Effect of insulin secretagogues on major cardiovascular events and all-cause mortality: A meta-analysis of randomized controlled trials

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Abstract *Background and aim:* In 2019, the Italian Society of Diabetology and the Italian Association of Clinical Diabetologists nominated an expert panel to develop guidelines for drug treatment of type 2 diabetes. This expert panel, after identifying the effects of glucose-lowering agents on major adverse cardiovascular events (MACEs) and all-cause mortality as critical outcomes, decided to perform a systematic review and meta-analysis on the effect of insulin secretagogues (sulfonylureas and glinides) with this respect.

Methods and results: A MEDLINE database search was performed to identify all RCTs, up to January 1st, 2020, with duration≥52 weeks, in which insulin secretagogues (glibenclamide, gliclazide, glimepiride, glipizide, chlorpropamide, repaglinide, nateglinide) were compared with either placebo or active comparators. The principal endpoints were MACE (restricted for RCT reporting MACEs within their outcomes) and all-cause mortality (irrespective of the inclusion of MACEs among the pre-specified outcomes). Mantel-Haenszel odds ratio (MH−OR) with 95% Confidence Interval (95% CI) was calculated for all the endpoints considered. Fourteen RCTs were included in the analysis for MACEs (919 in insulin secretagogues and 1,087 in control group). Insulin secretagogues were not significantly associated with an increased risk of MACEs in comparison with controls (MH−OR 1.08 [95% CI 0.96, 1.22], p = 0.20). When considering the 48 RCTs fulfilling criteria for inclusion in the analysis on all-cause mortality, insulin secretagogues were associated with a significantly increased risk of all-cause mortality (MH−OR 1.11 [1.00, 1.23], p = 0.04).

Conclusions: This meta-analysis suggests that insulin secretagogues are associated with an increased risk of all-cause mortality when compared with placebo or other anti-hyperglycaemic drugs.

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Introduction

In 2019, the Italian Society of Diabetology (Società Italiana di Diabetologia, SID) and the Italian Association of Clinical Diabetologists (Associazione Medici Diabetologi, AMD) decided to develop new guidelines for drug treatment of type 2 diabetes. The proposal was submitted to National authorities and approved for inclusion in the Italian National Guideline System (INGS). The INGS, which was created after the prescription of a national law [1], is designed as a standard reference for clinical practice in Italy. In order to be included in the INGS, guidelines need to be formulated following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) procedure [2], and to obtain a high rating on the Appraisal of Guidelines for Research and Evaluation (AGREE) [3] instrument.

SID and AMD nominated an expert panel for developing these guidelines, which included clinical diabetologists, a general practitioner, a dietitian, a nurse, a professional diabetes educator, a health economist, and a representative of patients with diabetes. Following the GRADE method [2], the expert panel firstly identified a number of relevant clinical questions; for each question, the panel then defined the outcomes affecting clinical decisions, rating also their relevance. For each outcome classified as "critical" for clinical decisions, a systematic review should be performed, collecting available clinical evidence and assessing its methodological strength.

The effects on major adverse cardiovascular events (MACE) and all-cause mortality were included among the critical outcomes for decision with respect to some of the questions on glucose-lowering pharmacological treatments. As a consequence, a series of systematic reviews of randomized controlled trials (RCT) focused on these outcomes is currently underway for all classes of anti-hyperglycemic drugs indicated for the treatment of type 2 diabetes.

The present paper reports the results of a systematic review and meta-analysis on the effect of insulin secretagogues (sulfonylureas and glinides) on the risk of both MACEs and all-cause mortality.

Methods

The present meta-analysis is reported following the criteria of PRISMA statement [4] (see Table S1 in Appendix).

Search strategy and selection criteria

MACE

A MEDLINE, and Cochrane Central Register of Controlled Trials search was performed to identify all RCTs published in English, up to January 1st, 2020, in which sulfonylureas (glibenclamide or gliclazide or glimepiride or glipizide or chlorpropamide) and glinides (repaglinide or nateglinide) were compared with either placebo/no therapy, current care or other active comparators. In order to explore the so-called "grey literature", Google and Google scholar databases was also searched. Selected articles were imported into Endnote and then duplicate articles were removed. Only anti-hyperglycemic drugs approved by 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 the systematic review were:

1) RCT reporting MACEs within their primary outcome, or as pre-defined secondary outcomes with event adjudication
2) RCT enrolling only patients with type 2 diabetes, or with available subgroup analyses for patients with type 2 diabetes
3) RCT enrolling at least 100 patients with type 2 diabetes
4) RCT with a duration of 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, with the exception of #1 (i.e., RCTs were included irrespective of the inclusion of MACEs among the primary or secondary outcomes).

Detailed information on the search string is reported in Supplementary materials (Table 2S).

Data extraction

The identification of relevant abstracts, the selection of studies, and the extraction of data was performed independently by two of the authors (M.M. and E.M.), and conflicts resolved by a third investigator (G.T.). For all RCTs, results reported in published papers were used as the primary source of information; when data on the clinical outcomes considered 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 outcomes (MACEs and deaths).

Data analysis

The principal endpoints of the meta-analysis were as follows:

1) 3-point MACE defined as nonfatal myocardial infarction, nonfatal ischemic stroke or cardiovascular death. Insulin secretagogues were compared either with placebo (no therapy) or active comparators different from insulin secretagogues.

2) all-cause mortality (including also RCTs not reporting MACE within the primary outcome, or as predefined secondary outcomes). Insulin secretagogues were compared either with placebo (no therapy) or active comparators different from insulin secretagogues.

Further pre-specified analyses on MACE and mortality were performed including only trials with sulfonylureas, and excluding those with glinides. A post-hoc subgroup analysis was performed for trials in which insulin secretagogues were used as monotherapy or in combination with other drugs.

For all-cause mortality, a post-hoc analysis was performed also including RCTs that used anti-hyperglycemic drugs not available in Europe but approved by other extra-European regulatory drug authorities and marketed in other parts of the world. In addition, post-hoc sub-group analyses were also performed for examining the effect on the risk of all-cause mortality of either individual insulin secretagogues approved by EMA *vs.* other comparators or insulin secretagogues *vs.* individual comparators. These subgroup analyses were repeated also including RCTs that used any antihyperglycemic drugs approved by other extra-European regulatory drug authorities and marketed in other parts of the world. Further post-hoc analysis on the risk of all-cause mortality was performed excluding comparisons with SGLT-2 (Sodium Glucose Transporter-2) inhibitors or GLP-1 (Glucagon-Like Peptide-1) receptor agonists, which have been associated with a reduction of mortality [5,6]. A meta-regression analysis correlating the duration of RCTs and all-cause mortality (MH–OR) was also performed in order to exclude a possible effect of trial duration on the risk of mortality.

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 endpoints considered, on an intention-to-treat basis, excluding RCTs with zero events, using a random-effects model. The fixed-effects model were used only for sensitivity analyses, due to the intrinsic clinical heterogeneity of the selected studies. Heterogeneity was assessed using I [2] statistics and calculating Kendall's tau without continuity correction. To estimate possible publication/disclosure bias we examined funnel plots for risk of 3-point MACEs and all-cause mortality and calculated the Begg adjusted rank correlation without continuity correction. The results of this latter test were reported in Supplementary materials.

All statistical analyses specified above were performed using Review Manager 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Metaregression analyses were performed using Comprehensive Metanalysis version 2·0 (Biostat, Inc., Englewood, NJ) software.

The GRADE methodology [2] was used to assess the overall quality of the eligible RCTs, using the GRADEpro GDT software (GRADEpro Guideline Development Tool. McMaster University, 2015. Available fromgradepro.org).

Results

Risk of 3-point MACE

Supplementary Figure S1 reports the flow summary of the meta-analysis. A total of 15 RCTs (Table 2S) fulfilling the inclusion criteria was initially identified, all reporting detailed information on 3-point MACE, with exception of one trial [7], which was therefore excluded from the principal analysis.

No publication bias was detected at a visual analysis of the Funnel plot (Figure S2). The overall quality of all included RCTs was high for all items of the Cochrane tool, with the exception of “performance bias” in two open-label trials [8–10](Figure S3).

The RCTs included in this analysis enrolled 12,507 and 13,930 patients in insulin secretagogues and comparator arms, respectively, with a mean age of 56 years; the mean trial duration was 162 weeks. All trials were performed with sulfonylureas and none with glinides. All the 14 RCTs reported at least one case of MACE (919 in the insulin secretagogue group and 1,087 in the control group). As shown in Fig. 1, insulin secretagogues were not significantly associated with an increased risk of 3-point MACEs in comparison with placebo/no therapy or other anti-hyperglycemic therapies (MH–OR 1.08 [95% CI 0.96, 1.22], p = 0.20). I [2] and Kendall's tau statistics did not show any significant between-study heterogeneity for risk of MACE (I [2]: 11%; tau [2] = 0.01, p = 0.33). Almost identical results were obtained using a fixed-effect model (MH–OR 1.07 [0.98, 1.18], p = 0.15).

When considering trials in which insulin secretagogues were given as first-line treatment (i.e. monotherapy) [9,11–14] *the MH–OR was* 1.08 [0.95, 1. 22], p = 0.27, whereas in those in which *insulin secretagogues* were administered as add-on therapy the MH–OR *was* 0.87 [0.59, 1. 30], p = 0.51.

Risk of all-cause mortality

Of the 48 RCTs fulfilling criteria for inclusion in the analysis on all-cause mortality (Table S2), two [15,16] did not report any information on this outcome; the analysis was therefore performed on 46 RCTs. No publication bias was detected at a visual analysis of the Funnel plot (Figure S4). The overall quality of all included RCTs was high for all items of the Cochrane tool, with the exception of “performance bias” in eleven open-label trials (Figure S5). The RCTs included in this analysis included 24,188 and 26,351 patients in insulin secretagogues and comparator arms, respectively, with a mean age of 58 years.; the mean trial duration was 140 weeks. Total deaths were 797 and 897 in insulin secretagogues and control groups, respectively. As reported in Fig. 2, insulin secretagogues were associated with a significantly increased risk of all-cause mortality in comparison with placebo/no therapy or other anti-hyperglycemic therapies (MH–OR 1.11 [1.00, 1.23], p = 0.04). I [2] statistics did not suggest any relevant heterogeneity across studies with respect to all-cause

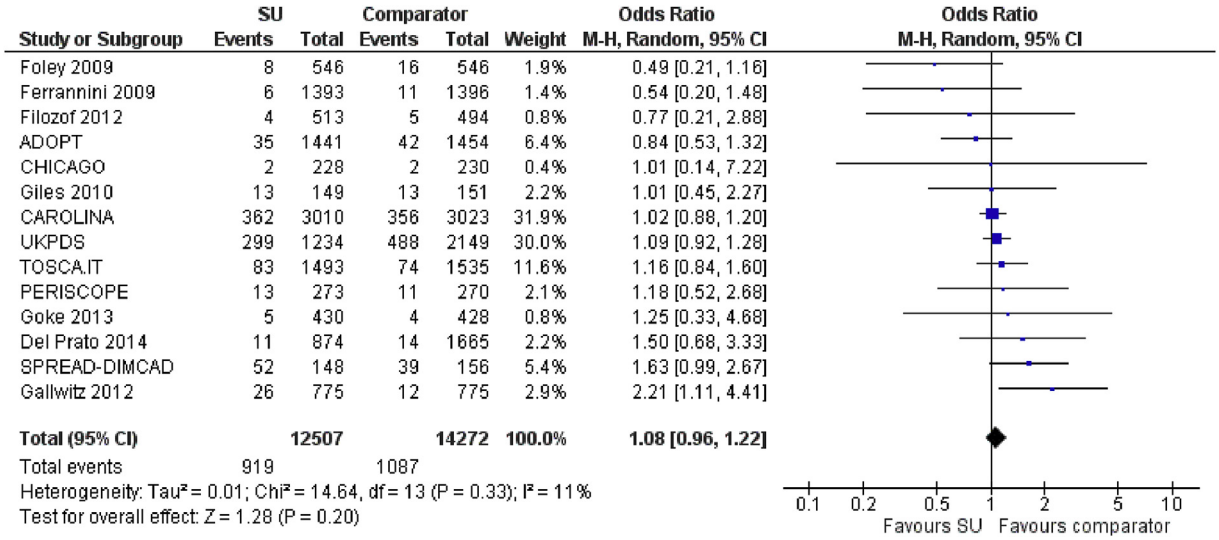

Figure 1 Risk of major adverse cardiovascular events (MACE) with insulin secretagogues *versus* other comparators approved by EMA and currently used in Europe (MH−OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals). A total of 14 RCTs were included in this pooled primary analysis.

mortality (I [2]: 0%; tau [2] = 0.0, p = 0.88). Identical results (MH−OR 1.11 [1.00, 1.23], p = 0.04; I^2: 0%; tau [2] = 0.0, p = 0.88) were observed when analysing RCTs with sulfonylureas only, excluding those (N = 3) with glinides.

A meta-regression analysis correlating trial duration with all-cause mortality (MH−OR) did not show any significant association (slope: −0.0004 [-0.001; 0.00032], p = 0.27).

A subgroup analysis comparing the risk of all-cause mortality for different insulin secretagogues and for different comparators did not reveal any significant difference (p-values for subgroup differences: 0.12 and 0.60, respectively; see Figure S6 and Figure S7). Only the use of glipizide was significantly associated with an increased risk of all-cause mortality, as shown in Figure S6. On the contrary, the use of insulin secretagogues as a class was significantly associated with increased mortality only in comparison with biguanides (Figure S7).

Similar results were obtained even when including also RCTs (n = 53) using, as comparators, antihyperglycemic drugs not currently available in Europe, as shown in Figures S8, S9, and S10. A further subgroup analysis excluding RCTs that compared insulin secretagogues with SGLT-2 inhibitors or GLP-1 receptor agonists did not substantially modify the obtained results (MH−OR 1.11 [1.00; 1.22]; p = 0.04), as shown in Figure S11.

Quality of evidence

Using the GRADE algorithm [2], the overall quality of evidence was rated as “high” both for risk of MACE and all-cause mortality (Table S4).

Discussion

The cardiovascular safety of sulfonylureas has been debated for a long time, mainly because of their interaction with myocardial [17−20] and cerebral [21] ATP-sensitive potassium channels (or K_{ATP} channels). About 40 years ago, a pioneering RCT, the University Diabetes Group Program, suggested an increase of all-cause mortality associated with the use of a first-generation sulfonylurea, tolbutamide [22]; however, the results of this study, which was not included in the present meta-analysis since tolbutamide is no longer available, were criticized because of its important methodological flaws [23]. In the following decades, several retrospective observational studies and non-randomized interventional studies reported a higher mortality rate in patients with type 2 diabetes using sulfonylureas, in comparison with other metformin or other antihyperglycemic drugs [24−29]. However, results of observational or non-randomized interventional studies are inevitably affected by residual prescription bias, which cannot be entirely eliminated with adjustment for available confounders [30]. Recent RCTs [10,31], failing to detect any significant increase in cardiovascular risk with sulfonylureas, compared with other active antihyperglycemic drugs, have reassured most clinicians on the cardiovascular safety of sulfonylureas [32].

The results of our updated systematic review and meta-analysis of RCTs corroborate prior observations that the use of sulfonylureas is not associated with any increase in the risk of 3-point MACEs (defined as nonfatal myocardial infarction, nonfatal ischemic stroke or cardiovascular mortality) in comparison with placebo/no therapy or other antihyperglycemic therapies (approved by EMA and currently used in Europe). This result was obtained in a substantial sample of patients (over 50,000 patients*years of observation in a total of 14 RCTs with nearly 2,000 recorded MACEs), with an upper confidence limit of 1.22 (pooled MH−OR 1.08 [95% CI 0.96, 1.22], p = 0.20). Notably, only part of these patients were enrolled in trials with MACE ad their primary endpoint; however, the other

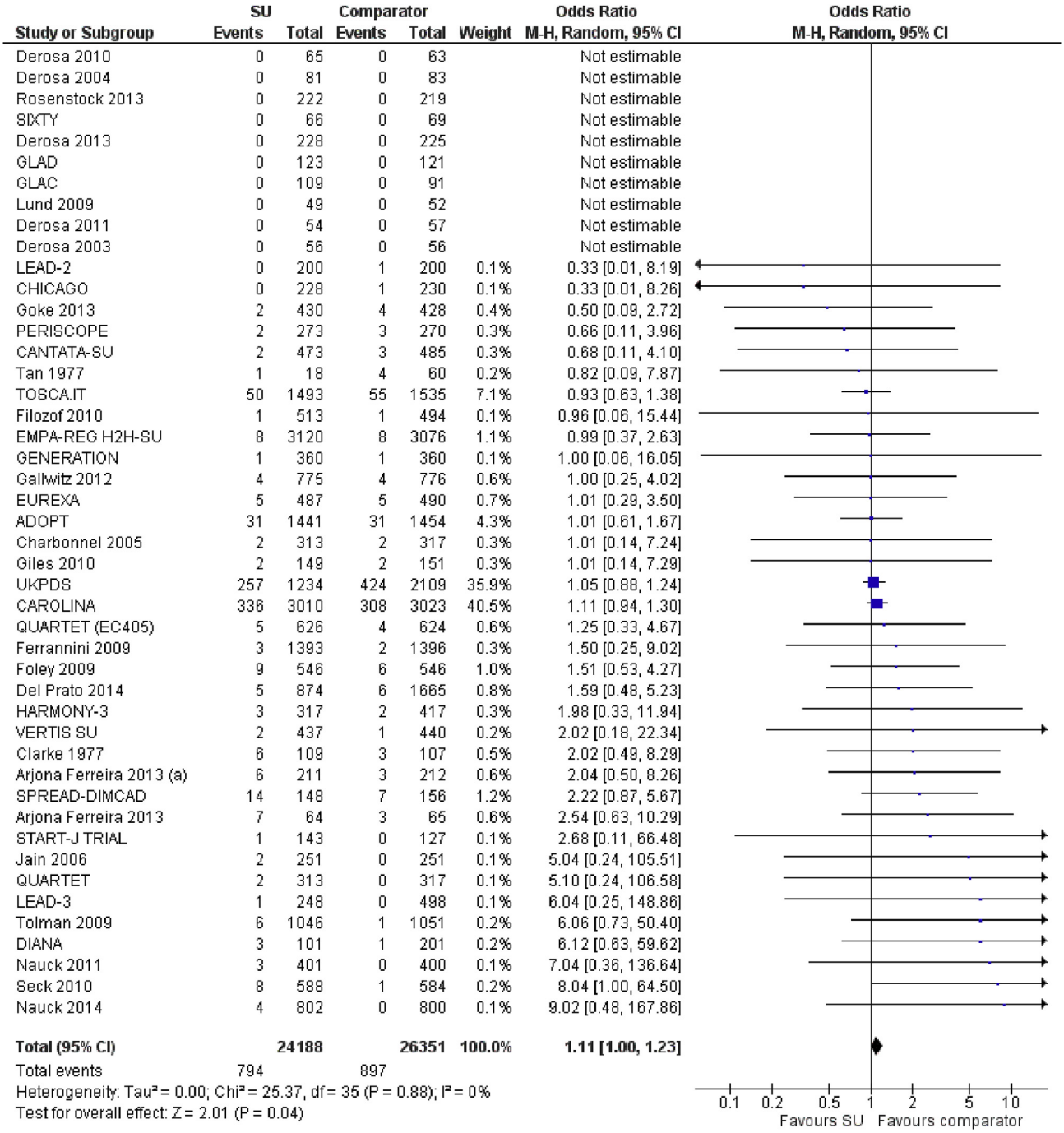

Figure 2 Risk of all-cause mortality with insulin secretagogues *versus* other comparators approved by EMA and currently used in Europe (MH–OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals). A total of 46 RCTs were included in this pooled primary analysis.

included trials designated MACE among predefined secondary endpoints with formal event adjudication, thus limiting the possibility of misclassification of cases.

On the other hand, the novel finding of our meta-analysis is that the use of sulfonylureas was significantly associated with an increase of all-cause mortality (pooled MH–OR 1.11 [1.00, 1.23], p = 0.04 for 46 eligible RCTs including 50,539 patients with a total of nearly 1700 deaths) compared with placebo/no therapy or other anti-hyperglycemic therapies that were approved by EMA and currently used in Europe. Notably, this finding was confirmed even when we included other RCTs (n = 7) using antihyperglycemic drugs that were not available in Europe but used in the United States or other extra-European countries. The observed increased risk of all-cause mortality with the use of sulfonylureas (11%) appears to be clinically relevant, and the quality of evidence is rated "high" based on the GRADE score [2]. However, we believe that this result should be interpreted with some caution for the following main reasons:

1) The increased risk of all-cause mortality with the use of sulfonylureas/glinides in comparison with placebo/no therapy or other antihyperglycemic drugs was only marginally significant; as a consequence, the possibility of a play of chance cannot be definitely excluded. In fact, p = 0.04 means a 4% probability that the difference is casual.
2) The results of any meta-analysis are inevitably affected by the criteria chosen for the inclusion of RCTs. In the present case, the criteria had been chosen in order to obtain a reliable evidence base for developing treatment guidelines for type 2 diabetes in Italy. For such reason, the analysis was principally limited (both in investigational and comparator arms) to antihyperglycemic drugs approved by EMA and currently used in Europe. However, it should also be noted that the inclusion of any antihyperglycemic drugs available in other extra-European countries did not essentially change our primary results. Other criteria could have also produced some substantial changes. For example, the adoption of more restrictive selection criteria (e.g., exclusion of open-label trials) would have reduced the overall sample size for pooled analyses; in this case, it would have been very difficult to reach significant differences between treatment arms [33]. On the other hand, the inclusion of currently unavailable sulfonylureas, such as tolbutamide, as in previous meta-analyses [26,34], would have provided an estimate of a wider increase in mortality risk associated with sulfonylureas/glinides.
3) Our meta-analysis included different sulfonylureas and glinides, which could have different effects on mortality risk. Although they share the same mechanism of hypoglycaemic action [35], sulfonylureas and glinides are chemically different; in addition, available evidence suggests differences in postprandial glucose control and hypoglycaemic risk [36,37]. However, results were identical even when excluding trials with glinides. In addition, individual sulfonylureas markedly differ in their affinity for myocardial ATP-sensitive potassium channels [20]. Previous observational and non-randomized interventional studies reported significant differences in risk of all-cause mortality across different sulfonylureas, with gliclazide possibly showing less unfavourable effects than other sulfonylureas [38,39]. It is noteworthy to mention that in this meta-analysis, there is no evidence of any significant between-study heterogeneity with respect to all-cause mortality (I [2]: 0%; tau [2] = 0.0, p = 0.88). Despite this, we performed some subgroup analyses examining the risk of all-cause mortality with the use of individual insulin secretagogues *versus* other comparators (Figure S4). The results of these subgroup analyses were essentially comparable to those of the primary pooled analysis, although only RCTs with glipizide appeared to be significantly associated with an increased risk of all-cause mortality. However, in interpreting the results of all these subgroup analyses, it is important to note that the number of total deaths observed with each sulfonylurea/glinide was in most cases too small to draw any reliable conclusion. In particular, the generalizability of this result to glinides is questionable.
4) Our meta-analysis also included different active comparators. Comparators could have, at least theoretically, beneficial or detrimental effects on mortality, affecting the final result. A subgroup analysis for different comparators did not reveal any significant differences (Figure S5); however, also in this case, it is important to note that the sample size for each drug class was insufficient to draw any definitive conclusions. Since two newer classes of antihyperglycemic drugs (i.e., SGLT-2 inhibitors and GLP-1 agonists) have been associated with decreased risk of mortality [5,40,41], a sensitivity analysis was also performed excluding RCTs with those comparators, confirming the results of the pooled primary analysis.
5) Finally, although the methodological quality of most RCTs included in the meta-analysis appeared to be satisfactory, some of the eligible RCTs had possible sources of bias. In particular, eight RCTs were open-label [10,16,42–46].

Despite all these limitations, given the clinical relevance of the outcome (all-cause mortality), we felt compelled to publish the present results, offering them to the consideration of scientists, regulatory authorities, and policymakers.

Mechanisms underlying the increase of mortality associated with sulfonylureas is beyond the aims of the present paper. Although the effect of sulfonylureas on MACE is not statistically significant, its odds ratio (1.08) is not very different from that observed for mortality, suggesting that the increase of mortality could be mainly due to cardiovascular causes; however, the present data do not allow to exclude possible effects on non-cardiovascular deaths.

In conclusion, this comprehensive meta-analysis of RCTs confirms that insulin secretagogues do not increase the risk of major cardiovascular adverse events. However, these results also suggest that the use of sulfonylureas is associated with an increase in the risk of all-cause mortality when compared with placebo/no therapy or other antihyperglycemic drugs.

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study and had final responsibility for the decision to submit for publication.

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

EM has received consultancy fees from Merck and Novartis speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis and research grants from Merck, Novartis, and Takeda. **MM** has received speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis and research grants from Bristol Myers Squibb; **RC, BP, and GT** has no relevant conflicts of interest to declare.

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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