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Sodium-glucose co-transporter inhibitors in insulin-treated diabetes: a meta-analysis

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Abstract

Background: Patients with insulin-treated type 2 diabetes (T2D) have a high risk of major adverse cardiovascular events. Sodium-glucose cotransporter inhibitors (SGLTi) improve outcomes without hypoglycemic risk.

Aims: To study the effect of SGLTi in patients with T2D with and without background insulin-treatment in outcome-driven RCTs.

Methods: Random effects models.

Results: A total of 54,374 patients with T2D were included in the analysis, of which 26,551 (48.8%) were treated with insulin. For 3P-MACE in patients without insulin treatment, the HR (95%CI) for the effect of SGLTi vs. placebo was 0.93 (0.81-1.05), with moderate heterogeneity ($I^2 = 49.2\%$, Q statistic $P = 0.11$). In insulin-treated patients, the HR (95%CI) was 0.88 (0.82-0.95), without evidence of heterogeneity ($I^2 = 0.0\%$, Q statistic $P = 0.91$). The pooled effect evidenced a 10% reduction of 3P-MACE with SGLTi (HR 0.90, 95%CI 0.85-0.96), without SGLTi-by-insulin interaction $P = 0.53$. For the composite outcome of HF hospitalisation or cardiovascular death in patients without insulin treatment, the HR (95%CI) for the effect of SGLTi vs. placebo was 0.77 (0.61-0.92), with marked heterogeneity ($I^2 = 66.8\%$, Q statistic $P = 0.02$). In insulin-treated patients, the HR (95%CI) was 0.77 (0.68-0.86), without significant heterogeneity ($I^2 = 31.7\%$, Q statistic $P = 0.25$). The pooled effect evidenced a 23% reduction of HF hospitalisations or cardiovascular death with SGLTi (HR 0.77, 95%CI 0.68-0.85), without SGLTi -by-insulin interaction $P = 0.98$.

Conclusion: SGLTi reduce cardiovascular events regardless of insulin use. However, the treatment effect is more homogeneous among insulin-treated patients, supporting the use of SGLTi for the treatment of patients with T2D requiring insulin for glycemic control.

47 *Key-words:* type 2 diabetes; insulin; sodium-glucose cotransporter 2 inhibitors;

48 cardiovascular outcomes; meta-analysis.

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Introduction

Patients with insulin-treated diabetes have a high risk of major adverse cardiovascular events (MACE), frequently leading to symptomatic heart failure (HF), hospitalizations and death¹. The risk of patients with type 2 diabetes (T2D) treated with insulin is higher than the risk of patients with T2D treated with oral anti-diabetic drugs only (i.e., non-insulin-treated diabetes)²⁻⁴. In patients with T2D, insulin treatment is associated with long-standing diabetes, poor cardiometabolic profile (higher body mass index, abdominal obesity, heart rate, blood pressure, triglycerides and lower HDL cholesterol) and a higher prevalence of micro- and macrovascular complications^{5, 6}.

Sodium-glucose cotransporter 1/2 or 2 inhibitors (SGLTi) have demonstrated to improve cardiovascular and kidney outcomes in patients with T2D and in patients with heart failure with reduced ejection fraction (HFrEF) with and without diabetes⁷⁻¹¹. The reduction of hospitalisations due to HF is particularly striking with these agents^{12, 13}. As patients with insulin-treated diabetes have a high-risk of cardiovascular complications, including HF, it is plausible that SGLTi provide major benefits to these patients by potentially reducing their risk of MACE, including HF hospitalisations and cardiovascular death. Furthermore, SGLTi may help controlling blood pressure, weight, and sodium retention, thus counteracting the deleterious effects associated with insulin-treatment without increasing the risk of hypoglycemic episodes¹⁴⁻²⁰.

Using updated data from large outcome-driven randomised controlled trials (RCTs) assessing the efficacy and safety of SGLTi versus placebo, we aim to study the effect of these agents in patients with T2D with and without background insulin-treatment.

Methods

Search strategy and selection criteria

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline²¹. We defined both MeSH terms (controlled language) and free text terms to express each component of PICO expression: P) Population, patients with diabetes; I) Intervention, SGLT inhibitors; C) Comparison, placebo and O) Outcomes, MACEs. The search query included the following and it was last searched on 22nd of November 2020: ("Diabetes Mellitus"[Mesh] OR diabetes) AND ("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR sglit inhibitors) AND ("Placebos"[Mesh] OR placebo) AND ("Randomized Controlled Trial" [Publication Type] OR randomized controlled trial) AND (cardiovascular death OR cardiovascular events). We did not restrict the search by language, date or publication status. Additionally, we have included recently published trials that were not displayed on PubMed at the time^{22, 23}. One hundred fifteen studies were initially identified, of which 108 were excluded because of inadequate study design, outcomes or topic of interest. Then we have assessed whether the identified trials displayed subgroup analyses in patients with and without background insulin treatment, resulting in 6 selected RCTs: 1) Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)⁷; 2) the CANVAS-Program, consisting of the Canagliflozin Cardiovascular Assessment Study (CANVAS) and A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus (CANVAS-R)⁸; 3) the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58)⁹; 4) the Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease (VERTIS-CV)²⁴; 5) the Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF)²²; and the 6) Effect of

Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED)²³. Trial eligibility was confirmed by 2 independent reviewers (J.P.F., A.C.O.), data extraction was performed by A.C.O and J.P.F, and the study quality was performed by J.P.F., A.C.O., and F.A.S. We have also cross-checked the RCTs selected to the present analysis with other recently published meta-analyses and the concordance was perfect^{12, 13, 25}. The Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE)¹⁰, which was primarily a kidney outcomes trial, did not report treatment effects in insulin subgroups and was not included in the analysis. A detailed description of each individual trial is provided in the respective main reports as above referenced.

The analyses were performed to assess heterogeneity of treatment effects in outcomes in patients with and without background insulin treatment.

Outcomes

The primary outcome in EMPA-REG OUTCOME, CANVAS-Program, DECLARE-TIMI 58, and VERTIS-CV was the composite of time-to-first of myocardial infarction, stroke, or cardiovascular death (3P-MACE). The primary outcome in SOLOIST-WHF and SCORED was the total number of deaths from cardiovascular causes and hospitalizations and urgent visits for HF (first and recurrent). On top of the primary outcome, the EMPA-REG OUTCOME trial reported the treatment effect of empagliflozin in patients with and without insulin treatment for the outcome of cardiovascular death. The DECLARE-TIMI 58 and VERTIS-CV reported the treatment effect of dapagliflozin and ertugliflozin, respectively, in patients with and without insulin treatment for the composite outcome of time-to-first of cardiovascular death or HF hospitalisation. For optimizing the consistency of outcomes across trials, the

EMPA-REG OUTCOME, CANVAS-Program, DECLARE-TIMI 58, and VERTIS-CV trials were meta-analyzed for the composite outcome of time-to-first 3P-MACE of myocardial infarction, stroke, or cardiovascular death. The EMPA-REG OUTCOME, DECLARE-TIMI 58, VERTIS-CV, SOLOIST-WHF, and SCORED trials were meta-analyzed for the outcomes of cardiovascular death (EMPA-REG OUTCOME) and composites of cardiovascular death or HF hospitalisations, as time-to-first event (DECLARE-TIMI 58 and VERTIS-CV) or first and recurrent (SOLOIST-WHF and SCORED). The studied trials and outcomes are displayed in *Table 1*.

Statistical analysis

A random-effect meta-analysis approach was used with heterogeneity assessed using the Cochran Q test statistic and Higgins and Thompson I^2 ²⁶. Heterogeneity was considered to be low, moderate, or high if I^2 was <25%, 25% to 75%, or >75%, respectively. The hazard ratio (HR) and respective 95% confidence intervals (95%CI) were extracted from the insulin subgroup analyses reported in the publications of each individual study. All studies, except DECLARE-TIMI 58, reported the HR (95%CI) for patients with and without insulin treatment. In DECLARE-TIMI 58 we have extracted the approximate HR (95%CI) from the forest plots. The number and proportion of patients with events in insulin subgroups were inconsistently reported and we show these numbers in a table whenever available. The meta-analysis was directly implemented on the HR (exponential) scale. The assessment of whether background insulin treatment could modify the effect of SGLTi on outcomes was performed using interaction term for subgroups and reported with a P-value for interaction. Records identified in each database were imported and managed through Microsoft Excel®. We assessed publication bias by visual inspection of funnel plots, with the ascertainment for potential asymmetry of published results by Egger's regression test and Duval and Tweedie's

trim-and-fill method. The statistical analyses were performed using Stata® software version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) and the package *meta*. The risk of bias in randomised trials was assessed with the RoB 2 tool²⁷. Two-sided P values <0.05 were considered significant.

Results

The characteristics of the patients from the RCTs included in this analysis are depicted in the *Table 2*. A total of 54374 patients with T2D were included in the analysis, of which 26551 (48.8%) were treated with insulin. The mean age of all trial participants was 66 years, 19702 (36.2%) were women, and 43806 (80.6%) were Caucasian. The number of participants per trial ranged from 1222 in SOLIST-WHF to 17160 in DECLARE-TIMI 58. The median follow-up ranged from 0.8 years in SOLIST-WHF to 4.2 years in DECLARE-TIMI 58 (*Table 2*). The assessment of risk of bias by visual inspection of funnel plots and quantitative assessment suggested no indication of publication bias. The risk of bias in randomized trials as assessed by the RoB 2 tool was low.

The number of events per trial and insulin subgroup are presented in the *Table 3*.

The treatment effect of SGLTi vs. placebo in patients with and without insulin treatment for the composite outcome of myocardial infarction, stroke or cardiovascular death and the composite of heart failure hospitalisation or cardiovascular death (cardiovascular death alone in the EMPA-REG OUTCOME trial) are presented in the *Table 3* and *Figure 1*.

For the composite outcome of myocardial infarction, stroke or cardiovascular death in patients without insulin treatment, the HR (95%CI) for the effect of SGLTi vs. placebo was 0.93 (0.81-1.05), with moderate heterogeneity ($I^2 = 49.2\%$, Q statistic $P = 0.11$). In insulin-treated patients, the HR (95%CI) for the effect of SGLTi vs. placebo was 0.88 (0.82-0.95),

without evidence of heterogeneity ($I^2 = 0.0\%$, Q statistic $P = 0.91$). The pooled effect evidenced a 10% reduction of 3P-MACE with SGLTi (HR 0.90, 95%CI 0.85-0.96), without significant interaction between subgroups of insulin (yes vs. no), interaction $P = 0.53$. *Figure 1, panel A.*

For the composite outcome of HF hospitalisation or cardiovascular death (cardiovascular death alone in the EMPA-REG OUTCOME trial) in patients without insulin treatment, SGLTi reduced the event rate by 23% (HR 0.77, 95%CI 0.61-0.92) but the treatment effect was heterogeneous ($I^2 = 66.8\%$, Q statistic $P = 0.02$). In insulin-treated patients, SGLTi significantly reduced HF hospitalisation or cardiovascular death (HR 0.77, 95%CI 0.68-0.86) without significant heterogeneity ($I^2 = 31.7\%$, Q statistic $P = 0.25$). The pooled effect evidenced a 23% reduction of HF hospitalisations or cardiovascular death with SGLTi (HR 0.77, 95%CI 0.68-0.85), without significant interaction between subgroups of insulin (yes vs. no), interaction $P = 0.98$. *Figure 1, panel B.*

Discussion

The present meta-analysis shows that SGLTi reduced the composite outcome of myocardial infarction, stroke or cardiovascular death and the composite outcome of HF hospitalisation or cardiovascular death regardless of insulin use at baseline. However, the treatment effect was more homogeneous and consistent among insulin-treated patients, highlighting the need for adding a SGLTi to the therapeutic armamentarium of patients with T2D requiring insulin for glycemic control.

In patients with T2D, insulin is used to lower blood glucose levels in patients that fail to achieve targets or that do not tolerate oral glucose-lowering therapies. However, the intensity of glucose lowering should be tailored to each individual patient as it may increase

hypoglycemic episodes and mortality^{28, 29}. Furthermore, insulin-treatment may lead to weight gain, fluid retention, higher blood pressure, and increase the risk of hypoglycemia without reducing cardiovascular complications³⁰⁻³². Patients with T2D who require insulin, usually have a poor glycemic and metabolic control, and have a high risk of cardiovascular complications, including HF hospitalisations and death from cardiovascular causes^{4, 33}. For these reasons, there is an urgent need to reduce the risk profile of insulin-treated patients, while also improving their metabolic components, reduce weight, and decrease the burden of hospitalisations and adverse cardiovascular outcomes. Inhibitors of the sodium glucose co-transporter have many beneficial effects beyond glucose control, and, indeed, may help to reduce weight, control blood pressure, limit sodium retention, reduce hospitalisations (HF-related in particular) and cardiovascular death, counteracting the negative effects of insulin. As shown in the present study, SGLTi reduce cardiovascular complications regardless of insulin treatment. However, the treatment effect was more homogeneous among insulin-treated patients leading to consistent reductions of cardiovascular complications, comprising HF hospitalisations and cardiovascular death across multiple populations with T2D, including patients with chronic kidney disease and worsening heart failure^{7-9, 22-24}. This effect was seen regardless of the type of SGLTi i.e., the SGLT1/2 inhibitor sotagliflozin and the remainder SGLT2 inhibitors had similar effects to reduce cardiovascular events regardless of insulin treatment, but with a more homogeneous effect among insulin-treated patients.

A recently published meta-analysis showed that in placebo-controlled RCTs SGLT2i reduced cardiovascular events and HF hospitalisations, independently of the presence of atherosclerotic cardiovascular disease, kidney function, and glycated hemoglobin levels²⁵. It is likely that insulin-treated patients also had higher burden of cardiovascular disease, worse

kidney and higher glycated hemoglobin levels; however, beyond the higher cardiovascular risk (with potentially larger treatment benefit), insulin-treated patients may experience a more consistent benefit from SGLTi due to the effects and mechanisms associated with insulin administration, such as weight gain and sodium retention that may be counterbalanced by SGLTi. Supporting this hypothesis, smaller “mechanistic” studies testing the effects of SGLT2i among insulin-treated patients also showed a beneficial effect of these agents. For example, a subsample of patients enrolled in the CANVAS-Program and receiving insulin at baseline were randomized to receive placebo (n =690), canagliflozin 100 mg (n =692), or canagliflozin 300 mg (n =690). Compared with the placebo both canagliflozin doses reduced glycated hemoglobin, fasting plasma glucose, body weight and blood pressure¹⁵. Similar findings were observed with dapagliflozin and empagliflozin in patients with inadequately controlled T2D on basal insulin^{16, 18} and obese difficult-to-treat patients with T2D requiring high doses of insulin¹⁷. It should be noted, that SGLT2i also reduced insulin requirements without increased risk of hypoglycemia¹⁷⁻¹⁹.

Limitations

Several limitations are acknowledged. Differences in eligibility criteria, patient characteristics, trial duration, and outcome definition may have affected the treatment effects and increased heterogeneity in the meta-analysis. However, evidence of some heterogeneity was only found among patients without background insulin treatment. The trials here reported, randomised patients to either a SGLTi or placebo but insulin treatment was not part of the randomisation procedure; therefore, these subgroup analyses should be regarded with caution because the treatment effect may be influenced by insulin itself, but also by the patients` characteristics, their risk profile, comorbidities (including heart failure and chronic kidney disease) or the quality of healthcare. Notwithstanding, the homogeneity

of effect across trials among insulin-treated patients suggests that SGLTi are a beneficial therapy for these patients. For purposes of the present analysis, we were limited to outcomes that had been reported by subgroups of insulin use and some outcome definitions varied between trials (e.g., time-to-first and total heart failure hospitalisations), however the treatment effects were similar across outcomes and this is not a major source of bias in our report. The number needed-to-treat to benefit is not reported because the data required for a reliable calculation of this estimate was not available in all trials.

Conclusions

The present meta-analysis shows that SGLTi reduce cardiovascular events regardless of insulin use. However, the treatment effect is more homogeneous among insulin-treated patients, supporting the use of SGLTi for the treatment of patients with T2D requiring insulin for glycemic control.

Disclosures

J.P.F. is consultant for Boehringer Ingelheim. All the other authors have no relevant conflicts of interest to report.

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381 Figure 1. Treatment effects by insulin treatment subgroups

382 (A) Myocardial infarction, stroke or cardiovascular death

383

384 (B) Heart failure hospitalisation or cardiovascular death

385

386 Legend: In (B) EMPA-REG OUTCOME estimates correspond to cardiovascular death only,
387 DECLARE-TIMI-58 and VERTIS CV estimates correspond to the time-to-first of cardiovascular
388 death or heart failure hospitalisation, and SOLOIST-WHF and SCORED estimates correspond
389 to cardiovascular death or first and recurrent heart failure hospitalisations; REML, restricted
390 maximum likelihood.