Effects of pioglitazone on cardiovascular events and all-cause mortality in patients with type 2 diabetes: A meta-analysis of randomized controlled trials

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Abstract *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. After identifying the effects of glucose-lowering agents on major adverse cardiovascular events (MACEs), all-cause mortality, and hospitalization for heart failure (HHF) as critical outcomes, the experts decided to perform a systematic review and meta-analysis on the effect of pioglitazone with this respect.

Data synthesis: A MEDLINE database search was performed to identify RCTs, up to June 1st, 2021, with duration≥52 weeks, in which pioglitazone was compared with either placebo or active comparators. The principal endpoints were MACE and HHF (restricted for RCT reporting MACEs within their outcomes), 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.

Eight RCTs were included in the analysis for MACEs and HF (5048 and 5117 patients in the pioglitazone and control group, respectively), and 24 in that for all-cause mortality (10,682 and 9674 patients). Pioglitazone neither significantly increased nor reduced the risk of MACE, all-cause mortality, and HHF in comparison with placebo/active comparators (MH−OR: 0.90, 95% CI 0.78−1.03, 0.91, 95% CI 0.77, 1.09, and 1.16, 95% CI 0.73, 1.83, respectively). Pioglitazone was associated with a significant reduction of MACE in patients with prior cardiovascular events (MH−OR 0.84, 95% CI 0.72−0.99).

Conclusions: This meta-analysis showed no significant effects of pioglitazone on incident MACE, all-cause mortality, and HHF.

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1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cardiovascular disease [1] and mortality [2]. Several cardiovascular outcome trials (CVOTs) have consistently shown that some glucose-lowering agents, such as glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i), significantly reduce the incidence of major cardiovascular adverse events (MACE), defined as a composite endpoint inclusive of non-fatal myocardial infarction and stroke, and cardiovascular mortality [3–7], particularly in T2DM patients with prior cardiovascular disease [3]. Furthermore, SGLT2i also significantly reduce the risk of hospitalization for heart failure (HHF).

The peroxisome proliferator-activated receptor-γ agonist pioglitazone is used for the treatment of T2DM, due to its favorable effects on blood glucose and insulin sensitivity [8,9]. This drug has also some beneficial effects on inflammation and cytokine production [10–12], thereby supporting a protective action on the cardiovascular system. Interestingly, a meta-analysis of randomized trials showed that pioglitazone can prevent restenosis after coronary artery angioplasty [13]. In the PROspective PioglitAzone Clinical Trial In MacroVascular Events (PROACTIVE) trial [14], involving subjects with T2DM and prior cardiovascular events, the difference between pioglitazone and placebo did not reach statistical significance for the principal study endpoint, which was a broadly defined composite of cardiovascular events. Conversely, a significant reduction of events was observed for a more narrowly defined main secondary endpoint of cardiovascular events. In the same trial, treatment with pioglitazone was associated with an increased risk of HHF [14].

To date, published meta-analyses of randomized trials on the cardiovascular effects of pioglitazone reported conflicting results. The incidence of myocardial infarction, stroke, and MACE has been reported to be either unchanged [15–17] or reduced [18,19] by pioglitazone. Similarly, mortality has been reported to be unchanged [18,19] or reduced [15,16], whereas HHF has been reported to be either unchanged [16,17] or increased [15,18,19].

In 2019, the Italian Society of Diabetology (SID) and the Italian Association of Clinical Diabetologists (AMD) decided to release new guidelines for the treatment of T2DM. Following the GRADE method [20], a panel of experts from the two societies identified MACE and all-cause mortality among the critical outcomes for clinical decision. Thus, this systematic review and meta-analysis of randomized controlled trials (RCTs) testing the effects of pioglitazone on the risk of MACE, all-cause mortality, and HHF was performed as a part of the development of the aforementioned new Italian guidelines for the treatment of T2DM.

2. Methods

The present meta-analysis was registered on PROSPERO website (CDR: #2021259834) and conducted following the PRISMA guidelines.

A MEDLINE, SCOPUS and EMBASE database search was performed to identify all available RCTs; published in English, up to June 1st, 2021, in which treatment with pioglitazone was compared with either placebo/no therapy, current care, or other active glucose-lowering 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, at EMA-approved doses, were considered, both as investigational drugs and comparators. Further inclusion criteria for the systematic review on MACE were:

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

For the systematic review on all-cause mortality, we applied the same inclusion criteria reported above, except for #1 (i.e., RCTs were included, irrespective of the presence of MACE among primary or secondary outcomes).

Detailed information on the search string is reported in the Supplementary material (Table S1).

The identification of relevant abstracts, the selection of studies, and the extraction were performed independently by two of the authors (M.M. and M.G.), and conflicts were resolved by a third investigator (E.M). An attempt to retrieve further articles was made by searching the so-called grey literature (i.e. references of previous original articles, meta-analyses, and Google scholar).

The following parameters/information were extracted from each eligible trial: first author, year of publication, name of investigational drug, comparator, duration of follow-up, number of patients in each treatment arm, and mean age.

2.1. Data analysis

For all eligible RCTs, results reported in published papers were used as the primary source of information; when data on the endpoints considered were not available in the primary publication, an attempt of retrieving information was made on http://www.clinicaltrials.gov.

The principal endpoints considered were the following:

1) MACE, defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death.
2) All-cause mortality (including also RCTs not reporting MACE within the primary outcome, or as predefined secondary outcome).
3) Hospital admission for heart failure.

The overall quality of each RCTwas assessed using the parameters proposed by the Cochrane Collaboration tool for assessing risk of bias [21].

2.2. Statistical analyses

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 trials with zero events, using a random-effects model. Heterogeneity was assessed using I [2]-statistics.The funnel plot for MACE was examined and Kendall's tau without continuity correction was calculated to estimate possible publication/disclosure bias.

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

3. Results

The flow diagram of the meta-analysis was summarized in supplementary Figure S1. A total of 24 eligible RCTs [14,22−44] (as specified in supplementary Table S2) fulfilled our inclusion criteria and were included in the meta-analysis on all-cause mortality. Eight of those RCTs [14,27,32,34,35,42−44] also considered MACE within their primary or adjudicated secondary endpoints and could, therefore, be included in the meta-analysis on MACE and HHF. The overall quality of eligible RCTs was satisfactory for the majority of the items of the Cochrane Collaboration's tool, except for "performance bias" (i.e., blinding of participants and personnel; as summarized in Supplementary Figure S3).

3.1. 3-Point MACE

Out of eight RCTs reporting information on adjudicated cardiovascular events, one [24] did not report the incidence of the first MACE as a composite endpoint and was, therefore, excluded from the analysis. Overall, these RCTs included 5048 T2DM patients treated with pioglitazone (with a total of 428 MACE) and 5117 T2DM patients treated with placebo or any other active comparators (with a total of 476 MACE). No publication bias was detected at the visual analysis of the Funnel plot (Supplementary Figure S2) and Egger's test (Kendall's tau without continuity correction: −0.01; p = 0.68). Treatment with pioglitazone neither significantly increased nor reduced the risk of MACE in comparison with either placebo or any other active comparators (MH−OR: 0.90, 95% CI 0.78−1.03, as assessed by a random-effect model), as shown in Fig. 1. Almost identical results were obtained using a fixed-effect model (data not shown).

However, as also shown in Fig. 1, when the eligible RCTs were stratified by prior history of cardiovascular events (primary vs. secondary CVD prevention), we found that treatment with pioglitazone was associated with a significant reduction of MACE in RCTs including T2DM patients with prior cardiovascular events (MH−OR 0.84, 95% CI 0.72−0.99; I^2 = 0%), but not in those without established cardiovascular disease (MH−OR 1.11, 95% CI 0.84−1.48; I^2 = 0%), with a non-significant trend for between-group difference (p for interaction of 0.09; Fig. 1).

3.2. All-cause mortality

Out of 24 studies included in the meta-analysis (10,682 and 9674 patients in the pioglitazone and control group, respectively), only one [44] did not report information on mortality. Twenty studies reported at least one death (249 vs. 273 in pioglitazone and control group, respectively) and, therefore, were included in the meta-analysis. Publication bias (Kendall's tau without continuity correction: Tau: −0.50, p = 0.006) was detected at a visual analysis of the Funnel plot (Figure S4).

As shown in Fig. 2, neither treatment with pioglitazone was associated with a significant increase nor with a reduction in the risk of all-cause mortality (MH−OR 0.91, 95% CI 0.77, 1.09; I^2 = 0%), with no significant differences between RCTs that included patients with or without prior cardiovascular events. Identical results were obtained using a fixed-effect model (MH−OR 0.90, 95% CI 0.76, 1.07).

3.3. Hospitalizations for heart failure

Out of eight RCTs reporting information on adjudicated cardiovascular events, one [44] did not report information on hospitalization for heart failure and only four trials reported at least one event. No publication bias was detected both at Egger's test (Kendall's tau without continuity correction: Tau: 0.00, p = 1.00) and at the visual analysis of the Funnel plot (Figure S5).

Overall, as shown in Fig. 3, treatment with pioglitazone was not associated with a significant increase in the risk of HHF (MH−OR 1.16, 95% CI 0.73, 1.83). A mild heterogeneity (I [2]: 31%) was detected for this endpoint. A significantly increased risk of incident heart failure was observed using a fixed-effect model (MH−OR 1.33, 95% CI 1.08, 1.63, p = 0.006). As also shown in Fig. 3, a significantly increased risk of HHF with pioglitazone use was observed in eligible RCTs including patients with, but not in those without prior cardiovascular events, with a non-significant trend for between-group difference (p for interaction: 0.06).

4. Discussion

The present meta-analysis performed on RCTsreporting adjudicated MACE within their primary or secondary endpoint showed no significant effect of pioglitazone on incident MACE in people with T2DM. Two previous meta-analyses had reported similar results [15−17], whereas the other two meta-analyses observed a significant reduction of MACE with pioglitazone [15,16]. Of the two latter studies, one was an individual patient-level time-to-event data meta-analysis including a limited number of trials [15]; the other was a wide meta-analysis, including also short- and very short-term trials, but not some relevant trials published more recently [26−29,31,32]. Moreover, these two latter meta-analyses did not perform analyses including only trials with adjudication of events, possibly explaining the discrepancies in results.

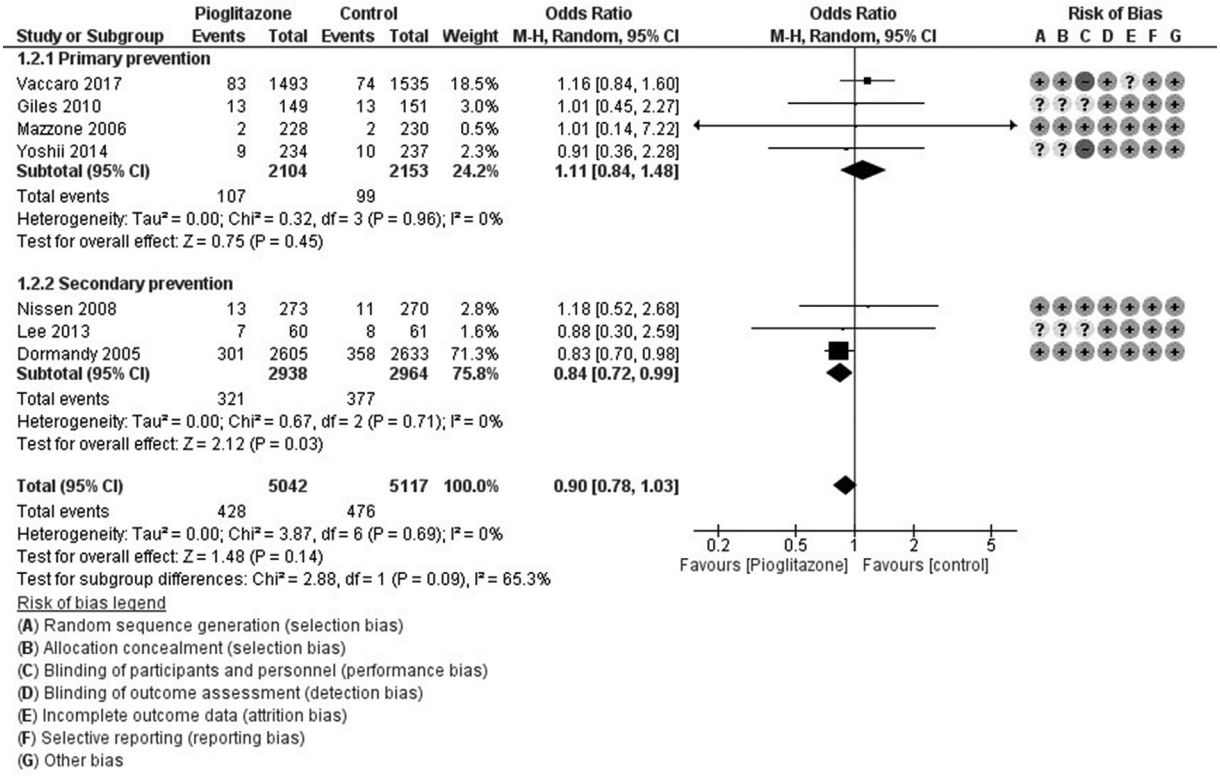

Figure 1 MACE with pioglitazone versus placebo/comparators (MH−OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals) in trials enrolling patients in primary and secondary prevention.

In a recent narrative review, De Fronzo et al. defined pioglitazone as "*the forgotten, cost-effective cardioprotective drug for T2DM*" [45]. Several mechanistic studies performed on pioglitazone suggested cardioprotective effects [46,47] with a marked anti-inflammatory action [47], possibly explaining some positive results in trials enrolling patients with or without T2DM undergoing percutaneous coronary angioplasty [32,48,49]. However, cardioprotective effects observed in experimental studies are not necessarily associated with actual clinical benefits in clinical trials. In fact, despite expectations arisen from pathophysiological studies, the PROactive trial [14] failed to show a significant effect of pioglitazone on the primary endpoint in patients with established T2DM, although some benefits were observed for some pre-defined cardiovascular secondary endpoints.

Notably, pioglitazone could have differential effects on the risk of MACE in T2DM patients in primary and secondary prevention, as clearly shown in the present meta-analysis. These results are in line with a recent meta-analysis, which included also trials on patients at high risk for diabetes, suggesting that pioglitazone could reduce the incidence of MACE in patients with established cardiovascular disease to a greater extent than those without [21]. Other antidiabetic agents have shown similar divergent results, with greater cardiovascular protection among patients with previous cardiovascular events [3].

Pioglitazone did not appear to modify all-cause mortality in the present meta-analysis. Although the analysis on all-cause mortality included also some trials with metabolic endpoints, the large majority of events was observed in cardiovascular outcome studies, and particularly in the PROactive [14] and TOSCA trials [50]. It should also be considered that the total number of recorded deaths (n = 522) in available trials was substantially lower than that of MACE, thus reducing the statistical power of this analysis.

In our meta-analysis, treatment with pioglitazone was associated with a significant increase in the risk of HHF among T2DM patients with prior cardiovascular events. Such effect was not detectable in eligible RCTs enrolling patients without prior cardiovascular events. However, it should be noted that the low incidence of HHF in primary prevention cohorts and the resulting small number of recorded events limited the reliability of this analysis. Pioglitazone, as well as other PPAR-γ agonists, induces fluid retention and therefore facilitates the occurrence of congestive heart failure. This detrimental effect is not correlated to any cardiotoxic effect of the drug, since pioglitazone does not reduce left ventricular systolic or diastolic function. All RCTs included in the present meta-analysis excluded patients with previous history of or with signs of heart failure; however, no RCT evaluated the presence of left ventricular dysfunction before enrolling patients; therefore, it is possible that some patients with

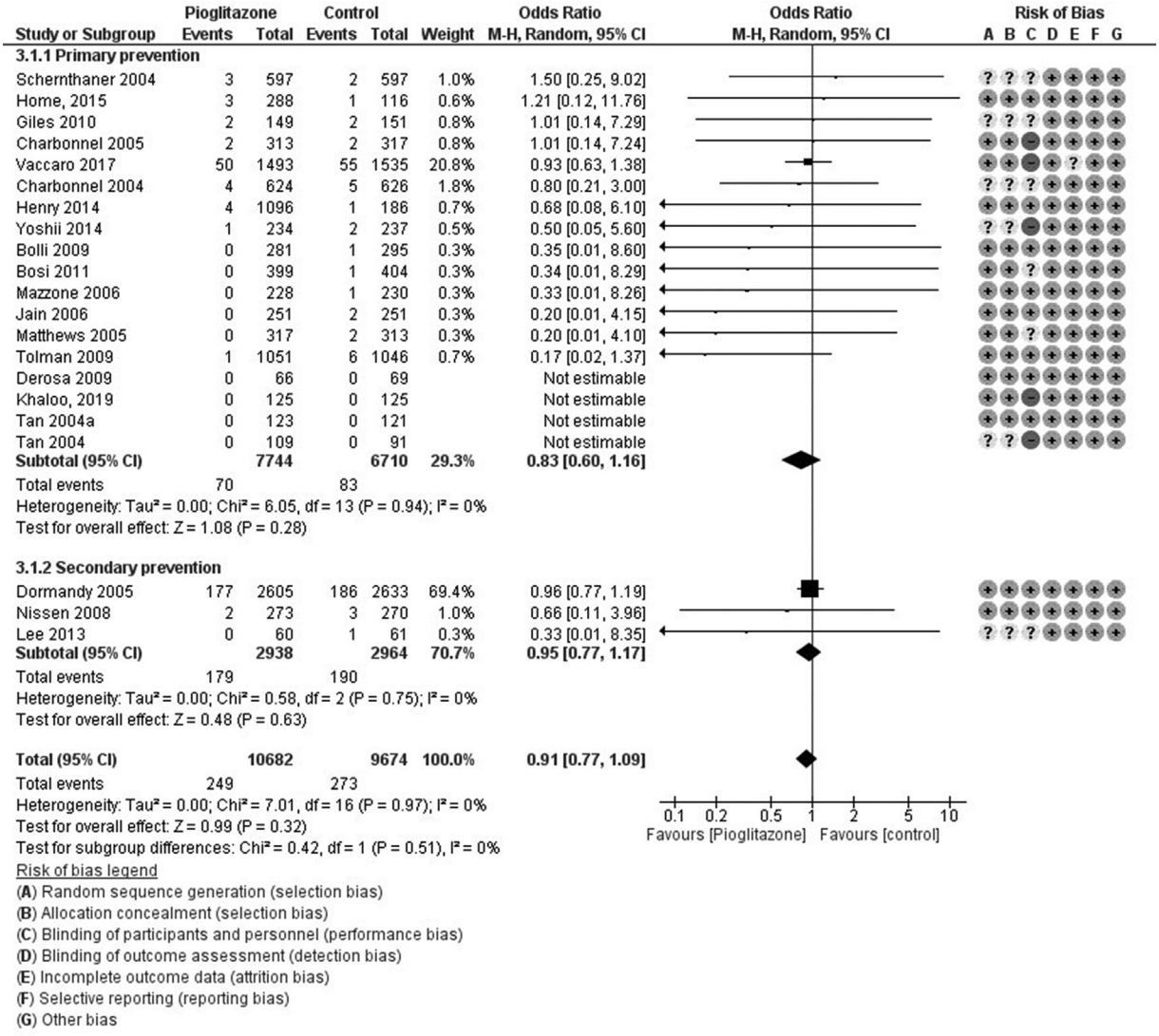

Figure 2 All-cause death with pioglitazone versus placebo/comparators (MH−OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals) in trials enrolling patients in primary and secondary prevention.

previous cardiovascular disease and unknown/undetected cardiac dysfunction have been allocated in pioglitazone arms, thus increasing the risk of HHF in this subpopulation of patients.

Collectively, the results of our meta-analysis should be interpreted with some degree of caution, due to the relatively small number of eligible RCTs with MACE within their pre-specified endpoints and of recorded events, mainly derived from one single trial (i.e. PROACTIVE trial [14]). Moreover, the inclusion criteria used are very stringent (i.e. only RCT with a duration of at least 52 weeks, with MACE within their primary or secondary endpoint) to obtain a reliable evidence base for developing treatment guidelines.

In conclusion, the present meta-analysis performed on RCTs reporting adjudicated MACE within their endpoints showed no significant effects of pioglitazone on incident MACE in patients with established T2DM. However, the possibility that pioglitazone can reduce the incidence of MACE in patients with established cardiovascular disease cannot be ruled out. The effect of pioglitazone on HHF, more pronounced in RCTs in secondary cardiovascular prevention, is not surprising and well specified in the pioglitazone summary of product characteristics.

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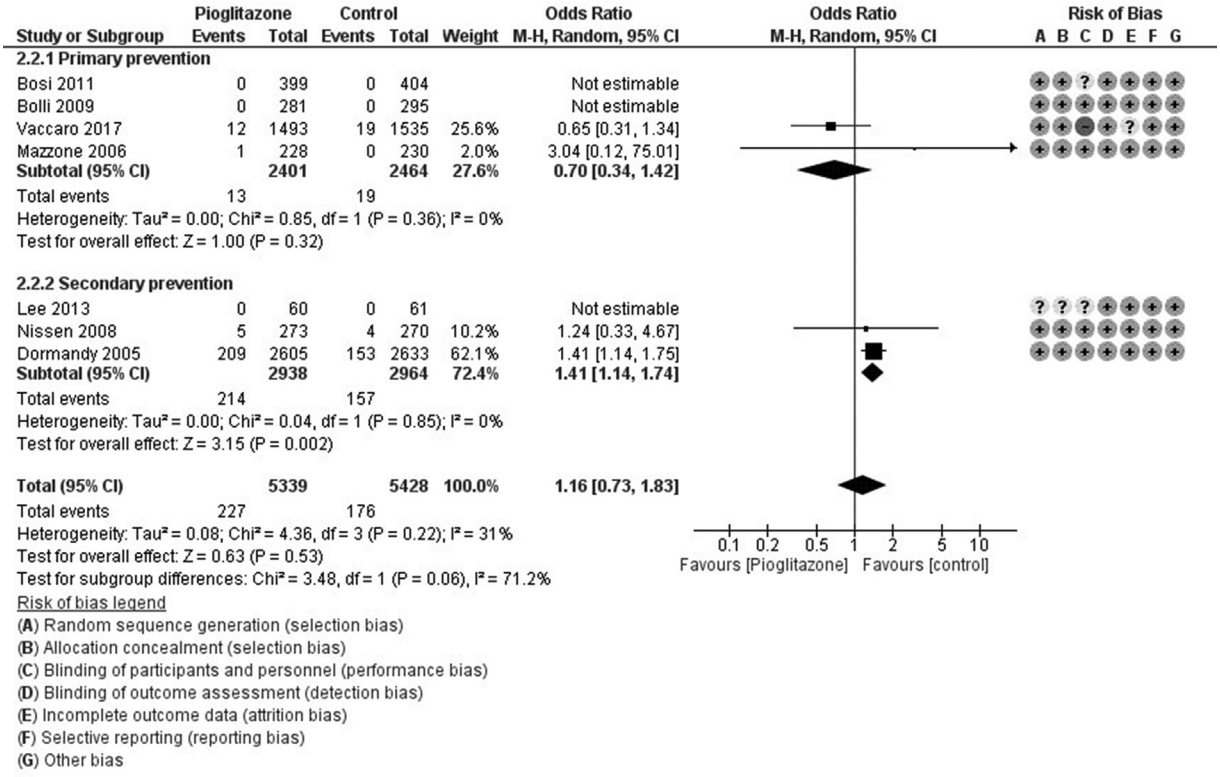

Figure 3 Hospitalization for heart failure with pioglitazone versus placebo/comparators (MH−OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals) in trials enrolling patients in primary and secondary prevention.

Contributors

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

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

BP, MG, GT, RC, and **AG** 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

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. **AG** has received speaking fees and/or advisory board invitations from Abbott, Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, MSD, Mundipharma, Novo-Nordisk, Sanofi. The other authors did not report any relevant conflicts of interest.

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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