exclusions, a total of 260 published RCTs fulfilling our inclusion criteria were identified (Table S4), with one study[35] reporting data on two RCTs, data for one trial deriving from two publications,[36,37] and 87 RCTs comparing the investigational drug with multiple comparators (80 and 7 with two and three comparators, respectively). Seven RCTs[38-44] did not report any information for the outcomes of interest and therefore were excluded from analyses.

We, therefore, collected data on metformin (n = 17 RCTs), pioglitazone (n = 20), α-glucosidase inhibitors (n = 9), insulin secretagogues (n = 42), dipeptidyl-peptidase-4 inhibitors (DPP-4i; n = 67), GLP-1 RA (n = 45), SGLT-2i (n = 42) and insulin (n = 18).

The overall quality was satisfactory in the majority of the included trials (with the exception of α-glucosidase inhibitors) for all items of the Cochrane tool (Figure S2), except for 'blinding of participants and personnel', for which a bias cannot be completely ruled out for α-glucosidase inhibitors, GLP-1 RA and insulin (open-label design or methods not satisfactorily described; Figure S2). Funnel plots for each class of glucose-lowering drugs for all-cause mortality, MACE, HHF,

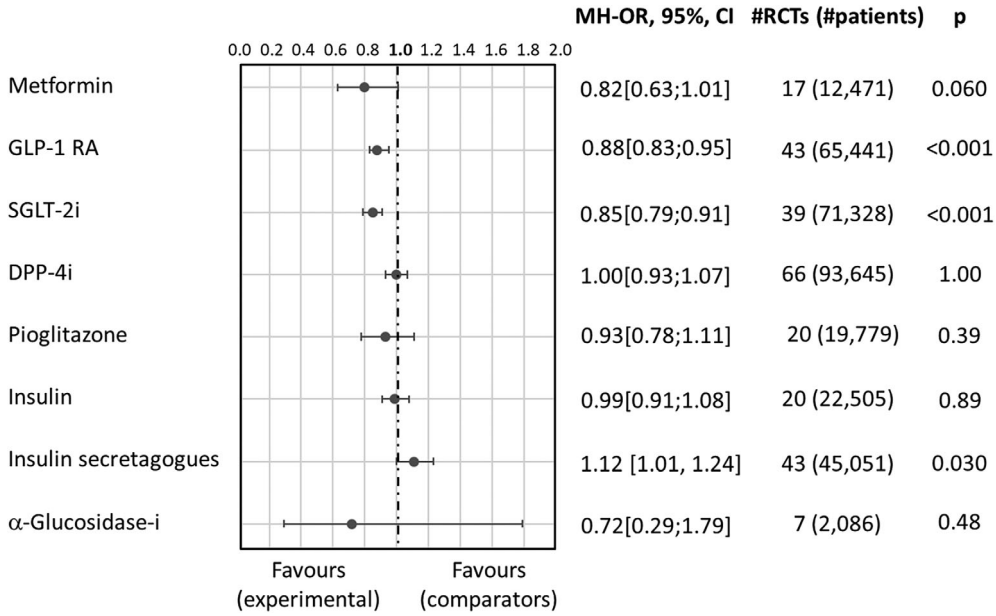

FIGURE 1 Effects of different classes of drugs on the risk of all-cause mortality (MH-OR, 95% CI: Mantel-Haenszel odds ratio with 95% confidence intervals). DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonists; RCT, randomized controlled trials; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

and composite renal outcome with at least 10 RCTs were reported in Figure S3. No publication bias was detected for any class of these drugs (Figures S3 and S4).

3.2 | Outcomes

3.2.1 | All-cause mortality

Treatment with either GLP-1 RA or SGLT-2i was associated with a significant reduction in all-cause mortality (Figure 1), which was also observed for placebo-controlled RCTs (Table S5). Insulin, pioglitazone, α-glucosidase inhibitors and DPP-4i were neutral in this respect, whereas metformin use showed a non-significant trend toward reduction of all-cause mortality. Insulin secretagogues were associated with a significant increase in all-cause mortality (Figure 1) when compared with other treatments/placebo. The increase in all-cause mortality was confirmed [MH-OR 1.16 (1.03-1.30); $p = .01$; $I^2 = 0\%$] when excluding trials comparing sulphonylureas with drugs with proven beneficial effects on either one of those outcomes (i.e. SGLT-2i, GLP-1 RA, metformin and pioglitazone). Despite the low heterogeneity, a subgroup analysis with individual molecules of this drug class was performed, detecting no significant differences (Figure S5). Forest plots for each class of drugs are reported in Figure S6. No heterogeneity was detected for any of the glucose-lowering agents considered (Figure S6).

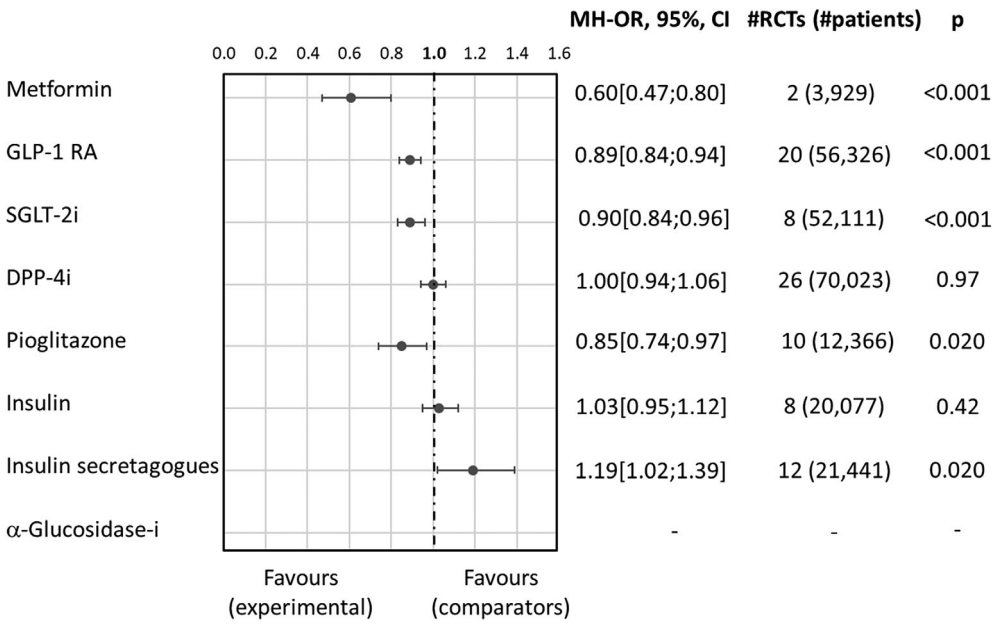

FIGURE 2 Effects of different classes of drugs on the risk of 3-point major adverse cardiovascular events (MH-OR, 95% CI: Mantel-Haenszel odds ratio with 95% confidence intervals). DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonists; RCT, randomized controlled trials; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

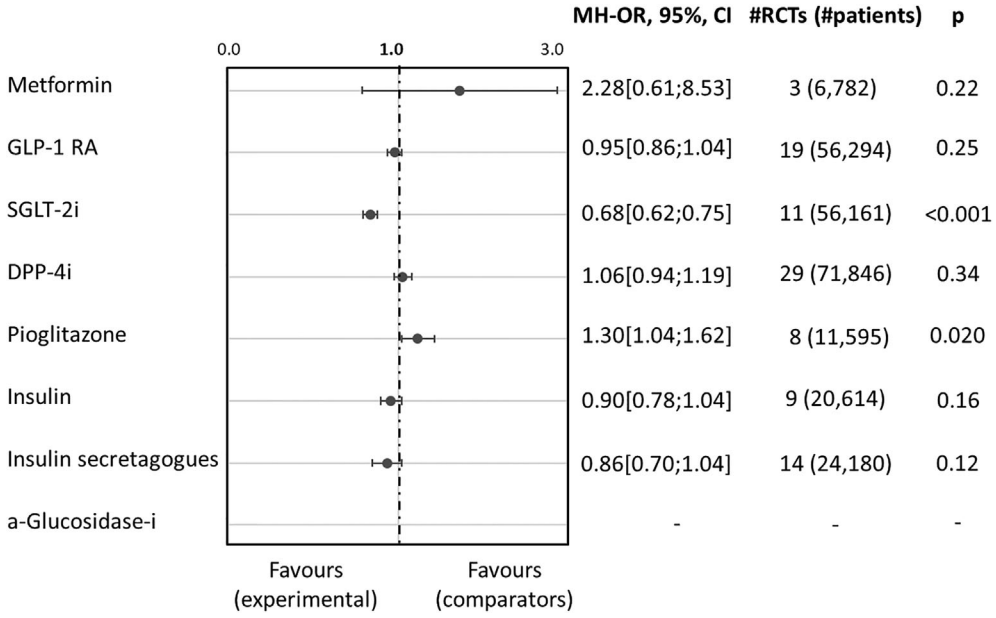

FIGURE 3 Effects of different classes of drugs on the risk of hospitalization for heart failure (logarithmically transformed; MH-OR, 95% CI: Mantel-Haenszel odds ratio with 95% confidence intervals). DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonists; RCT, randomized controlled trials; SGLT-2i, sodium-glucose co-transporter-2 inhibitor

TABLE 1 Effects of different classes of drugs on renal endpoints

Outcome	Glucose-lowering agents MH-OR [95% CI]							
	Metformin	GLP-1 RA	SGLT-2i	DPP-4i	Pioglitazone[a]	Insulin	Insulin secretagogues[a]	α-Glucosidase-i
Renal outcomes								
Worsening albuminuria[c]	[b]	0.81 [0.66; 1.00]*	0.67 [0.55; 0.80]	0.85 [0.76,0.95]	[b]	[b]	[b]	[b]
No. of studies (patients)	[b]	5 (42 093)	5 (42 837)	2 (23 471)	[b]	[b]	[b]	[b]
Doubling of creatinine[d]	[b]	0.92 [0.74; 1.14]	0.58 [0.44; 0.79]	1.30 [0.67; 2.53]	[b]	1.34 [0.95; 1.90]*	[b]	[b]
No. of studies (patients)	[b]	4 (19 277)	4 (29 809)	3 (17 104)	[b]	1 (577)	[b]	[b]
Renal death	2.14 [0.86;9.94]	1.19 [0.53, 2.66]	0.43 [0.15; 1.24]	0.87 [0.39,1.93]	[b]	[b]	2.02 [0.97;4.21]*	[b]
No. of studies (patients)	1 (3625)	4 (26 025)	3 (17 449)	8 (32 368)	[b]	[b]	3 (10 472)	[b]

Abbreviations: CI, confidence intervals; CV, cardiovascular; DPP-4i, dipeptidyl-peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonists; i, inhibitors; MH-OR, Mantel-Haenzel odds ratio. SGLT-2i, sodium-glucose co-transporter-2 inhibitor.

[a]One study reported the following renal outcome: 'new or worsening CKD' comparing pioglitazone vs. sulphonylureas: (MH-OR: 0.98 [0.82; 1.18]).

[b]Unknown effect.

[c]Worsening albuminuria: incident microalbuminuria in normoalbuminuric subjects or incident macroalbuminuria in microalbuminuric subjects.

[d]From baseline.

*$P < .10$.

A post-hoc sensitivity analysis for RCTs with a duration ≥104 weeks also confirms the main results of our primary analyses (Table S6). GRADE evaluation is reported in Table S7.

3.2.2 | 3-point MACE

Compared with other glucose-lowering agents/placebo, the use of metformin, GLP-1 RA, SGLT-2i or pioglitazone was associated with a significant reduction of 3-point MACE (Figure 2), which was also observed for placebo-controlled RCTs (Table S5). Insulin and DPP-4i were neutral in this respect, whereas insulin secretagogues were associated with a significant increase in 3-point MACE (Figure 2). The increase of the risk of MACE with insulin secretagogues was no longer statistically significant when excluding trials versus SGLT-2i, GLP-1 RA, metformin and pioglitazone [MH-OR 1.19 (0.94-1.50); $p = .16$; $I^2 = 52\%$). Despite the low heterogeneity, a subgroup analysis with individual insulin secretagogue was performed, detecting no significant differences (Figure S7). No RCTs performed on α-glucosidase inhibitors and adjudicating cardiovascular events reported data on MACE. Forest plots for each class of drugs are reported in Figure S8. Heterogeneity (low) was detected only for insulin secretagogues and SGLT-2i (Figure S8).

A post-hoc sensitivity analysis for RCTs with a duration ≥104 weeks also confirms the main results of our primary analyses, with the only exception of insulin secretagogues (showing a non-statistical trend toward increased risk of MACE) (Table S6). GRADE evaluation is reported in Table S7.

3.2.3 | Hospitalization for heart failure

Among the included classes of glucose-lowering agents, only SGLT-2is were associated with a significant reduction of HHF (Figure 3), as also confirmed in placebo-controlled RCTs (Table S5); on the contrary, pioglitazone use was associated with an increased risk of HHF (Figure 3). No RCTs on α-glucosidase inhibitors reported data on this outcome. Forest plots for each class of drugs are reported in Figure S7. Heterogeneity was detected only for metformin (high) and for DPP-4i (low), respectively (Figure S9). Subgroup analysis with individual DPP-4i showed that only saxagliptin was significantly associated with an increased risk of HHF (Figure S10).

A post-hoc sensitivity analysis for RCTs with a duration ≥104 weeks also confirms the results obtained for SGLT-2i, but not those for pioglitazone, which was no longer associated with higher rates of HHF (Table S6). GRADE evaluation is reported in Table S7.

3.2.4 | Renal outcomes

SGLT-2is were associated with a significant reduction of progression of albuminuria and serum creatinine levels (doubling creatinine). No significant effects were observed for the other classes of glucose-lowering agents (Table 1).

Forest plots for classes of drugs with more than one RCT reporting information on renal outcomes are reported in Figures S8-S13. High heterogeneity was detected for SGLT-2i, GLP-1 RA and metformin for the progression of albuminuria (Figures S11-S13). GRADE evaluation is reported in Table S7.

4 | DISCUSSION

The number of pharmacological options for the treatment of hyperglycaemia in patients with T2DM has been steadily increasing over the years. The attainment of satisfactory glycaemic control is an effective means of preventing the onset and progression of long-term microvascular[31,45,46] and possibly macrovascular[4,31,47] complications of diabetes. However, the choice of different drugs to reach therapeutic targets could affect the risk of long-term outcomes.

The effect of different glucose-lowering agents on the risk of 3-point MACE was assessed by several trials, the majority of which were performed to comply with regulatory requirements.[48] Two classes of drugs, namely SGLT2i and GLP-1 RA, are associated with a significant reduction in the risk of 3-point MACE. For this reason, they are now considered among the first-choice drugs in patients with T2DM and with previous cardiovascular events and/or at high cardiovascular risk.[17,29,49,50] Despite apparently different results in trials with different molecules, the analysis of RCTs with GLP-1 RA did not show any relevant heterogeneity. For both drug classes, the risk reduction of MACE was also associated with a significant reduction in all-cause mortality, thus confirming previous results.[9,12,51]

There are two other therapeutic options, besides GLP-1 RA and SGLT2i, which are associated with a significant reduction in the risk of 3-point MACE: metformin and pioglitazone. Metformin had already been associated with a reduction of MACE,[15,52] whereas results on pioglitazone were contrasting.[14,16] Differences across published meta-analyses could, at least in part, depend on sample size, characteristics of included trials, and case mix. Notably, in our meta-analysis, the risk reduction of MACE with metformin or pioglitazone was rated as 'high certainty of evidence' with the GRADE system, similarly to SGLT2i and GLP-1 RA. Neither metformin nor pioglitazone was associated with a significant reduction in all-cause mortality; however, the number of events recorded in RCTs included in the analysis might have been insufficient to detect clinically relevant effects. In fact, the estimated odds ratio for all-cause mortality with metformin was similar to that of GLP-1 RA and SGLT2 inhibitors, although not statistically significant because of a smaller sample size.

Insulin and DPP-4i do not appear to affect the risk of 3-point MACE or all-cause mortality. Data on α-glucosidase inhibitors are insufficient to draw any reliable conclusion: no trial fulfilled criteria for inclusion in the meta-analysis for MACE, and the assessment of all-cause mortality could be performed on five RCTs only, enrolling approximately 2000 patients. More evidence was available for insulin secretagogues. Previous meta-analyses had shown a significant increase in all-cause mortality,[28,53] which was also confirmed in the present analysis. Conversely, we also observed a significant increase in MACE risk, which had not been previously reported.[28,53] In contrast with a recent meta-analysis,[28] the present data include also results from RCTs with formal adjudication of cardiovascular events, even when MACE were not among the principal endpoints; this allows for the inclusion of a wider data set. The effects of insulin secretagogues on the risk of both all-cause mortality and MACE show a high degree of certainty at GRADE scoring. These results are in line with some previous analyses, reporting an increased risk of stroke in randomized trials,[54] and an increased risk of MACE in observational studies.[55] The majority of available trials for these outcomes compares insulin secretagogues with other active drugs; it is possible that part of the apparent detrimental effect of sulphonylureas is due to the benefit of comparators. However, a post-hoc analysis excluding all trials versus drugs with known or probable protective cardiovascular effects (SGLT-2i, GLP-1 RA, metformin and pioglitazone) confirms the increase of all-cause mortality; the negative effect on MACE does not reach statistical significance, but the small number of available trials limits the reliability of this latter analysis. The blockade of a myocardial and/or cerebral ATP-dependent potassium channel, resulting in the suppression of ischaemic preconditioning, has been suggested as a possible explanation for the adverse cardiovascular effects associated with long-term use of sulphonylureas and glinides.[56] For this reason, molecules with lower affinity for this myocardial ATP-dependent potassium channel, such as gliclazide, have been considered potentially safer than other drugs of the same class.[57] Despite a low heterogeneity of results of insulin secretagogues on the risk of MACE and all-cause mortality, we performed a subgroup analysis for RCTs with different molecules, showing no significant difference. Notably, the blockade of the myocardial ATP-dependent potassium channel should theoretically induce a reduction of myocardial function in patients with coexisting ischaemic heart disease[58]; conversely, insulin secretagogues did not appear to affect the risk of HHF in available clinical trials, suggesting different and, still unknown, mechanisms. On the other hand, the effects on mortality could be partly mediated by the increase in hypoglycaemic risk,[4] although the absence of any apparent effect of insulin on mortality seems in contrast with this hypothesis.

The duration of eligible RCTs could affect in a relevant manner some of the outcomes explored, such as the risk of MACE and renal composite endpoints. For this reason, a sensitivity analysis was performed on trials with a duration ≥104 weeks, which provided similar results.

SGLT-2is have been shown to reduce the incidence of HHF also in subjects without diabetes,[21,59,60] and they are currently indicated for the treatment of heart failure with reduced ejection fraction, regardless of the presence or absence of T2DM. The present meta-analysis confirms that treatment with SGLT2i leads to a significant reduction in HHF also in patients with T2DM, with a high degree of certainty of evidence at GRADE rating. Conversely, this meta-analysis confirms that pioglitazone use is associated with a significant increase in the risk of HHF, as previously described.[61] Other classes of glucose-lowering drugs do not show either beneficial or detrimental effects on this specific outcome. In particular, DPP-4i, as a class, appear to be neutral for HHF.[25,62] However, despite the low

heterogeneity of our results, as saxagliptin had been associated with increased risk for HHF, we performed a subgroup analysis of trials with different molecules of the class, showing no detrimental effects of all individual molecules on this specific cardiovascular outcome, with the exception of saxagliptin.

The RCT effects of glucose-lowering agents on renal outcomes have been studied to a lesser extent and for fewer molecules. There are several publications on SGLT-2i showing a consistent protective effect across RCTs on the risk of end stage kidney disease, decline of the estimated glomerular filtration rate, renal transplantation/dialysis and death.[18,33,60,63,64] We show here that SGLT2is are effective both in reducing albuminuria and preventing the decline of the estimated glomerular filtration rate, whereas GLP-1 RA showed only a non-significant trend toward a reduction of albuminuria, not confirming the results of some previous meta-analyses on a smaller number of trials.[60,65-67]

In the present meta-analysis, a significant reduction of the progression of albuminuria was also detected with DPP-4i. This result confirms a previous meta-analysis of placebo-controlled RCTs[68] and it is at variance with a pooled analysis of patient-level data from trials with linagliptin, showing neutral effects on the progression of albuminuria.[69] However, these data should be interpreted cautiously, considering the small number of available RCTs fulfilling the criteria for inclusion in the present analysis. Previously reported data on the reduction of albuminuria[16,70] with the use of pioglitazone could not be verified in our meta-analysis because none of the eligible RCTs adjudicated renal events; consequently, no trials could be included. Similarly, data on the effects of insulin and insulin secretagogues on this outcome are scarce, and no trial with α-glucosidase inhibitors could be included in the analysis.

The present meta-analysis collects a very wide body of evidence from RCTs, usually of good methodological quality. However, some limitations should be recognized. Patients enrolled in clinical trials are not fully representative of the population of people with diabetes, and trial procedures are not identical to routine clinical practice. In some instances, drug doses in clinical trials can be different from the median doses in clinical practice. Many of the larger RCTs available were designed for assessing the effect of different drugs on risk of MACE, enrolling patients with T2DM with previous cardiovascular events and/or at high cardiovascular risk; the average cardiovascular risk of enrolled patients could therefore be considerably higher than that of the general population with T2DM seen in clinical practice. Moreover, in a small fraction of RCTs (with small sample size), despite the adjudication of cardiovascular events, only individual components of MACE, but not MACE as a composite endpoint, were reported. In these studies, MACE were calculated as the sum of its individual components, possibly leading to an overestimation of the number of events. However, this bias, if present, occurred in both the treatment and the control groups. In addition, most data on cardiovascular and renal outcomes are derived from a relatively small number of large-scale placebo-controlled trials. On the other hand, data from active comparisons for these endpoints are relatively scarce. It should also be considered that in placebo-controlled trials primarily designed for cardiovascular and/or renal outcomes, investigators were allowed to modify concurrent glucose-lowering therapies in both treatment arms; as rescue therapies were more common in placebo arms, the difference between treatment groups could have been partly affected by differences in concurrent glucose-lowering therapy. The use of different investigational treatments in combination with other glucose-lowering agents, either as background or rescue therapy, raises the possibility of drug interactions; however, drugs for type 2 diabetes are used in combination in the majority of patients in clinical practice. In addition, characteristics of enrolled patients, duration of treatment, and trial procedures differed across drug classes, preventing direct comparisons among different treatment options. Another limitation could be represented by the relative paucity of available data for some drug classes on some endpoints. The limited number of available trials prevented the exploration of publication bias for some endpoints. One of the limiting factors for including a wider number of trials was the restriction to trials that adjudicated events. This choice, while limiting the number of trials, should be considered a strength of our meta-analysis, avoiding potentially misleading misclassifications of events.

In conclusion, the results of our large and updated meta-analysis of RCTs with external adjudication of events show that treatment with some classes of glucose-lowering drugs (metformin, pioglitazone, SGLT2i and GLP-1 RA) significantly reduces the risk of 3-point MACE, whereas insulin and DPP-4i are neutral, and insulin secretagogues appear to have a detrimental effect. In addition, SGLT2i and GLP-1 RA significantly reduce all-cause mortality, which is increased by use of insulin secretagogues. SGLT2i and, to a lesser extent, GLP-1 RA significantly improve adverse renal outcomes. Finally, SGLT2i reduce, and pioglitazone increases, the risk of HHF. The results of this updated meta-analysis need to be considered in the choice of drug treatment for T2DM, which cannot be merely based on the effect of glucose-lowering drugs on long-term glycaemic control.

AUTHOR CONTRIBUTIONS

MM and EM designed the study, collected and analysed the data, and wrote the manuscript. RC, BP, MG, AG and GT were involved in collecting the data and revising the manuscript. All the authors approved the final version of this manuscript. MM takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

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CONFLICT OF INTEREST

RC, MG, AG and GT declare that they have no competing interests; MM has received speaking fees from AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi and Novartis, and research grants from Bristol Myers Squibb; EM has received consultancy fees from Merck and Novartis, speaking fees from AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi and Novartis, and research grants from Merck, Novartis and Takeda; RC has received consultancy fees from Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Astra-Zeneca, Sanofi-Aventis and Roche Diabetes Care, speaking fees from AstraZeneca, Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Sanofi-Aventis, Mundipharma Pharmaceutical, Abbott, MSD, Neopharmed Gentili, Menarini, Essex Italia, Ascensia Diabetes, BP has received consultancy and speaking fees from Eli-Lilly and Novo Nordisk.

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