Effects of insulin 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. This expert panel, 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, decided to perform a systematic review and meta-analysis on the effect of insulin with this respect.

Data synthesis: A MEDLINE database search was performed to identify all RCTs, up to June 1st, 2021, with duration≥52 weeks, in which insulin 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.

Six RCTs (enrolling 8091 patients and 10,139 in the insulin and control group, respectively) were included in the analysis for MACEs and HF, and 18 in that for all-cause mortality (9760 and 11,694 patients in the insulin and control group, respectively). Treatment with insulin neither significantly increased nor reduced the risk of MACE, all-cause mortality, and HHF in comparison with placebo/active comparators (MH-OR: 1.09, 95% CI 0.97–1.23; 0.99, 95% CI 0.91, 1.08; and 0.90, 95% CI 0.78, 1.04, respectively).

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

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1. Introduction

Type 2 diabetes mellitus (T2DM) is associated with a high risk of cardiovascular disease and mortality [1]. Several cardiovascular outcome trials (CVOTs) have shown that some hypoglycemic drugs, such as glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2i), reduce major cardiovascular adverse events (MACE) and mortality [2–7], particularly in T2DM patients with prior cardiovascular disease [3,4].

The cardiovascular safety of insulin has been debated for a long time. Results of observational studies exploring the possible relation between insulin therapy, mortality and cardiovascular disease are conflicting, with some investigations reporting a substantial increase in risk [8–11]. However, observational studies are inevitably affected by prescription bias, which cannot be entirely eliminated by multiple adjustments for available confounders [8,12]. Notably, the results obtained in observational studies were not supported by those of randomized controlled trials (RCT) [13,14], nor by systematic reviews of RCTs [15–17].

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 [18], 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 insulin 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: #42021259838) 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 insulin was compared with either placebo/no therapy, current care, or other active glucose-lowering comparators. Selected articles were imported into Endnote and duplicate items were removed. Only 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 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) 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 B.P.), and conflicts were resolved by a third investigator (E.M).

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, mean age, incidence of MACE (see definition below), all cause mortality, and hospitalizations for heart failure.

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 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 [19].

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. In the case of trials with zero events in which the number of patients treated with the active drug is different from that of comparators, this exclusion could lead to distortion. For this reason, for all the principal endpoints, a sensitivity analysis was performed with continuity correction, imputing one event for each treatment group in trials with zero events. 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.

A post-hoc analysis excluding trials without cardiovascular endpoint was performed for all-cause mortality. Despite the fact that concerns on the cardiovascular safety of rosiglitazone [20] were not confirmed by further and more accurate analyses [21,22], a post-hoc analysis was performed excluding trials versus rosiglitazone.

All statistical analyses specified above were performed using Review Manager 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. The GRADE methodology [18] 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).

3. Results

The flow diagram of the meta-analysis was summarized in supplementary Figure S1. A total of 18 eligible RCTs (as specified in supplementary Table S2) fulfilled our inclusion criteria and were included in the meta-analysis on all-cause mortality. Six of those RCTs 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 S2) due to the open-label design of all included trials.

3.1. 3-Point MACE

Out of six RCTs reporting information on adjudicated cardiovascular events, one [23] reported zero events. Overall, these RCTs included 8091 T2DM patients treated with insulin (with a total of 1269 MACE) and 10,139 T2DM patients treated with placebo or any other active comparators (with a total of 1535 MACE). No publication bias was detected at the visual analysis of the Funnel plot (Supplementary Figure S3) and at Egger's test (Kendall's tau without continuity correction: −0.03; p = 0.71). Treatment with insulin was not associated with significant differences in the incidence of MACE (MH-OR: 1.09 [0.97, 1.23], with a random-effect model), as shown in Fig. 1. Similar results were obtained using a fixed-effect model (MH-OR: 1.07 [0.99, 1.16], p = 0.11). Another sensitivity analysis, imputing one case per arm in RCTs reporting zero events, was also performed (MH-OR: 1.07 [0.99, 1.16], p = 0.11). A subgroup analysis considering different comparators was performed: MH-OR for RCTs comparing insulin with GLP-1 receptor agonists [24–26] and with oral antidiabetic drugs [13,23,27] was 1.64 [0.85, 3.15], p = 0.14 and 1,06 [0.98, 1.16], p = 0.15, respectively.

3.2. All-cause mortality

Out of 18 studies included in the meta-analysis (9760 and 11,694 patients in the insulin and control group, respectively; Table S2), 13 reported at least one death (1151 vs. 1481 in insulin and control group, respectively) and were therefore included in the meta-analysis. Possible publication bias was detected at a visual analysis of the Funnel plot (Figure S3), but it was not confirmed by Kendall's tau (Tau: 0.24, p = 0.13).

As shown in Fig. 2, treatment with insulin was not associated with significant changes in all-cause mortality (MH-OR: 0.99 [0.91, 1.08]; I^2 = 0%).

A sensitivity analysis, imputing one case per arm in RCTs reporting zero events, was performed (MH-OR: 0.99 [0.91, 1.08], p = 0.86). Two post-hoc analyses excluding RCTs with adjudicated cardiovascular endpoints and using rosiglitazone as comparator showed similar results (MH-OR: 0.94 [0.34, 2.61], p = 0.91 and MH-OR: 0.99 [0.91, 1.08], p = 0.87, respectively). A subgroup analysis considering different comparators was performed: MH-OR for RCTs comparing insulin with GLP-1 receptor agonists [24–26,28–33] and sulfonylureas [14,34–36] was 1.23 [0.60, 2.55], p = 0.57 and 1.01 [0.84, 1.22], p = 0.91, respectively.

3.3. Hospitalizations for heart failure

Out of six RCTs reporting information on adjudicated cardiovascular events, one [23] did not report any case of HHF. The total number of HHF was 871 (342 and 429 in the insulin and control group, respectively). No publication bias was detected both at Egger's test (Kendall's tau without continuity correction: Tau: 0.02, p = 0.90) and at the visual analysis of the Funnel plot (Figure S3).

Overall, as shown in Fig. 3, treatment with insulin was not associated with a significant increase in the risk of HHF (MH-OR 0.90 [0.78, 1.04]).

A sensitivity analysis, imputing one case per arm in RCTs reporting zero events, was performed (MH-OR: 0.90 [0.78, 1.04], p = 0.15). A subgroup analysis considering different comparators was performed: MH-OR for RCTs comparing insulin with GLP-1 receptor agonists [24–26] and with oral antidiabetic drugs [13,23,27] was 0.92 [0.34, 2.48], p = 0.87 and 0.90 [0.77, 1.04], p = 0.15, respectively.

3.4. Quality of evidence

Using the GRADE algorithm [18], the overall quality of evidence was rated as "moderate" for all the outcomes considered (Table S4).

4. Discussion

Summarizing results of available clinical trials, insulin treatment does not appear to modify the incidence of cardiovascular events and hospitalization for heart failure, nor to affect all-cause mortality in patients with type 2 diabetes. This result is consistent with that of two previous meta-analyses on the same issue [15–17]. Of those, one [17] included only trials on basal insulin, with the exclusion of studies performed with prandial, pre-mixed, or basal-bolus insulin schemes, whereas the other [15] was performed a few years ago, and it could not include several recent trials [23–26,30,32,37]. In addition, both previous meta-analyses included short-term trials, attenuating the potential effects of insulin on cardiovascular disease [15–17]. In fact, based on experimental data, insulin has

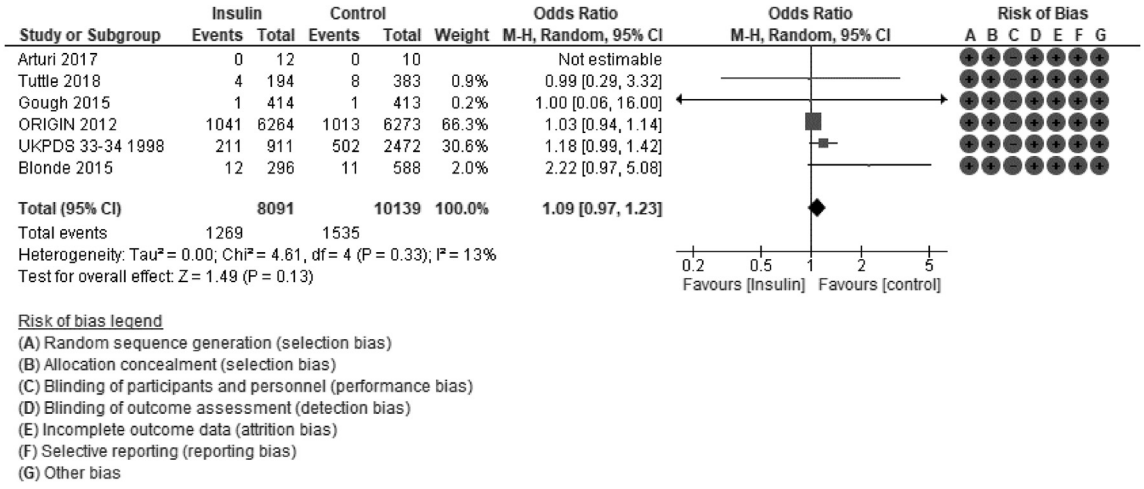

Figure 1 MACE with insulin versus placebo/comparators (MH-OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals) in trials enrolling patients with T2DM.

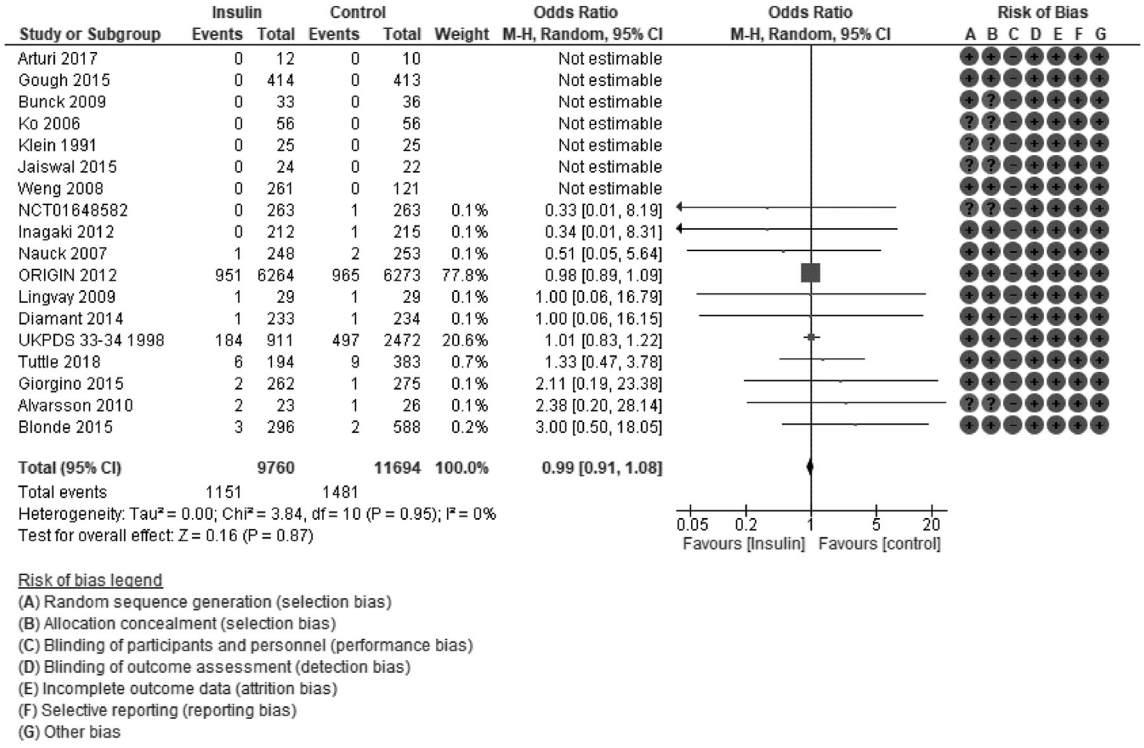

Figure 2 All-cause mortality with insulin versus placebo/comparators (MH-OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals) in trials enrolling patients with T2DM.

been suggested to have both pro-atherogenic [8–11] and anti-atherogenic effects [38,39]; such effects, if clinically relevant, are unlikely to develop within the first few months of treatment. Therefore, the inclusion of short-term trials would reduce the chance of observing either beneficial or detrimental effects of insulin on atherogenesis.

This result is at variance with that of several observational studies [8–11], reporting an increased cardiovascular risk associated with insulin therapy. This discrepancy can be due to confounders affecting epidemiological analyses [8]: insulin therapy can be a marker of disease severity, with patients receiving a prescription for insulin after failing to other glucose-lowering drugs. Comorbidities and concurrent conditions affecting cardiovascular risk (e.g., renal impairment), which are difficult to assess in large administrative databases, can also be associated with a higher chance of receiving a prescription for insulin.

Epidemiological and experimental evidence suggests a possible role of hyperinsulinemia in the development of cardiovascular disease [40–46]. The reduction of cardiovascular risk reported for metformin [27,47] could be due, at least partly, to the reduction of hyperinsulinemia. On

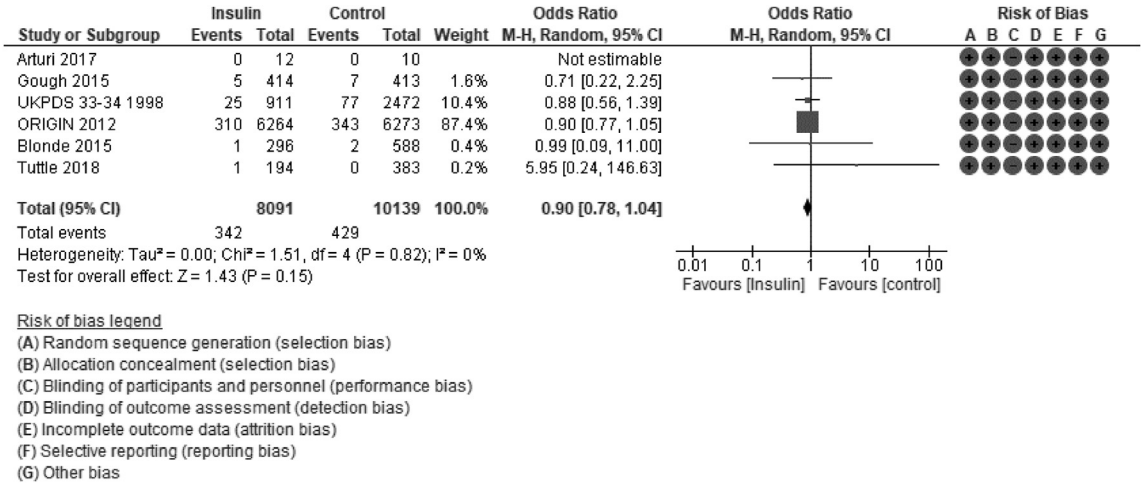

Figure 3 Hospitalization for heart failure with insulin versus placebo/comparators (MH-OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals) in trials enrolling patients with T2DM.

the other hand, clinical trials with drugs with a greater insulin-sensitizing effect than metformin, such as pioglitazone, provided conflicting results with respect to cardiovascular risk [48–51].

Cardiovascular risk is strongly associated with HbA1c levels [52] and the amelioration of glycemic control has been demonstrated to reduce the incidence of MACE [53–55]. Insulin, particularly in the short/medium-term [56], is an effective glucose-lowering agents; however, insulin therapy increases the risk of hypoglycaemia, that could be associated with a higher risk of cardiovascular mortality [54]. It has been shown that the reduction of HbA1c with drugs associated with a high risk of hypoglycaemia is not associated with a reduction of neither incident cardiovascular disease nor mortality [57].

Several limitations of the present meta-analysis should be recognized. Although the methodological quality of most included RCTs was satisfactory, some of the eligible RCTs had possible sources of bias, mainly due to their open-label design (all studies). This methodological flaw determined the downgrade of the GRADE score from "high" to "moderate", suggesting caution in interpreting the results. In addition, a possible publication bias for all-cause mortality cannot be ruled out. Moreover, it should be considered that 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 to RCTs including MACE among their pre-specified endpoints, thus reducing the number of events. However, the latter point should not represent a major limitation; in fact, trials with metabolic endpoints generally enrol a smaller number of patients, usually at lower cardiovascular risk. Our meta-analysis also included trials with different active comparators, some of which could have beneficial or detrimental effects on MACE, mortality, and hospitalization for heart failure, thus affecting the final result. Unfortunately, subgroup analyses for different comparators were not possible because of the limited number of trials for each drug class.

In conclusion, the present meta-analysis performed on RCTs reporting adjudicated MACE within their endpoints showed no significant effects of insulin on incident MACE, HHF, and mortality in patients with established T2DM.

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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, BN,** 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. **BN** was an employee of NovoNordisk. 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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