All-cause mortality and cardiovascular events in patients with type 2 diabetes treated with alpha-glucosidase inhibitors: A meta-analysis of randomized controlled trials

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Abstract *Aim:* Alpha-glucosidase inhibitors are approved drugs for treating type 2 diabetes (T2DM); however, their effects on mortality and cardiovascular safety are unclear. This meta-analysis was aimed at evaluating the effects of alpha-glucosidase inhibitors on all-cause mortality and major cardiovascular events (MACE).
Data synthesis: A Medline, Embase, Cochrane database searching for alpha-glucosidase inhibitors was performed up to July 1st, 2021. All randomized controlled trials (RCT) with a duration ≥52 weeks and comparing the effects of alpha-glucosidase inhibitors with placebo or active drugs were collected. Further inclusion criteria were: RCT reporting MACE within their primary outcome, or as pre-defined secondary outcome; and RCT enrolling at least 100 patients with T2DM. Mantel-Haenszel odds ratio (MH–OR) with 95% confidence intervals were calculated for the aforementioned outcomes. A total of eight RCTs, enrolling 1124 and 908 patients on alpha-glucosidase inhibitors and comparators, respectively, were identified. No trials reported information on MACE. Treatment with alpha-glucosidase inhibitors was not associated with a significant increase of all-cause mortality compared with other therapies or no therapy/placebo (MH–OR 0.76 [0.28; 2.05]).
Conclusions: The evidence of beneficial or detrimental effects of alpha-glucosidase inhibitors on all-cause mortality and cardiovascular events is not sufficient to draw any conclusions.

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Introduction

Alpha-glucosidase inhibitors are approved drugs for treatment of type 2 diabetes mellitus (T2DM), with a specific effect on postprandial glucose excursion [1–3]. The STOP-NIDDM trial, performed in patients with impaired glucose tolerance, reported fewer major cardiovascular events in the acarbose arm [4], but the very small number of recorded events limited the reliability of this observation. A pooled analysis of phase 3 randomized controlled trials (RCT) showed a protective effect of acarbose on cardiovascular events in comparison with either placebo or active comparators [5]; however, the events considered were very heterogeneous (e.g., including peripheral artery occlusion, revascularization procedures, angina, and heart failure) and the number of observed events was small. Other available classes of drugs for type 2 diabetes, which showed a greater efficacy on glucose control than alpha glucosidase inhibitors [6] also reported wide data demonstrating their cardiovascular safety or cardiovascular benefits [7–9]. A systematic assessment of existing evidence on cardiovascular effects of alpha glucosidase inhibitors is therefore relevant for clinical decision-making.

In 2019, the Italian Society of Diabetology (SID) and the Italian Association of Clinical Diabetologists (AMD) decided to prepare new guidelines for the treatment of T2DM. Following the GRADE method [10], a panel of experts from the two societies identified major cardiovascular events (MACE) and all-cause mortality among the critical outcomes for clinical decision. This systematic review and meta-analysis of RCTs testing the effects of alpha-glucosidase inhibitors (acarbose or miglitol) on MACE and all-cause mortality was performed as a part of the development of the aforementioned new Italian guidelines.

Methods

The meta-analysis was reported following the criteria of PRISMA statement [11] and registered in advance on PROSPERO website with the following number #CRD420 21259346.

A MEDLINE, Embase, and Cochrane database search was performed to identify all RCTs published in English, up to April 1st, 2020, in which alpha-glucosidase inhibitors (acarbose or miglitol) were compared with either placebo/no therapy, current care or other active comparators. Selected articles were imported into Endnote and then duplicate articles were removed. Only drugs approved by European Medicine Agency (EMA) and currently available in Europe (i.e. acarbose and miglitol), at EMA-approved doses, were considered, both as investigational drugs and as comparators. Further inclusion criteria for the systematic review on MACE were:

1) RCTs reporting MACE within their primary outcome, or as pre-defined secondary outcome with event adjudication
2) RCTs enrolling only patients with T2DM, or with available subgroup analyses for patients with T2DM
3) RCTs enrolling at least 100 patients with T2DM
4) RCTs' duration of follow-up of at least 52 weeks

For the systematic review on all-cause mortality, the same above-mentioned inclusion criteria were applied, with the exception of # 1 (i.e., trials were included irrespective of the presence of MACE among primary or secondary outcomes). Detailed information on the search string was reported in supplementary materials (Table S1). The identification of relevant abstracts, the selection of studies, as well as the extraction of data were performed independently by two of the authors (M.M. and M.G.), and conflicts resolved by a third investigator (E.M). An attempt to retrieve further articles was made by searching references of previous articles, previous meta-analyses, or Google Scholar. The following parameters/information were extracted from each eligible RCT: first author, year of publication, name of investigational drug, comparator, duration of follow-up, number of patients in each arm, and mean age of participants, number of MACE, death, hospitalization for heart failure, information on randomization, allocation, and blinding procedures, management of patients lost at follow-up and other possible bias (e.g. funding).

The principal study outcomes were.

1) 3-point MACE defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.
2) all-cause mortality (including also RCTs not reporting MACE within their primary outcome, or as predefined secondary outcome).

The risk of bias of the included RCTs was assessed using the parameters proposed by the Cochrane Collaboration's tool.

Mantel-Haenszel odds ratio (MH–OR) with 95% Confidence Intervals (95% CI) were calculated for all the study outcomes considered, on an intention-to-treat basis, excluding RCTs with zero events, using a random-effects model. Funnel plot for each study outcome was examined in order to estimate possible publication/disclosure bias. A post-hoc sensitivity analysis with continuity correction was performed, imputing one event for treatment arm in trials with zero events.

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

Results

Figure 1 of supplementary materials (Fig. S1) shows the flow diagram of the meta-analysis. A total of 8 eligible RCTs (summarized in Table S2) fulfilled our inclusion criteria and were included in the meta-analysis. A further RCT[8] using acarbose, that enrolled a large number of participants (n = 763), was not included in the meta-analysis, because it was published as abstract only. Attempts to

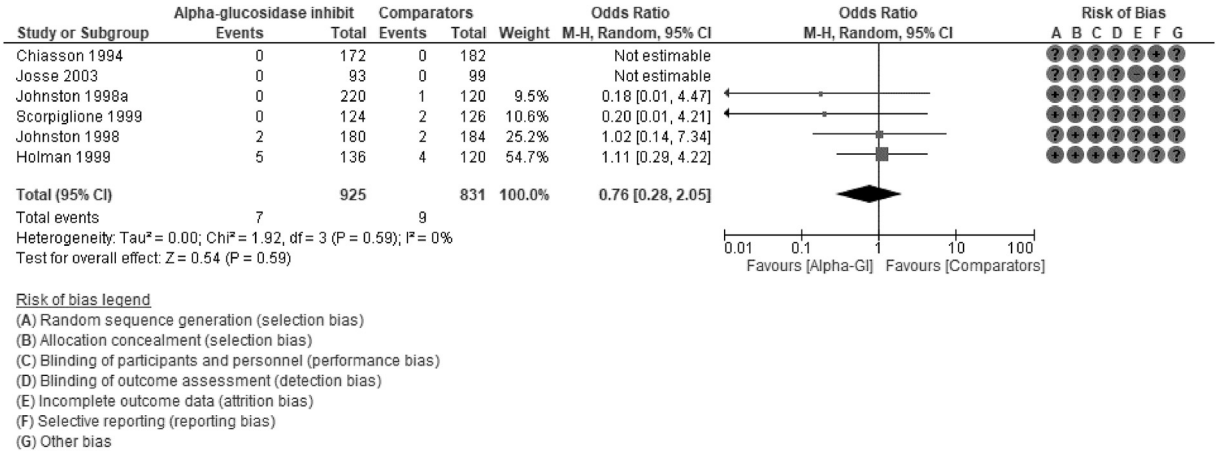

Figure 1 All-cause mortality with alpha-glucosidase inhibitors versus placebo/comparators (MH−OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals) in trials included in the meta-analysis.

contact the corresponding author of this study failed so far. None of the eligible RCTs reported any information on MACE and, therefore, no analysis was performed for this outcome. Conversely, all the 8 RCTs included in the meta-analysis (involving a total of 1124 and 908 T2DM patients treated with either alpha-glucosidase inhibitors or with placebo/active comparators, respectively) reported information on all-cause mortality. As shown in Fig. 1, treatment with alpha-glucosidase inhibitors was not significantly associated with increased or decreased risks of all-cause mortality compared with other therapies/placebo or no therapy (MH−OR 0.76 [0.28, 2.05]). The corresponding figure, when excluding trial comparing alpha-glucosidase inhibitors with active comparators, was (MH−OR: 0.81[0.28; 2.37], p = 0.82). Similar results were obtained with continuity correction (MH−OR: 0.81[0.34; 1.97], p = 0.65). The risk of bias of all eligible RCTs was low for the majority of the items of the Cochrane Collaboration's tool (Fig. S3). I^2-statistics did not show any significant heterogeneity (Tau^2 = 0.00, p = 0.85; I^2: 0%).

Discussion

To date, the effect of alpha-glucosidase inhibitors on MACE in people with T2DM is unknown due the lack of published RCTs with 3-point MACE within their primary outcome or as pre-defined secondary outcome with event adjudication. Moreover, trials with metabolic endpoints did not report any information on MACE, preventing sensitivity analyses. A previous pooled analysis on phase III RCTs [5] on acarbose treatment reported some cardiovascular benefits; however, the small number of recorded cardiovascular events, the lack of event adjudication, and the heterogeneous definition of "cardiovascular events" prevent any reliable conclusion on the cardiovascular safety of this class of glucose-lowering drugs. Notably, the results of our comprehensive and updated meta-analysis of RCTs (published up to July 1, 2021) showed neutral effects of treatment with alpha-glucosidase inhibitors on all-cause mortality, with no significant heterogeneity or publication bias. However, we believe that this result should be interpreted with some degree of caution, due to the relatively small number of RCTs included and the relatively poor methodological quality of some trials, inevitably affecting the overall quality of our meta-analysis. Moreover, the inclusion criteria of RCTs had been chosen to obtain a reliable evidence base for developing treatment guidelines. For this reason, the present analysis was limited (both in investigational and comparator arms) to alpha-glucosidase inhibitors available in Europe and RCTs with a sufficient follow-up length (at least 52 weeks).

In conclusion, the results of our meta-analysis show there is no reliable evidence of any beneficial or detrimental effects of treatment with alpha-glucosidase inhibitors on all-cause mortality in people with T2DM, whereas no reliable conclusion can be drawn for their cardiovascular safety.

Role of funding sources

This research was performed as a part of the institutional activity of the unit, with no specific funding. All expenses, including salaries of the investigators, were covered by public research funds assigned to the unit. The manuscript was drafted and revised by the authors in accordance with ICJME standards for authorship. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Author contributors

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

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

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

1. Writing manuscript.
2. 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

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; **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. All the other authors have no conflict of interests to declare.

All the authors approved the final version of the 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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