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Peripheral artery disease and amputations with Sodium-Glucose co-Transporter-2 (SGLT-2) inhibitors: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: Concerns have been raised on the risk of lower limb amputations with SGLT-2 inhibitors. Aim of the present metanalysis is the assessment of the effect of SGLT-2inhibitors on peripheral artery disease and lower limb amputations in randomized controlled trials performed in patients with type 2 diabetes.

Methods: A Medline and Embase search for "Canaglifozin" OR "Dapaglifozin" OR "Empagliflozin" OR "Ertuglifozin" OR "Ipraglifozin" OR Tofoglifozin" OR "Luseoglifozin" was performed, collecting randomized clinical trials (duration > 12 weeks) up to December 1st, 2018, comparing SGLT-2i at approved dose with placebo or other active comparators different from SGLT-2 inhibitors. Furthermore, unpublished studies were searched in the www.clinicaltrials.gov register. Separate analyses were performed for individual molecules of the class. In addition, a separate analysis was performed for placebo-controlled trials. Mantel-Haenszel odds ratio with 95% Confidence Interval (MH-OR) was calculated for all outcomes defined above.

Results: A total of 27 trials fulfilling the inclusion criteria was identified. The overall incidence of peripheral artery disease was increased with SGLT-2 inhibitors (MH-OR: 1.26 [1.04, 1.52]). The increase of risk was statistically significant only with canagliflozin. MH-OR for amputation in the three cardiovascular safety trials with SGLT-2 inhibitors was 1.22 [0.59–2.52].

Conclusions: At present, there is no reason to believe that empagliflozin or dapagliflozin increase the risk of either peripheral artery disease of lower limb amputations. Canagliflozin could be associated with a specific risk, which needs to be further investigated.

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1. Introduction

Sodium-Glucose co-Transporter-2 (SGLT-2) inhibitors, which are widely used in the treatment of type 2 diabetes, have shown favourable effects on different cardiovascular endpoints, such as heart failure [1–3], major cardiovascular events [1,3], and cardiovascular mortality [3]. The finding of an increased risk of lower limb amputations in a large-scale cardiovascular safety trial with canagliflozin [1] was therefore unexpected. Although the two available trials with dapagliflozin and empagliflozin did not highlight any significant increase in amputations [2,3], a meta-analysis suggested that SGLT-2 inhibitors, as a class, could determine a specific risk of amputations [4]. No specific attempt has been made to meta-analyze data on amputations from trials with different SGLT-2 inhibitor molecules and that from cardiovascular safety trials beyond fixed model analysis. In addition, the effect of SGLT-2 inhibition on the incidence of peripheral artery disease, reported as serious adverse event in randomized trials, has not yet been systematically explored.

Aim of the present metanalysis is the assessment of the effect of SGLT-2 inhibitors on peripheral artery disease and lower limb amputations in randomized controlled trials performed in patients with type 2 diabetes.

2. Materials and methods

This meta-analysis is reported following the criteria of PRISMA statement [5]. The present metanalysis has been registered on PROSPERO website (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019119767).

2.1. Data sources and searches

An extensive Medline search for Canagliflozin OR Dapagliflozin OR Empagliflozin OR Ertugliflozin OR Ipragliflozin OR Luseogliflozin OR Tofogliflozin was performed, collecting all randomized clinical trials on humans up to December 1st, 2018. Furthermore, completed but yet unpublished studies with the drugs specified above were searched in the *www.clinicaltrials.gov* register. The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed independently by the two of the authors (I.D. and B.N.), and conflicts resolved by the third investigator (M.M.).

2.2. Study selection

A meta-analysis was performed including all randomized clinical trials with a duration of at least 52 weeks, enrolling patients with type 2 diabetes, comparing approved doses of SGLT-2 inhibitors (i.e., canagliflozin 100/300 mg, dapagliflozin 5/10 mg, empagliflozin 10/25 mg, ertugliflozin 5/15 mg, ipragliflozin 25/50 mg, luseogliflozin 2.5/5 mg, and tofogliflozin 20 mg) with placebo or other active comparators different from SGLT-2 inhibitors. Sergliflozin and remogliflozin were discontinued and therefore they have not been included in the search strategy, as well as sotagliflozin which has not been yet approved.

Trials with a shorter duration were excluded, because they could not yield relevant information on incidence of peripheral artery disease, which had been chosen as the principal outcome variable. Trials enrolling nondiabetic, or type 1 diabetic subjects were excluded.

2.3. Data extraction and quality assessment

Results of unpublished trials were retrieved, if available, on www.clinicaltrials.gov or Food and Drug Administration (FDA, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name) and European Medicines Agency (EMA, www.ema.europa.eu) reviews of approved drugs. All those sources were also used to complete information on results of published trials, when not reported in publications (including the primary trial publications, and subsequent reviews and/or pooled analyses reporting data on individual trials). For all published trials, results reported in published papers were used as the primary source of information, when available.

The quality of trials was assessed using the parameters proposed by the Cochrane Collaboration.

2.4. Data synthesis and analysis

The principal outcome considered was the incidence of peripheral artery disease, as reported by investigators as serious adverse event. The definitions used for this endpoint are summarized in Table 1 of Supplementary materials. A further outcome was amputation of lower limbs, specified as serious adverse event.

Mantel-Haenszel odds ratio with 95% Confidence Interval (MH-OR) was calculated for all outcomes defined above, on an intention-to-treat basis. Separate analyses were performed for individual molecules of the class. In addition, a separate analysis was performed for placebo-controlled trials.

Heterogeneity was assessed by using I^2 statistics. Even when low heterogeneity was detected, a random-effects model was applied as the primary analysis, because the validity of tests of heterogeneity can be limited with a small number of component studies. Fixed effect models were applied for sensitivity analysis, together with a random-effect model analysis with continuity correction (i.e., inputing one event per group in trials with zero events). To estimate possible publication/disclosure bias a funnel plots was examined for peripheral artery disease. All analyses were performed using Review Manager 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

3. Results

Fig. 1 of Supplementary materials reports the trial flow summary. A total of 27 trials fulfilling the inclusion criteria was identified [1–3,6–28]. The characteristics of retrieved trials are summarized in Table 2 of Supplementary materials.

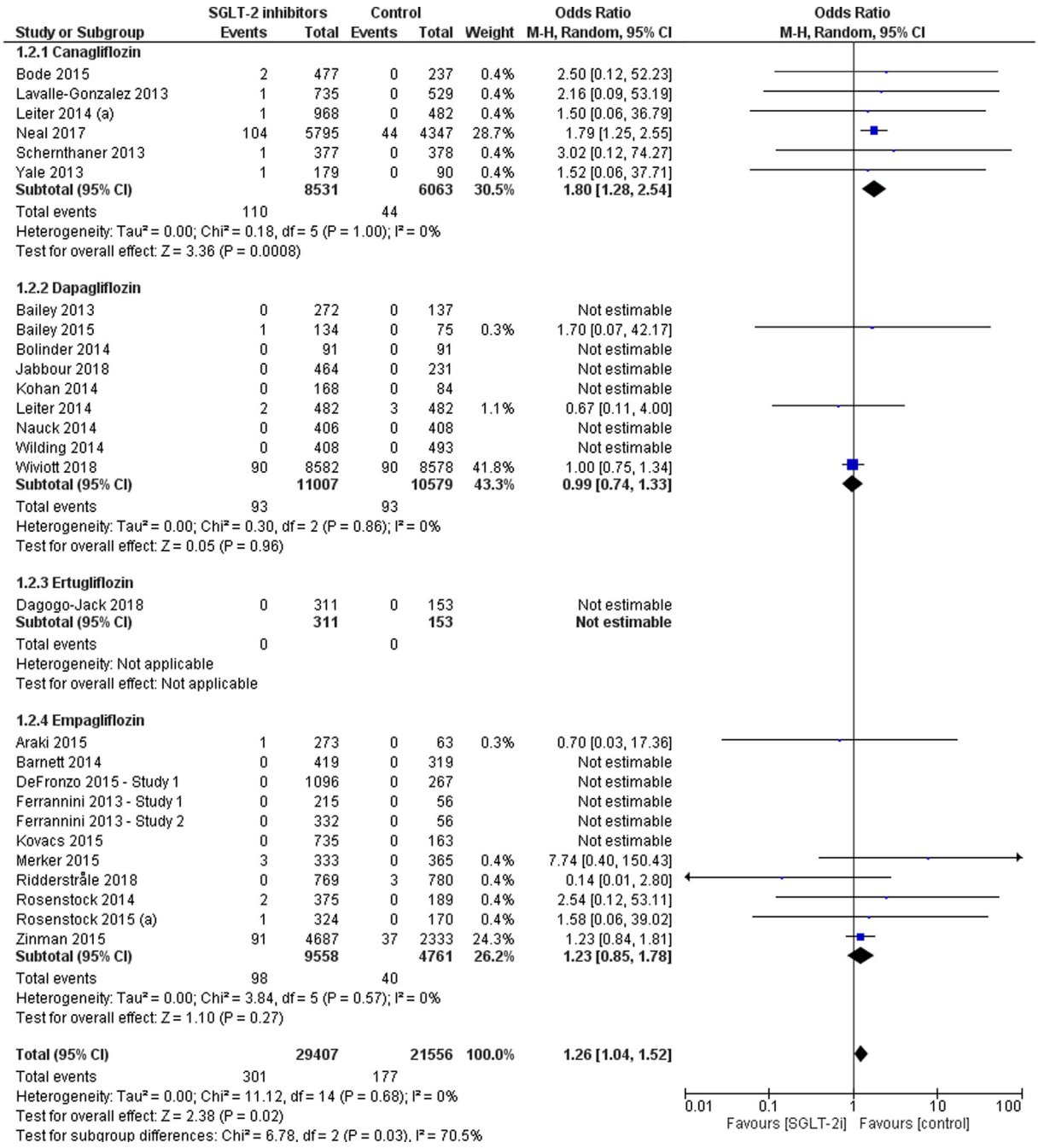

Fig. 1 – Risk of peripheral artery disease for SGLT-2 inhibitors versus different comparators (MH-OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

Retrieved trials enrolled 29,404 and 21,556 patients in SGLT-2 inhibitor and comparator groups, respectively, with a mean duration of treatment of 84.0 weeks. The mean age, duration of diabetes, baseline HbA1c, and BMI of enrolled patients at baseline were 59.0 years, 8.3 years, 8.0%, and 30.9 Kg/m^2, respectively. Information on incidence of peripheral artery disease and amputation was retrieved from all trials. No publication bias was detected at visual analysis of Funnel plot (Fig. 2 Supplementary materials).

Cases of peripheral artery disease were reported in 14 trials (3, 6, and 5 with dapagliflozin, canagliflozin, and empagliflozin, respectively), with 301 cases in SGLT-2 inhibitors and 177 cases in control groups. The overall incidence of peripheral artery disease was increased with SGLT-2 inhibitors (MH-OR 1.26 [1.04–1.52]; Fig. 1). Similar results were obtained in a sensitivity analysis with fixed-effect model (MH-OR 1.27 [1.05–1.53]). When trials with different molecules were analysed separately, the increase of risk was statistically significant with canagliflozin, but not with empagliflozin or dapagliflozin; the difference across molecules was statistically significant (p = 0.02). In the sensitivity analysis with continuity correction (Fig. 2), the effect of SGLT-2 inhibitors on the risk of peripheral artery disease was no longer significant, whereas the increase of risk with canagliflozin maintained

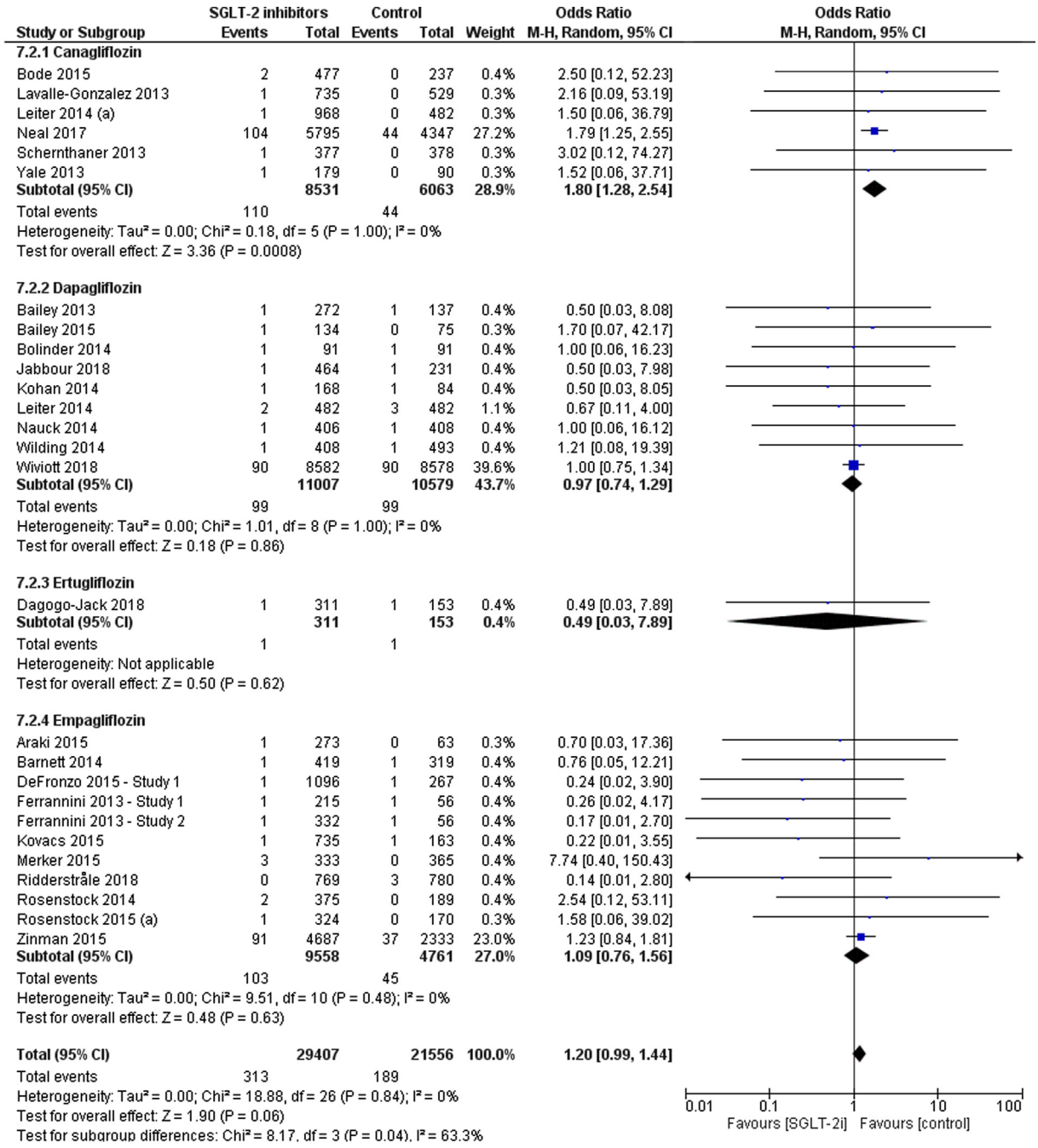

Fig. 2 – Risk of peripheral artery disease for SGLT-2 inhibitors versus different comparators in a sensitivity analysis witfh continuity correction (MH-OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

statistical significance. Similar results were obtained when placebo-controlled trials were analysed separately (Fig. 3 of Supplementary materials).

Data for amputations were collected from all trials. However, only the three cardiovascular safety studies [1–3] reported events, whereas all the other trials reported zero events of amputations as serious adverse events. Combining the results of three trials, MH-OR with random effect model was 1.22 [0.59–2.52], whereas the analysis with fixed effect model provided a MH-OR of 1.28 [1.10–1.49]. The sensitivity analysis with continuous correction did not show any increase in risk for SGLT-2 inhibitors as a class (MH-OR 0.81 [0.54–1.22]), whereas a significantly increased risk was observed with canagliflozin (Fig. 4 of Supplementary materials); conversely, a significant reduction of risk was observed with empagliflozin.

4. Discussion

The present meta-analysis shows an apparent increase of risk of peripheral artery disease with SGLT-2 inhibitors, which is not confirmed in analyses with continuity correction. This

possible increase in risk is driven by one drug, i.e. canagliflozin, with no evidence of risk with the other molecules of the class. Similarly, the risk of amputations is increased with canagliflozin, whereas the results on SGLT-2 inhibitors as a class depend on methods used for data analysis.

The choice of statistical methods for data synthesis in meta-analyses is often crucial for determining the results. In particular, the use of fixed effect models in case of heterogeneity can lead to a relevant distortion [29]. For example, the increased risk of amputations with SGLT-2 inhibitors as a class, which had been reported in a previous meta-analysis [4], is present only with fixed effect models, but it disappears when correctly applying random effect models. Another relevant point is that of continuity correction: trials with zero events are excluded from usual analyses. However, when there is a high number of trials with zero events, and the sample size is not equal across treatment groups, this can lead to a bias (e.g., if samples treated with the investigational drug in trials with zero events are larger than those of control arms, the possible increase in risk with the drug will be overestimated). On the other hand, continuity correction can artificially underestimate between-group differences.

The analysis of data from multiple trials is particularly problematic in case of relevant heterogeneity, which can be determined by differences in study protocols, case mix, duration of follow-up, or by differences in treatments. The attempt at combining data from different molecules of the same class can be misleading if there are differences among drugs for efficacy or safety. This is, apparently, the case of SGLT-2 inhibitors with respect to amputations and peripheral artery disease: the increase in risk was observed with canagliflozin [1], but not with empagliflozin [3] or dapagliflozin [2].

The results obtained with canagliflozin should be interpreted with caution. The increased risk of amputations, and the associated risk of peripheral artery disease, are driven by one single study [1]. Notably, a trial published after the completion of this meta-analysis, the CREDENCE study [29], did not show any significant increase in amputation rate (70 vs 63 cases, with a HR of 1.11); unfortunately, the same trial has not disclosed data on peripheral artery disease so far. The same consideration should be made when interpreting the results of empagliflozin, which has an apparently protective effect with respect to amputations, which is also driven by one trial [3].

The mechanisms underlying the possibly increased risk of amputations with canagliflozin are obscure. Canagliflozin induces volume depletion and increases haematocrit, thus producing an increase in blood viscosity [30]; this could theoretically contribute to occlusion of small peripheral blood vessels, leading to toe amputation. However, a similar effect on haematocrit has been reposted also for the other molecules of the class [3,30]. In addition, in the CANVAS trial program canagliflozin was also associated with an increased number of reported cases of peripheral artery disease, which would suggest a pro-atherogenic effect. However, the decision to report a peripheral artery disease as a serious adverse event could be the consequence of an acute vessel occlusion, rather than of a long-term atherosclerotic process. In addition, canagliflozin is very unlikely to be atherogenic, considering its reported beneficial effects on major cardiovascular events [1].

The differences in results on amputations between canagliflozin and the other molecules of the class could also be the effect of differences in the characteristics of available trials. Although the general design of the three cardiovascular safety trials with SGLT-2 inhibitors is similar (i.e., treatment versus placebo in patients at high cardiovascular risk, with major cardiovascular events as the principal endpoint), there are minor, but potentially relevant, differences in inclusion and exclusion criteria, median study duration, and management of study procedures [1–3]. The possibility that the results of one trial (CANVAS trial program [1]) on a non-prespecified endpoint (amputations) are a play of chance should also be considered.

Some limitations of the present meta-analysis should be considered. The possible heterogeneity among molecules with respect to the endpoints considered limitations the reliability of analyses on SGLT-2 inhibitors as a class. Peripheral artery disease was not a pre-specified endpoint of any of the included trials. Although information on serious adverse events was retrieved for all studies, the definition of peripheral artery disease was based on the choice of investigators, with no pre-defined diagnostic criteria, no information on pre-existing disease, and no adjudication of cases. The possibility that one case was described with two different definitions of peripheral artery disease, and was therefore counted twice, cannot be ruled out. Such a limitation would be overcome by a meta-analysis of patient-level data. Furthermore, the large majority of cases of peripheral artery disease, and the totality of amputations, derived from the three cardiovascular outcome trials [1–3]; this limits the generalizability of results to patients at lower cardiovascular risk. For all those reasons, further data should be collected in order to draw more definitive conclusions.

At present, there is no reason to believe that empagliflozin or dapagliflozin increase the risk of either peripheral artery disease of lower limb amputations. Canagliflozin could be associated with a specific risk, which needs to be further investigated.

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Research involving Human Participants and/or Animals and Informed consent

For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors.

Declaration of Competing Interest

Ilaria Dicembrini has received speaking fees from Novonordisk .

Benedetta Tomberli, Giorgio Baldereschi, and Fabrizio Fanelli have no conflict of interest.

Besmir Nreu is presently employee of Novo Nordisk.

Edoardo Mannucci 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.

Matteo Monami 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.

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.

Contributor statements

Matteo Monami and Edoardo Mannucci were involved in each of the following points:

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

Ilaria Dicembrini, Benedetta Tomberli, Besmir Nreu, Giorgio Baldereschi and Fabrizio Fanelli were involved in each of the following points:

1. Data Collection.
2. Manuscript revision.

All the authors approved the final version of this manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.05.028.

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