Cardiovascular events and all-cause mortality in patients with type 2 diabetes treated with dipeptidyl peptidase-4 inhibitors: An extensive meta-analysis of randomized controlled trials

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Abstract *Aims:* Meta-analyses of randomized trials on Dipeptidyl Peptidase-4 inhibitors (DPP4i) reported discordant results on major cardiovascular events (MACE), mortality, and heart failure. Aim of this meta-analysis of randomized trials is the assessment of the cardiovascular safety of DPP4i.
Data synthesis: A Medline, Embase, Cochrane database search for sitagliptin, vildagliptin, omarigliptin, saxagliptin, alogliptin, trelagliptin, anagliptin, linagliptin, gemigliptin, evogliptin, and teneligliptin was performed up to up January 1st, 2020. All trials with a duration ≥24 weeks and comparing the effects of DPP4i with placebo or active drugs were collected. Mantel–Haenszel odds ratio (MH-OR) with 95% Confidence Interval (95% CI) was calculated for all outcomes defined above. A total of 182 eligible trials were identified. DPP-4i were not associated with an increased risk of MACE (MH-OR 0.99 [0.93, 1.04]), all-cause mortality (MH-OR 0.99 [0.93, 1.06]), and heart failure (MH-OR 1.05 [0.96, 1.15]) with no significant differences across individual molecules, except for saxagliptin, which was associated with an increased risk of heart failure.
Conclusions: As a class, DPP4i are not associated with any increase or reduction of MACE, all-cause mortality, and heart failure. Saxagliptin seems to be associated with an increased risk of hospitalization for heart failure.

Introduction

Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cardiovascular disease [1] and mortality [2]. Evidence from randomized controlled trials (RCTs) shows that intensive glucose control in patients with T2DM is capable of reducing the risk of major cardiovascular

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events (MACE) [3] and microvascular complications [4], but not all-cause mortality [5]. In addition, several recently published cardiovascular outcome trials suggested that some glucose-lowering agents, such as Glucagon-Like Peptide 1 Receptor Agonists (GLP-1 RA) and Sodium Glucose-Transporter-2 inhibitors (SGLT-2i), could exert some extra-glycemic protective effects on overall mortality and cardiovascular morbidity [6–11].

Many meta-analyses on RCTs with cardiovascular endpoints with Dipeptidyl Peptidase-4 inhibitors (DPP4i) have been performed, all showing neutral effects on MACE and mortality in comparison either with placebo or active comparators [12–15]; however, when considering comprehensive meta-analyses including also trials with metabolic endpoints, results are not concordant, with some meta-analyses reporting no beneficial effects on cardiovascular morbidity and mortality [16,17] and some others showing a reduction of MACE and mortality [18]. In particular, some meta-analyses comparing DPP-4i with sulfonylureas reported a statistically significant reduction of MACE [19–21] and mortality [19] in favor of DPP-4i. Moreover, (similar) discordant results were observed for hospitalization for heart failure, with some studies reporting a higher risk versus placebo/active comparators with DPP-4i [22–24]and some others showing no risk [12–16,25] or higher risk only for some molecules of the class (i.e. saxagliptin) [22,26].

The present meta-analysis was performed in the process of developing the Italian guidelines for the treatment of T2DM. These guidelines, which have been promoted by the Italian Society of Diabetology (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 clinical practice in Italy, using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method [27]. The effects on the risk of all-cause mortality and MACE were included among critical outcomes for clinical decision-making about the use of the most appropriate glucose-lowering agents in people with T2DM. As a consequence, a series of systematic reviews and meta-analyses of RCTs primarily focused on these two outcomes are currently underway for all classes of anti-hyperglycemic drugs used for the treatment of T2DM. The aim of the present meta-analysis is the assessment of the effect of DPP4i treatment on the incidence of cardiovascular endpoints and mortality, collecting all available evidence from RCTs.

Methods

The present meta-analysis is part of a wider and currently ongoing systematic review, which has been registered on the PROSPERO website (#CRD42020153344; https://www.crd.york.ac.uk/prospero/#recordDetails). This meta-analysis is reported following the criteria of PRISMA statement [16].

Search strategy and selection criteria

A MEDLINE, Cochrane database, EMBASE, and www.clinicaltrials.gov search was performed to identify all clinical trials (English only), up to January 1st, 2020, with a duration of follow-up of at least 24 weeks, in which DPP-4i (sitagliptin or vildagliptin or omarigliptin or saxagliptin or alogliptin or trelagliptin or anagliptin or linagliptin or gemigliptin or evogliptin or teneligliptin) were compared with either placebo or active comparators. Studies performed on animals, type 1 diabetes, gestational diabetes, non-diabetic subjects, or pediatric populations were excluded. Trials on DPP-4i not yet approved/withdrawn or with not approved doses and comparing two different DPP-4i were also excluded. Medical reviews of the same drugs by EMA and FDA were also searched for further unpublished trials. An attempt to retrieve results of further completed, but yet unpublished RCTs, was performed by searching the www.clinicaltrials.gov register. Detailed information on the search string is reported in Supplementary materials (Table 1S).

Identification of relevant abstracts, selection of studies, and data extraction were performed independently by two of the authors (C.M. and B.N.), and conflicts were resolved by a third investigator (M.M.).

The following parameters/information were extracted: first author, year of publication, name, and dose of the investigational drug, comparator, add-on therapy, duration of follow-up, number of patients, mean age, duration of diabetes, HbA1c, body mass index (BMI), and proportion of women and Caucasians, MACE, nonfatal myocardial infarction (MI), nonfatal stroke, fatal and nonfatal MI, fatal and nonfatal stroke, cardiovascular and all-cause death, and heart failure in each arm; when they were not listed as adverse events of special interest, we collected only cases reported as serious adverse events.

Data analysis

For all (published) trials, 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 www.clinicaltrials.gov. The quality of trials was assessed using the parameters proposed by the Cochrane Collaboration.

The principal endpoints were MACE, and the secondary endpoints were all-cause death and heart failure. MACE were defined as a composite endpoint of nonfatal MI, nonfatal stroke, and cardiovascular mortality. Heart failure was defined as hospitalization for heart failure, or, if unavailable, heart failure was reported as a serious adverse event.

Statistical analyses

Mantel–Haenszel odds ratio (MH-OR) with 95% Confidence Interval (95% CI) was calculated for all outcomes defined above, on an intention-to-treat basis. Heterogeneity was

assessed by using I^2 statistics. A random-effects model was applied in the primary analysis, whereas fixed-effect models were applied for sensitivity analysis.

Funnel plots were examined to estimate possible publication/disclosure bias and a quantitative measurement (Egger's test) was used to assess funnel plot asymmetry [28].

Subgroup analyses were performed, whenever possible, for different drugs of the class, different classes of comparators, and trials with cardiovascular or non-cardiovascular outcomes. For heart failure, we also performed a further subgroup analysis for trials including or excluding patients with previous heart failure (trials not explicitly reporting this information were considered as not excluding patients with heart failure). All analyses specified above were performed using Review Manager 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Results

Trial characteristics

Figure 1 reports the trial flow summary. A total of 193 trials fulfilling inclusion criteria was identified; of those, 16 were unpublished (Table 2S). Eleven trials did not report information for any of the endpoints considered and were therefore excluded from the current meta-analysis (Table 3S). Out of 182 trials, 45, 23, and 22 did not report any information on MACE, all-cause death, and heart failure, respectively (Tables 4S and 5S).

The principal characteristics of the 182 trials included in the analysis are reported in Tables 4S and 5S. The overall quality was satisfactory in the majority of trials for all items of the Cochrane tool, except for "blinding of participants and personnel" which cannot be completely ruled out for several trials (open-label design or methods not satisfactorily described; Fig. 1S).

MACE

Out of 137 studies reporting information (57,453 patients in DPP-4i and 52,454 patients in the control group), 104 reported at least one event (2784 and 2778 with DPP-4i and comparators, respectively). No publication bias was detected at a visual analysis of the Funnel plot (Fig. 2S), as confirmed by Egger's test (Kendall's tau without continuity correction: −0.03; p = 0.65).

DPP-4i were not associated with a significant increase in the risk of MACE (MH-OR 0.99 [0.93, 1.04]; Fig. 2), with no evidence of heterogeneity (I^2: 0%). Similar results were obtained using a fixed-effect model (MH-OR 0.98 [0.93, 1.04], p = 0.64). No significant differences across individual molecules of the class (Fig. 2) were observed. A nonsignificant trend toward a reduction of the risk of MACE was detected in non-cardiovascular outcome trials (P = 0.07), with a p for interaction of 0.07 (Fig. 3). DPP-4i did not increase the risk of MACE nor in comparison with placebo or any other comparators (Fig. 3S).

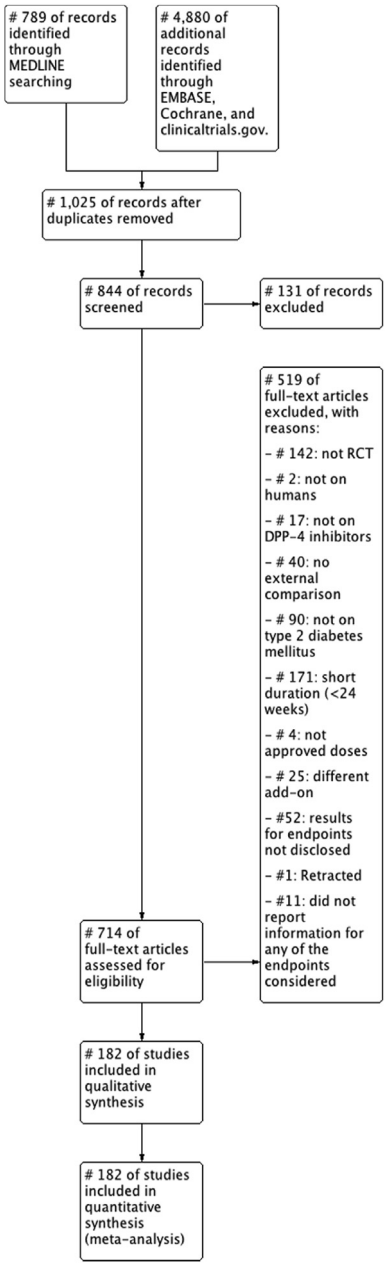


Figure 1 Trial flow diagram.

All-cause death

Out of 159 studies (73,488 patients in DPP-4i and 65,153 patients in the control group), 80 reported at least one event (1986 and 1989 with DPP-4i and comparators, respectively). No publication bias (Kendall's tau without continuity correction: Tau: 0.01, p = 0.87) was detected at a visual analysis of the Funnel plot (Fig. 4S).

DPP-4i were not associated with a significant increase in the risk of all-cause mortality (MH-OR 0.99 [0.93, 1.06]; Fig. 4). No heterogeneity (I^2: 0%) was detected for this endpoint. Similar results were obtained using a fixed-effect model (MH-OR 0.99 [0.92, 1.05], p = 0.66). A lower risk for all-cause mortality with DPP-4i was observed in trials

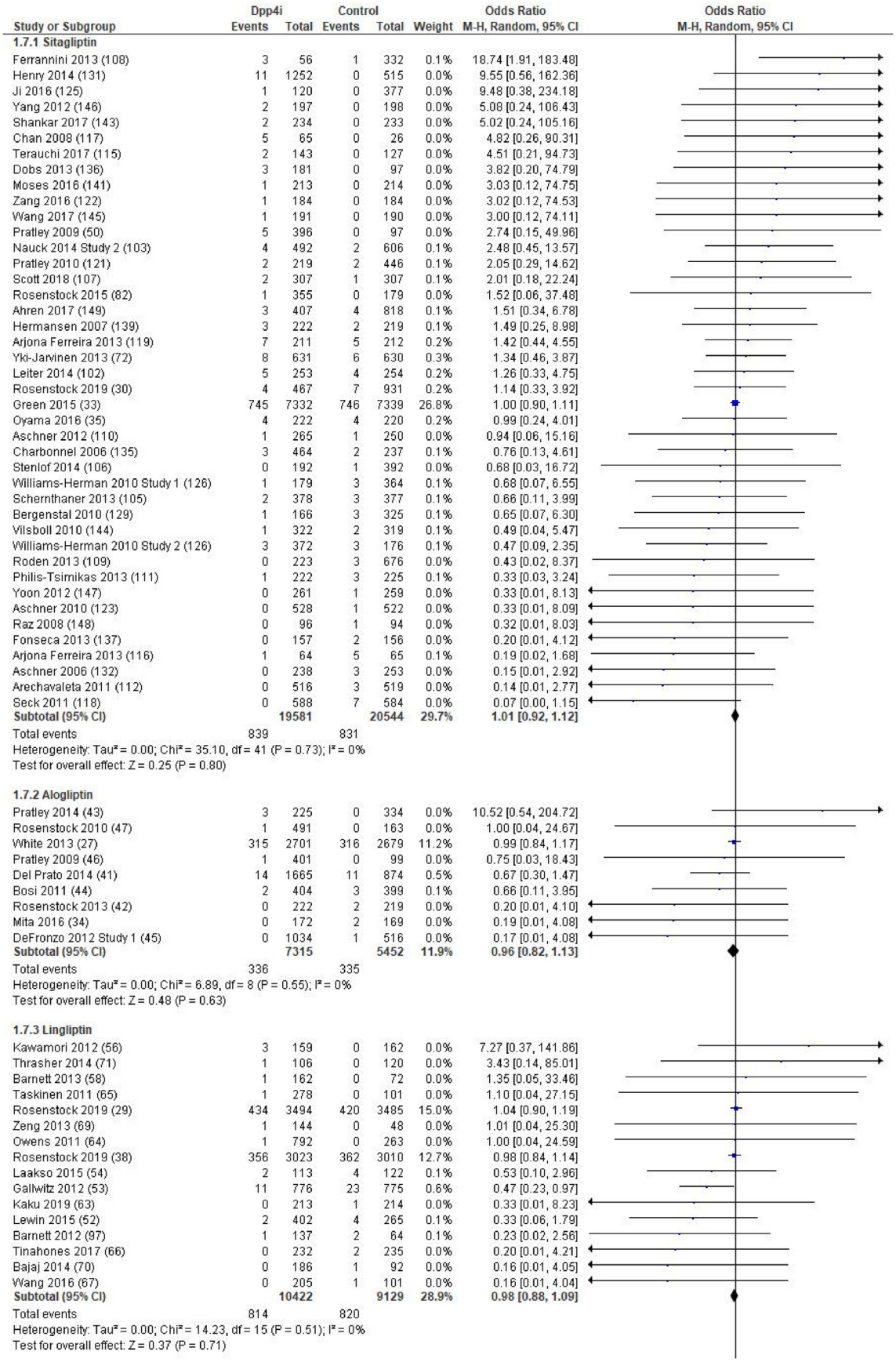
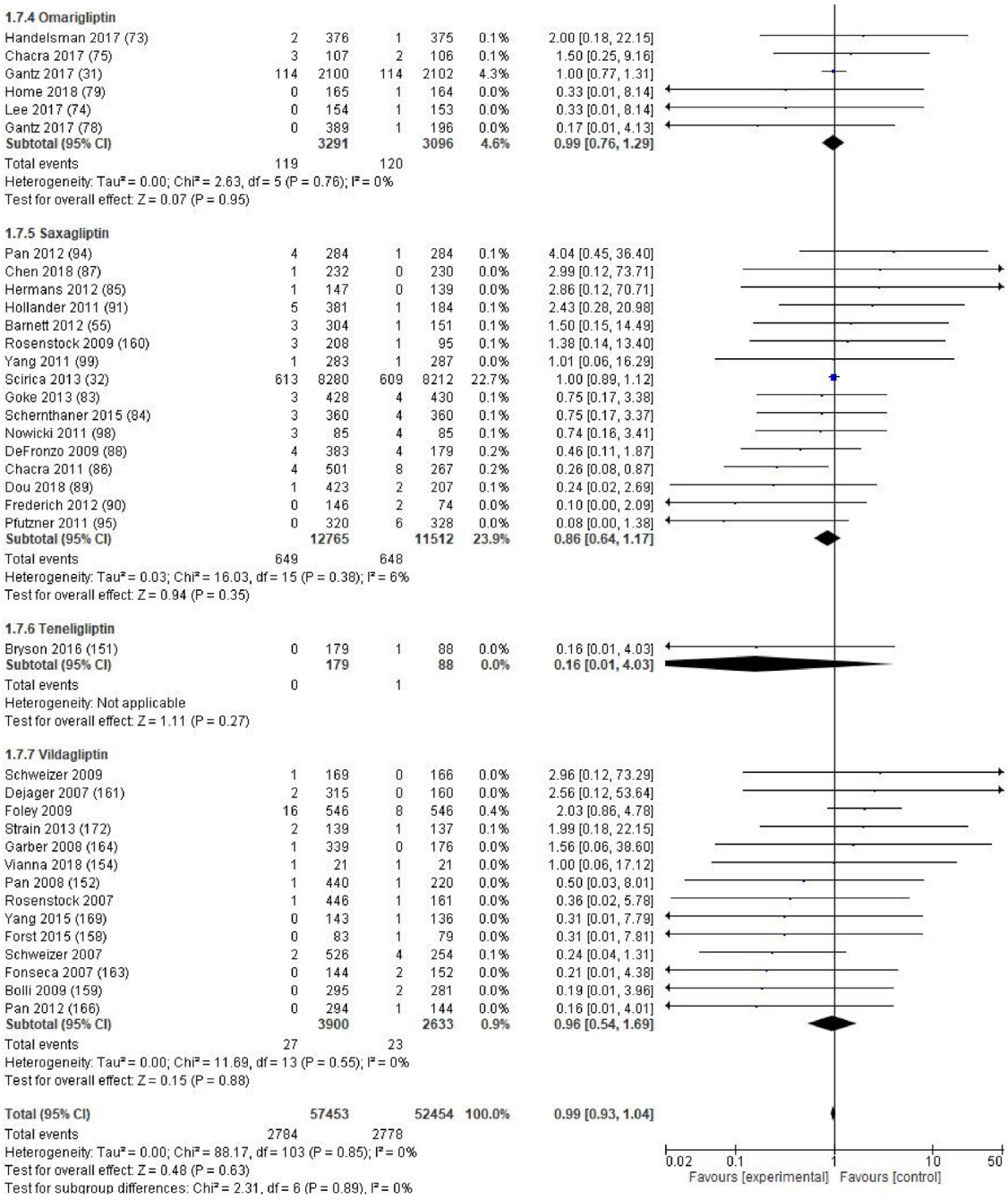


Figure 2 Risk of MACE for individual DPP-4 inhibitors (MH-OR, 95% CI: Mantel–Haenszel Odds Ratio, with 95% of Confidence Intervals). For references, see Supplementary Materials.



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without cardiovascular endpoints (MH-OR: 0.75 [0.58, 0.98]), but not in those with cardiovascular endpoints (MH-OR: 1.01 [0.93, 1.09]), with a statistically significant difference between groups of trials (p for interaction: 0.04; I^2: 77%; Fig. 3). No significant differences across individual DPP-4i (Fig. 5S) and different comparators (Fig. 6S) were detected (p for interaction >0.20).

Heart failure

Out of 160 studies (43,887 patients in DPP-4i and 41,829 patients in the control group), 56 reported at least one event (1049 and 993 with DPP-4i and comparators, respectively). No publication bias was detected both at Egger's test (Kendall's tau without continuity correction: Tau: −0.04, p = 0.42) and at the visual analysis of the Funnel plot (Fig. 7S).

Overall, DPP-4i were not associated with a significant increase in the risk of heart failure (MH-OR 1.05 [0.96, 1.15]; Fig. 8S). No heterogeneity (I^2: 0%) was detected for this endpoint. Similar results were obtained using a fixed-effect model (MH-OR 1.04 [0.95, 1.14], p = 0.36). A significantly higher risk was observed for saxagliptin (MH-OR: 1.22 [1.03, 1.45]), but not for the other molecules of the

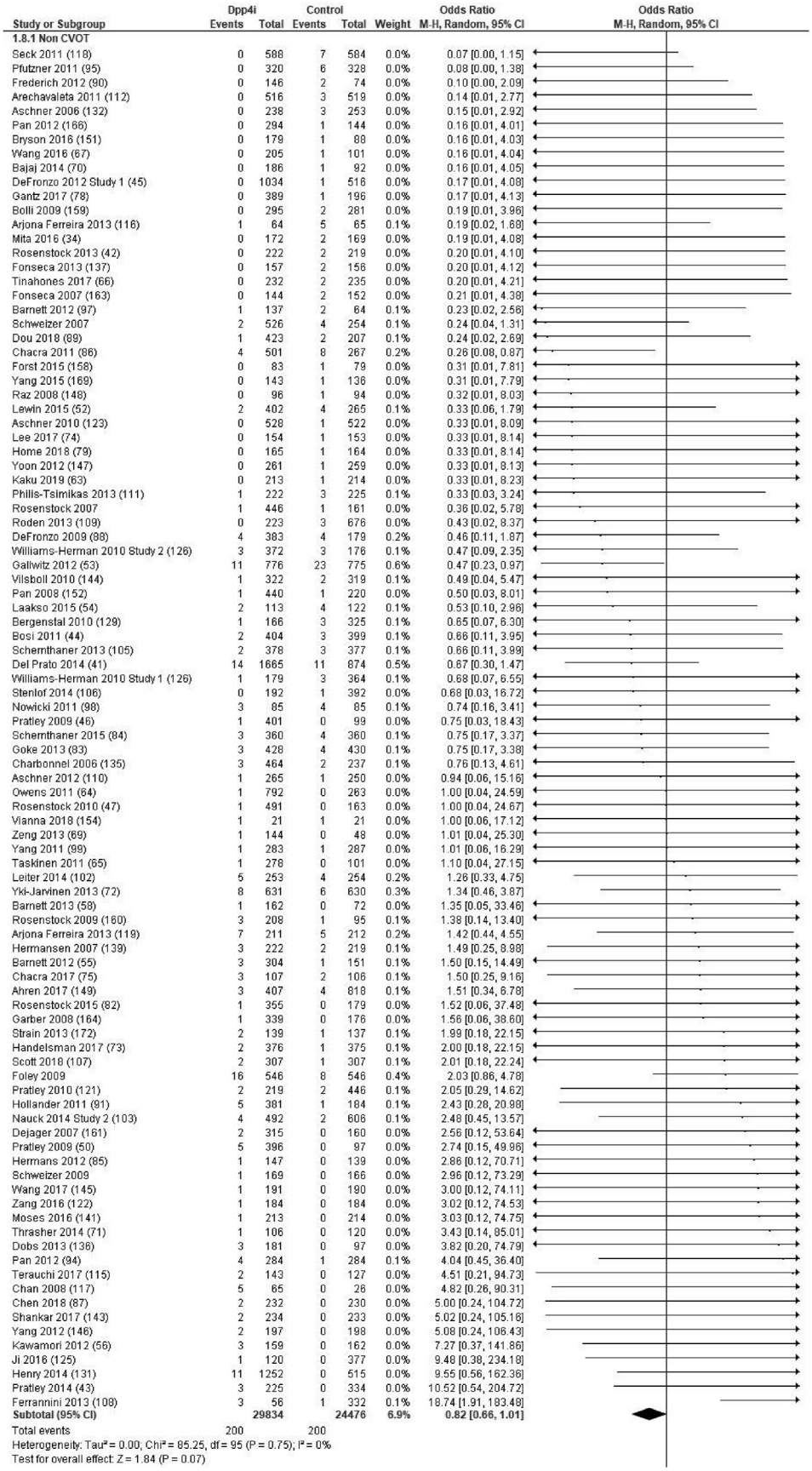
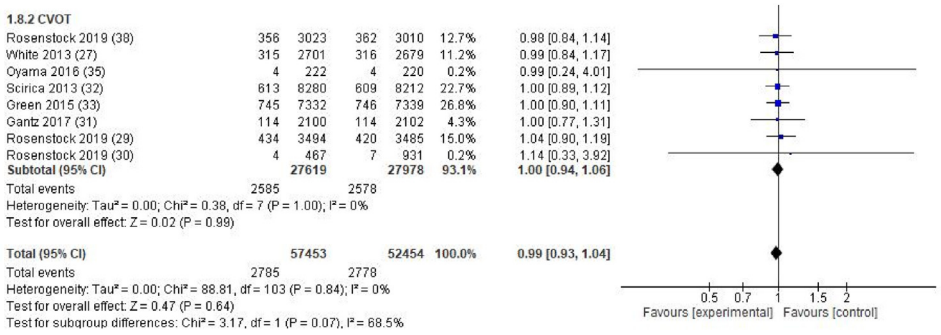


Figure 3 Risk of MACE for DPP-4 inhibitors in trials with and without cardiovascular endpoints (MH-OR, 95% CI: Mantel–Haenszel Odds Ratio, with 95% of Confidence Intervals). For references, see Supplementary materials.



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class (Fig. 8S). No significant differences were observed between trials including (n = 27) or excluding (n = 26) patients with previous heart failure (MH-OR: 1.06 [0.96; 1.16] vs. 1.03 [0.80; 1.32], respectively; I^2: 0%; p for interaction 0.84; Fig. 9S).

Discussion

DPP-4i have shown many beneficial effects on cardiovascular risk factors [29,30] and vascular function [31], raising great interest in their potential to reduce cardiovascular events. However, several cardiovascular outcome trials and many meta-analyses did not confirm these expectations [12–17]. The main strength and originality of the present meta-analysis is represented by the inclusion of a higher number of randomized trials seems to confirm the cardiovascular safety of this class of drugs, which does not appear to increase, neither to reduce, the incidence of MACE, confirming other previous meta-analyses [12–17]. Similarly, the results of the present paper on the effects of DPP-4i on all-cause mortality show neutrality, which is in line with previously reported data [16,17].

However, some meta-analyses performed on trials with metabolic endpoints have shown a reduction in both MACE [18–21] and all-cause mortality [18,19] with DPP-4i.

Some of these meta-analyses were performed only on trials comparing DPP-4i with sulfonylureas [19–21]; this latter class of drugs could have some detrimental effect on the incidence of MACE or its components (e.g. nonfatal stroke [32,33]), as suggested by several studies [32–35], and therefore such results could be attributable to a worse cardiovascular safety profile of sulfonylureas, than to an actual protective effect of DPP-4i. A previous meta-analysis performed by our research group showed a reduction of MACE in favor of DPP-4i in comparison with other glucose-lowering agents/placebo [18]. However, at the time of that meta-analysis, several cardiovascular outcome trials on DPP-4i had not yet been published; the lack of inclusion of several trials with cardiovascular endpoints, which did not report any advantage in favor of DPP-4i concerning the incidence of MACE, could have led to an overestimation of the putative cardioprotective effect of DPP-4i. On the contrary, a differential effect of DPP-4i on cardiovascular morbidity and mortality based on baseline cardiovascular risk of patients with T2DM cannot be completely ruled out, as suggested by the results (nonstatistical trend) of this meta-analysis.

Another point of originality of the present meta-analysis is represented by sub-analyses according to study design (cardiovascular or efficacy endpoint); in fact, in trials with non-cardiovascular endpoints performed on samples of patients with lower cardiovascular risk, DPP-4i showed a significant protective effect on all-cause mortality. The mean differences between cardiovascular and non-cardiovascular outcome trials are the overall cardiovascular risk (as estimated by the incidence of MACE in the comparator arm) and the proportion of patients with previous cardiovascular events. This result is surprising since a wider reduction in the incidence of events is generally expected in populations at greater risk [7]. A possible explanation could be the relatively short duration of trials with metabolic endpoints; in fact, previous analyses had shown a greater cardiovascular benefit in shorter-term RCTs with DPP4i, when compared to longer-term studies [36]; however, by exploring the survival curves of cardiovascular outcome trials, no early beneficial effects of DPP-4i were detected [37–40]. It can be speculated that in cardiovascular outcome trials better metabolic control, imposed by protocols in all treatment groups (i.e. trying to achieve a near-normal glycemic control also in placebo groups), could have prevented between-group differences in all-cause mortality. Moreover, non-cardiovascular outcome trials are more often performed comparing the investigational drug (in this case DPP-4i) with active comparators, which could not be neutral for mortality (e.g. GLP-1 RA [41], SGLT-2i [8], and insulin secretagogues [34]). However, no differences were observed in subgroup analyses comparing different classes of drugs with DPP-4i, despite a nonsignificant trend toward a reduction of all-cause mortality when compared to sulfonylureas (also suggested by several previous meta-analyses [19]).

The effect of DPP4i on heart failure is a controversial issue. Several concerns on this issue have been raised due to the results of the SAVOR study, which reported a significantly increased risk of hospitalization for heart failure with saxagliptin in comparison with placebo [42]. This result, in line with that observed in a post-hoc analysis of the EXAMINE trial with alogliptin [43], was

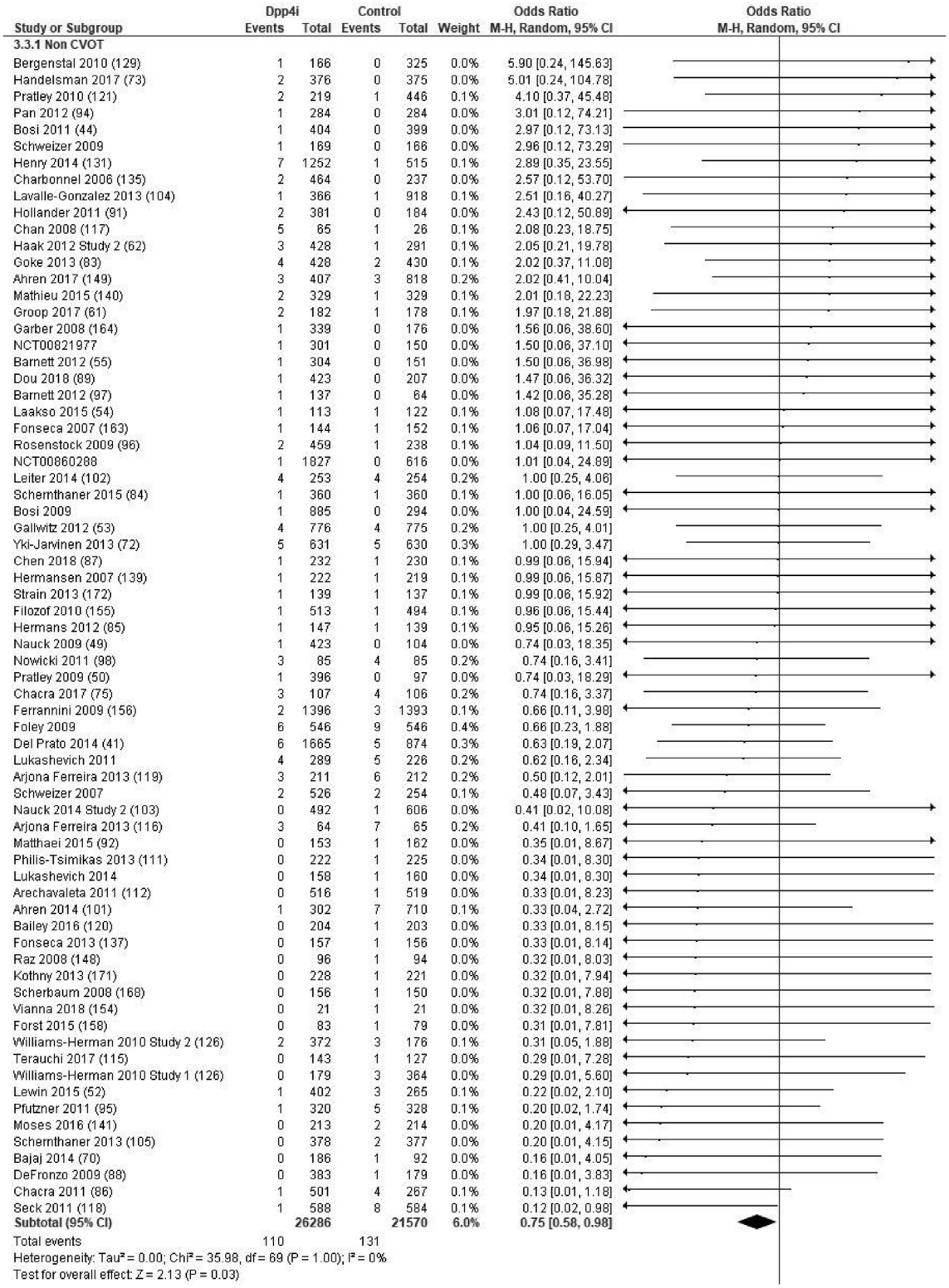

Figure 4 Risk of all-cause mortality for DPP-4 inhibitors with or without cardiovascular endpoint (MH-OR, 95% CI: Mantel–Haenszel Odds Ratio, with 95% of Confidence Intervals). For references, see Supplementary materials.

not confirmed by other recently published cardiovascular outcome trials on other molecules of the class [39,40]. Several meta-analyses, including the present one, seem to confirm the overall safety of DPP-4i on incident heart failure [12–16,25], except for saxagliptin which was significantly associated with an increased risk of hospitalization for heart failure [22,26]. This finding should be interpreted with caution because mainly driven by a single trial (i.e. the SAVOR trial [37]), and affected by heterogeneous definitions of this adverse event. In

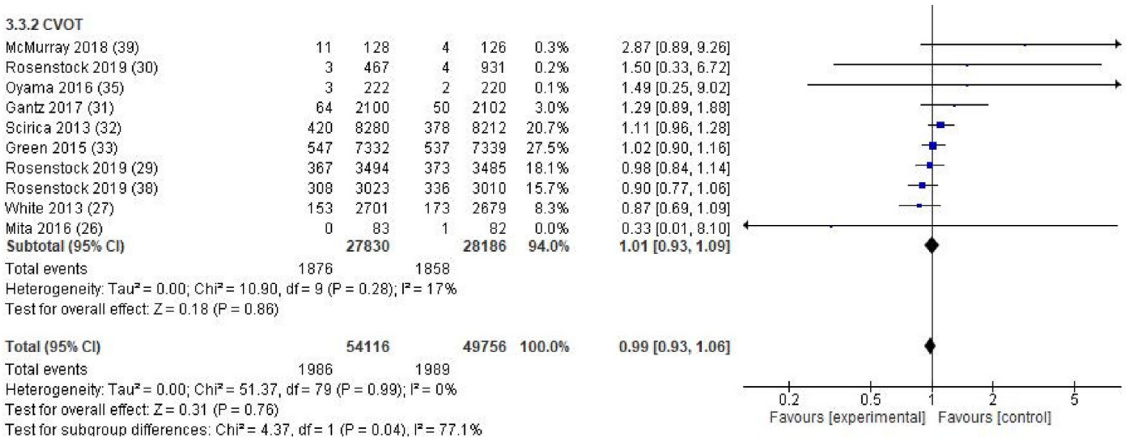

Figure 4 (*continued*).

addition, another molecule of the class, vildagliptin, for which no large-scale cardiovascular outcome trial is available, was associated with a higher end-systolic left ventricular volume in comparison with placebo in a study on patients with diabetes and heart failure [44]. However, a possible specific detrimental effect of saxagliptin on cardiac function cannot be completely ruled out and deserves further investigation.

Some limitations of the current meta-analysis should be acknowledged:

1) Events were not formally adjudicated for the majority of the included trials, although adjudication (i.e. cardiovascular outcome trials) did not appear to affect results in subgroup analyses.
2) One of the usual problems in performing meta-analyses is the heterogeneity across the eligible RCTs of criteria used for the definition of clinical outcomes different from all-cause mortality. In this case, the diagnostic criteria adopted for defining MACE and hospitalization for heart failure are comparable across cardiovascular outcome trials, but not in metabolic outcome trials, which often do not perform any formal adjudication of events. However, subgroup analyses did not show any difference in the risk of MACE or heart failure in trials with and without cardiovascular endpoint and trials excluding or including subjects with a previous diagnosis of heart failure. Paradoxically, the only significant difference observed between cardiovascular and non-cardiovascular outcome trials was that regarding all-cause mortality, which does not pose any issues of diagnostic definition.
3) The definition of heart failure differs across trials and it is both inconsistent and heterogeneous. In cardiovascular outcome trials heart failure is defined as an event leading to hospitalization; whereas, cases of heart failure in non-cardiovascular trials include all those that were reported as serious adverse events; the possibility that some events of acute heart failure were considered life-threatening without leading to hospitalization, although unlikely, should be considered. Furthermore, no formal adjudication of heart failure was performed in the majority of non-cardiovascular trials, allowing for misclassifications. Moreover, some trials formally excluded patients with previously diagnosed heart failure and some others did not, possibly introducing a selection bias. However, no significant differences were observed between trials including or excluding patients with previous heart failure.
4) This meta-analysis includes trials with different duration, ranging from 24 to 307 weeks; trial duration could theoretically affect the results on the considered outcomes. The statistical tests did not show any relevant heterogeneity across trials, but the results of the I^2 test could underestimate heterogeneity when the number of included trials is very large.

In conclusion, DPP4i are not associated with any increase or reduction of major cardiovascular events, all-cause mortality, and heart failure. Saxagliptin seems to be associated with an increased risk of hospitalization for heart failure, which is not present for the other drugs of the class.

Contributors

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

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

BN, **BR**, **MG**, **AG** and **CM** were involved in each of the following points:

1. Data Collection.
2. Manuscript revision.

Role of funding

This research was performed as a part of the institutional activity of the unit, with no specific funding. All expenses, including the salaries of the investigators, were covered by public research funds assigned to the unit. The manuscript was drafted and revised by the authors following 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 it for publication.

Declaration of competing interest

BN is presently an employee of Novo Nordisk; **CM, MG, and AG** have no conflicts of interest to declare; **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 authors approved the final version of this manuscript. Dr. Matteo Monami 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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