Effect of metformin on all-cause mortality and major adverse cardiovascular events: An updated meta-analysis of randomized controlled trials

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Abstract *Aims:* The Italian Society of Diabetology and the Italian Association of Clinical Diabetologists are developing new guidelines for drug treatment of type 2 diabetes. The effects of anti-hyperglycaemic drugs on all-cause mortality and major adverse cardiovascular events (MACEs) were included among the critical clinical outcomes. We have therefore carried out an updated meta-analysis on the effects of metformin on these outcomes.
Data synthesis: A MEDLINE and EMBASE search was performed to identify all randomized controlled trials (RCTs) with duration ≥52 weeks (published up to August 2020), in which metformin was compared with either placebo/no therapy or active comparators. MACEs (restricted for RCT reporting MACEs within their study endpoints) and all-cause mortality (irrespective of the inclusion of MACEs among the pre-specified endpoints) were considered as the primary endpoints. Mantel-Haenszel odds ratio (MH−OR) with 95% confidence interval was calculated for all endpoints considered. Metformin was associated with a nonsignificant reduction of all-cause mortality (n = 13 RCTs; MH−OR 0.80 [95% CI 0.60, 1.07]). However, this association became statistically significant after excluding RCTs comparing metformin with sulfonylureas, SGLT-2 inhibitors or GLP-1 analogues (MH−OR 0.71 [0.51, 0.99]). Metformin was associated with a lower risk of MACEs compared with comparator treatments (n = 2 RCT $ MH−OR 0.52 [0.37, 0.73]), $p < 0.001$. Similar results were obtained in a post-hoc analysis including all RCTs fulfilling criteria for inclusion in the analysis (MH−OR: 0.57 [0.42, 0.76]).
Conclusions: This updated meta-analysis suggests that metfomin is significantly associated with lower risk of MACEs and tendentially lower all-cause mortality compared to placebo or other anti-hyperglycaemic drugs.
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Introduction

It is known that treatment with metformin significantly improves glucose control in people with type 2 diabetes, with no weight gain and negligible risks of hypoglycaemic events [1,2]. In addition, treatment with metformin has been reported to be associated with a lower risk of cardiovascular morbidity and mortality in the UK Prospective Diabetes Study (UKPDS) over 20 years ago [3], although our previously published meta-analysis of randomized controlled trials (RCT), published in 2011, provided unclear results on this issue [4]. For all the aforementioned reasons, metformin is still considered the first-line glucose-lowering drug for treatment of type 2 diabetes [5,6]. More recently, however, other anti-hyperglycaemic agents with sustained efficacy and low hypoglycaemic risk have been developed [7–9]. In particular, sodium glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have been shown to consistently reduce the risk of major adverse cardiovascular events (MACEs) in high-risk patient groups [10–12]. As a consequence, some recent guidelines proposed that these newer anti-hyperglycaemic drugs might be used as a first-line therapy for type 2 diabetes, as an alternative to metformin [13,14]. In particular, the recent guideline issued by the European Society of Cardiology in collaboration with the European Association for the Study of Diabetes recommended the use of either SGLT-2 inhibitors or GLP-1 receptor agonists as first anti-hyperglycaemic drugs (instead of metformin) in all drug-naïve type 2 diabetic patients with prior history of cardiovascular disease and in those with multiple cardiovascular risk factors [14].

To date, an expert panel of the Italian Society of Diabetology (Società Italiana di Diabetologia, SID) and the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD) is developing new guidelines for drug treatment of type 2 diabetes, following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) procedure [15]. This expert panel, which includes clinical diabetologists, a general practitioner, a dietitian, a nurse, a professional diabetes educator, as well as a health economist and a representative of patients with diabetes has identified relevant clinical questions and patient-important outcomes critically affecting clinical decisions in diabetes clinical practice. The effects on risk of all-cause mortality and MACEs were included among the most important outcomes for clinical decision-making about the use of the most appropriate glucose-lowering agents in people with type 2 diabetes. As a consequence, a series of systematic reviews and meta-analyses of RCTs primarily focused on these two patient-important outcomes are currently underway for all classes of anti-hyperglycaemic drugs used for treatment of type 2 diabetes.

The present study reports the results of a systematic review and meta-analysis of RCTs comparing the effects of metformin with placebo/no therapy or other glucose-lowering drugs in adults with type 2 diabetes.

Methods

The present systematic review and meta-analysis is reported following the criteria of PRISMA statement [16] (see Table S1 in Appendix) and registered in Open Science Framework (osf.io/arw8e).

Search strategy and selection criteria

3-point MACEs

A MEDLINE and EMBASE search was performed to identify all RCTs published in English, up to August 31st, 2020, in which metformin was compared with either placebo/no therapy, current care or other active comparators. To explore the so-called "grey literature", Google and Google Scholar databases were also searched. Selected articles were imported into Endnote and then duplicate articles were removed. Only anti-hyperglycaemic drugs approved by the European Medicine Agency (EMA) and currently available in Europe, at EMA-approved doses, were considered, both as investigational drugs and comparators.

Further inclusion criteria for our systematic review were:

1) MACEs should be reported within the primary endpoint of the RCT, or as pre-defined secondary endpoints with event adjudication
2) enrolment limited to adult patients with established type 2 diabetes, or available subgroup analyses for patients with type 2 diabetes
3) enrolment of at least 100 patients with type 2 diabetes
4) duration of the follow-up of at least 52 weeks

All-cause mortality

For the systematic review on all-cause mortality, the same aforementioned inclusion criteria were also applied, except for the criterion #1 (i.e., we included all RCTs, irrespective of the inclusion of MACEs among the primary or secondary study endpoints).

Detailed information on the search string is reported in online-only supplementary material (Table S2).

Data extraction

The identification of relevant abstracts, the selection of studies and the extraction of data was performed independently by two of the authors (MM and EM), and conflicts resolved by a third investigator (GT). For all eligible RCTs, results reported in published papers were used as the primary source of information. When data on the clinical endpoints of interest were not available in the primary publication, an attempt of retrieving information was made on clinicaltrials.gov. No attempt was made at contacting authors and/or sponsors (depending on data property) for retrieval of missing data.

For all eligible RCTs, the following parameters/information were extracted: first author, year of publication, name of the investigational drug, comparator, duration of

the trial, number of patients randomly assigned to each treatment arm, mean age and number of clinical endpoints (MACEs and total deaths).

Data analysis

The two principal outcomes of the meta-analysis were as follows:

1) 3-point MACEs was defined as non-fatal myocardial infarction, non-fatal ischemic stroke, or cardiovascular mortality. Metformin was compared with either placebo/no therapy or other active comparators different from metformin
2) all-cause mortality (including also RCTs not reporting MACEs within the primary study endpoint, or as pre-defined secondary endpoints). Metformin was compared with either placebo/no therapy or other active comparators different from metformin

For all-cause mortality, we also performed a post-hoc analysis excluding comparisons with SGLT-2 inhibitors or GLP-1 receptor agonists, which have been associated with a significant reduction of all-cause mortality [11,17]. A further post-hoc analysis was also performed for the risk of MACEs, including all eligible RCT irrespective of the inclusion of MACEs among the primary or secondary study endpoints.

The risk of bias of the eligible RCTs was assessed using the parameters proposed by the Cochrane Collaboration.

Mantel-Haenszel odds ratio (MH–OR) with 95% Confidence Interval (95% CI) was calculated for all the outcomes considered, on an intention-to-treat basis, excluding RCTs with zero clinical endpoints, using a random-effects model. The fixed-effect model was used only for sensitivity analyses, due to the intrinsic clinical heterogeneity of the eligible RCTs. Heterogeneity was assessed using the I [2]-statistics and calculating the Kendall's tau without continuity correction. To estimate the existence of possible publication/disclosure biases, we examined funnel plots for risk of both 3-point MACEs and all-cause mortality and calculated the Egger's test (see online-only Supplementary material).

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

The GRADE methodology [15] was used to assess the overall quality of the eligible RCTs, using the GRADEpro GDT software (GRADEpro Guideline Development Tool. McMaster University, 2015. Available from gradepro.org).

Results

3-point MACEs

Supplementary Fig. S1 reports the flow summary of our meta-analysis. A total of three RCTs fulfilling the inclusion criteria were initially identified, all reporting detailed information on 3-point MACEs, with exception of one RCT [18], which was therefore excluded from the principal analysis.

Publication bias was not assessed due to the low number of RCTs included. The overall quality of the two eligible RCTs was high for all items of the Cochrane tool, except for "blinding of participants and personnel (performance bias)" for the UKPDS-34 trial [3].

The two RCTs included in this meta-analysis enrolled a total of 498 and 599 adults with type 2 diabetes, who were treated with metformin and active comparators, respectively (Table S3). As shown in Fig. 1, metformin use was associated with a significantly lower risk of 3-point MACEs (MH–OR 0.52 [95% CI 0.37, 0.73], $p < 0.001$), with no evidence of any significant heterogeneity (I [2] = 0%). Interestingly, metformin use remained significantly associated with a lower risk of 3-point MACEs (MH–OR: 0.57 [0.42, 0.76]), even in a post-hoc analysis that included all RCTs, irrespective of the inclusion of MACEs among the primary or secondary study endpoints (Fig. S2).

All-cause mortality

All the 13 RCTs fulfilling the criteria for inclusion in our meta-analysis of all-cause mortality (Table S2) reported information on this specific outcome. As shown in Fig. S2, no significant publication bias was detected. The overall quality of all included RCTs was high for all items of the Cochrane tool, except for "performance bias" (Fig. S3). This meta-analysis included a total of 4217 and 5944 type 2 diabetic patients in the metformin and comparator arms, respectively; the mean age of participants was 55 years; the mean RCT duration was 131 weeks. Total deaths were 107 and 337 in metformin and comparator arms, respectively. As shown in Fig. 2, metformin use was associated with a borderline (non-significant) reduction of all-cause

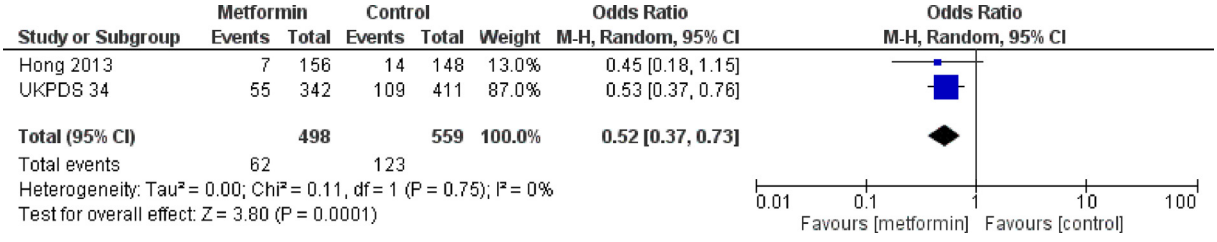

Figure 1 Risk of major adverse cardiovascular events (MACE) with metformin *versus* other active comparators approved by EMA and currently used in Europe (MH–OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

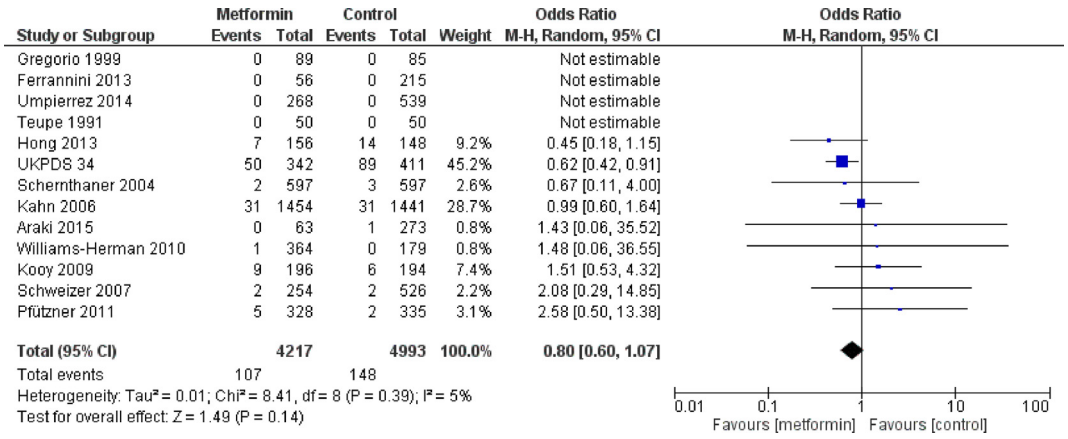

Figure 2 Risk of all-cause mortality with metformin *versus* other active comparators approved by EMA and currently used in Europe (MH−OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

mortality (MH−OR 0.80 [95%CI 0.60, 1.07], p = 0.14). I^2-statistics did not reveal any significant heterogeneity across the eligible studies for all-cause mortality (I^2 = 5%; Tau^2 = 0.3, p = 0.55). This result was further confirmed in a sensitivity analysis using a fixed-effect model (MH−OR 0.79 [0.60, 1.02]).

However, when we excluded RCTs in which use of metformin was compared with sulphonylureas, GLP-1 receptor agonists or SGLT-2 inhibitors, the association between metformin use and reduced risk of all-cause mortality became statistically significant (MH−OR 0.71 [0.51, 0.99]; I^2 = 0%, tau [2] = 0.3; Fig. S5).

A subgroup analysis, comparing metformin use with different classes of anti-hyperglycaemic drugs, did not show any significant differences between the two treatment arms (Fig. S6).

Quality of evidence

Using the GRADE algorithm [15], the overall quality of evidence was rated as “moderate” for the risk of MACEs (Table S4).

Discussion

Worldwide, there is an increasing incidence of type 2 diabetes. Metformin is still the recommended first-line anty-hyperglycaemic drug for people with established type 2 diabetes. Despite this, the effects of metformin on patient-important outcomes are still not clarified. In particular, the cardiovascular safety of metformin has been debated for a long time, after the publication in 1998 of the pioneering UKPDS-34 trial [3]. A previous meta-analysis of 35 RCTs, published by our group in 2011, reported a significant risk reduction of MACEs only in RCTs comparing metformin with placebo/no therapy (MH−OR 0.79 [95% CI 0.64−0.98], p = 0.031), but not in RCTs comparing metformin use with other active comparators (MH−OR 1.03 [0.72−1.77], p = 0.89)[4]. However, it is important to note that this latter meta-analysis included many RCTs in which MACEs were reported as serious adverse events without any formal adjudication, with the possibility of (some) misclassification bias. In addition, the aforementioned meta-analysis also included comparisons of metformin with some anti-hyperglycaemic drugs that are now no longer available on the market (at least in Europe), such as rosiglitazone. Similarly, a recent meta-analysis, including 13 studies (9 observational cohort studies, 3 RCTs, and 1 nested case−control study) reported that compared with other active glucose-lowering agents, the use of metformin was significantly associated with lower risks of all-cause mortality (pooled relative risk 0.71 [0.61−0.84]) and cardiovascular events (pooled relative risk 0.76 [0.60−0.97]) in patients with type 2 diabetes and mild/moderate chronic kidney disease. However, this latter meta-analysis also included observational cohort studies and there was a high heterogeneity in the results of the pooled primary analyses (I [2] = 79% for all-cause mortality and I^2 = 87% for MACEs, respectively) [19]. Another meta-analysis has recently examined the effects of metformin monotherapy in adults with type 2 diabetes [20]. The authors included RCTs with at least one year’s duration comparing metformin monotherapy with no intervention, behaviour changing interventions or other glucose-lowering drugs. They concluded that there is no clear evidence whether metformin monotherapy influences patient-important outcomes, such as all-cause and cardiovascular mortality [20].

That said, although metformin has been available for over 60 years, its cardiovascular benefits are still scarcely documented in large RCTs. To date, there are only two RCTs in which MACEs were either the primary study endpoint or a pre-specified secondary endpoint with event adjudication [3,21]. In our updated systematic review and meta-analysis, combining the results of these two eligible RCTs, we found that metformin use is significantly associated with a lower risk of MACEs compared with other active comparator treatments. However, it should be noted that the strength of this evidence is relatively low, because of the relatively small sample size of the two eligible RCTs. In particular, MACEs were only a fraction of a much wider primary study endpoint (also including microvascular

diabetic complications) in the UKPDS-34 trial; in addition, in this trial the comparison of metformin with other glucose-lowering drugs was an exploratory analysis performed only in a subgroup of type 2 diabetic patients who were overweight or obese [3]. In the other RCT included in our meta-analysis, MACEs were a secondary study endpoint, although pre-specified and adjudicated, of a relatively small RCT with a primary metabolic endpoint [21]. On the other hand, it should be noted that the significant risk reduction of MACEs we observed with the use of metformin is further confirmed in our post-hoc analysis including RCTs in which MACEs were not a pre-specified secondary study endpoint. However, we believe that the results of this post-hoc analysis, although clinically interesting, should be interpreted with some caution, because MACEs that occurred in some of these RCTs were not adjudicated, with the possibility of some misclassification of cases.

All-cause mortality is a 'hard' clinical outcome even when it is not included among the pre-specified study endpoints, because this outcome is unequivocal and it does not need any adjudication. It is important to underline that in the RCTs included in our meta-analysis, the recorded total deaths were numerically lower in the metformin arm than in the other active comparator arms, but the difference between the treatment arms did not reach statistical significance. We believe that the relatively small sample size can at least in part explain the lack of any statistical significance despite an estimate of risk reduction of 20% (MH−OR 0.80 [0.60, 1.07], p = 0.14). Notably, the risk reduction of all-cause mortality with metformin use reached statistical significance when we excluded RCTs comparing metformin with other anti-hyperglycaemic agents which can modify risk of all-cause mortality (i.e., sulfonylureas [22], GLP1 receptor agonists [11,23] or SGLT2 inhibitors [12,23]). This finding is also in line with the risk reduction in MACEs we observed in diabetic patients treated with metformin when compared with other active comparators. In addition, it is also reasonable to hypothesize that the possible protective effect of metformin on all-cause mortality may require RCTs with longer periods of follow-up than those available in the literature.

Collectively, the quality of each meta-analysis depends mostly on the quality of the included studies. Since metformin is a long-established glucose-lowering therapy for type 2 diabetes, it is inevitable that this type of analysis has to accommodate trial designs that span different 'eras' (from a diabetes care perspective) and adopt different judgement criteria. In this case, although the overall quality of eligible RCTs was satisfactory, biases could not be definitely excluded for some of these RCTs. In addition, the included RCTs were heterogeneous for study design, comparators, case mix and trial duration; nevertheless, no substantial heterogeneity was detected at statistical analysis. That said, the main limitation of our meta-analysis, which should be carefully considered in the interpretation of results, is the relatively small size of samples enrolled in the eligible RCTs, especially in those comparing the effects of metformin on MACEs.

Despite the limitations mentioned above, this updated meta-analysis of RCTs shows that compared with placebo or other anti-hyperglycaemic agents, treatment with metformin may significantly reduce cardiovascular morbidity and mortality in adults with type 2 diabetes, with a possible beneficial effect also on risk of all-cause mortality.

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Author contributors

MM and **EM** were involved in each of the following points:

1. Design.
2. Data Collection.
3. Analysis.
4. Writing manuscript.

RC, BP, and **GT** were involved in each of the following points:

1. Manuscript revision.

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of competing interest

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All the authors approved the final version of this manuscript. Dr. Edoardo Mannucci is the person who 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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