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

2

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22

23 **Abstract**

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

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

29 *Methods:* Random effects models.

30 *Results:* A total of 54,374 patients with T2D were included in the analysis, of which 26,551  
31 (48.8%) were treated with insulin. For 3P-MACE in patients without insulin treatment, the  
32 HR (95%CI) for the effect of SGLTi vs. placebo was 0.93 (0.81-1.05), with moderate  
33 heterogeneity (I<sup>2</sup> =49.2%, Q statistic P =0.11). In insulin-treated patients, the HR (95%CI)  
34 was 0.88 (0.82-0.95), without evidence of heterogeneity (I<sup>2</sup> =0.0%, Q statistic P =0.91). The  
35 pooled effect evidenced a 10% reduction of 3P-MACE with SGLTi (HR 0.90, 95%CI 0.85-0.96),  
36 without SGLTi-by-insulin interactionP=0.53. For the composite outcome of HF  
37 hospitalisation or cardiovascular death in patients without insulin treatment, the HR (95%CI)  
38 for the effect of SGLTi vs. placebo was 0.77 (0.61-0.92), with marked heterogeneity (I<sup>2</sup>  
39 =66.8%, Q statistic P =0.02). In insulin-treated patients, the HR (95%CI) was 0.77 (0.68-0.86),  
40 without significant heterogeneity (I<sup>2</sup> =31.7%, Q statistic P =0.25). The pooled effect  
41 evidenced a 23% reduction of HF hospitalisations or cardiovascular death with SGLTi (HR  
42 0.77, 95%CI 0.68-0.85), without SGLTi -by-insulin interactionP=0.98.

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

46

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

48 cardiovascular outcomes; meta-analysis.

49

50

## 51 **Introduction**

52 Patients with insulin-treated diabetes have a high risk of major adverse cardiovascular  
53 events (MACE), frequently leading to symptomatic heart failure (HF), hospitalizations and  
54 death<sup>1</sup>. The risk of patients with type 2 diabetes (T2D) treated with insulin is higher than the  
55 risk of patients with T2D treated with oral anti-diabetic drugs only (i.e., non-insulin-treated  
56 diabetes)<sup>2-4</sup>. In patients with T2D, insulin treatment is associated with long-standing  
57 diabetes, poor cardiometabolic profile (higher body mass index, abdominal obesity, heart  
58 rate, blood pressure, triglycerides and lower HDL cholesterol) and a higher prevalence of  
59 micro- and macrovascular complications<sup>5, 6</sup>.

60 Sodium-glucose cotransporter 1/2 or 2 inhibitors (SGLTi) have demonstrated to  
61 improve cardiovascular and kidney outcomes in patients with T2D and in patients with heart  
62 failure with reduced ejection fraction (HFrEF) with and without diabetes<sup>7-11</sup>. The reduction  
63 of hospitalisations due to HF is particularly striking with these agents<sup>12, 13</sup>. As patients with  
64 insulin-treated diabetes have a high-risk of cardiovascular complications, including HF, it is  
65 plausible that SGLTi provide major benefits to these patients by potentially reducing their  
66 risk of MACE, including HF hospitalisations and cardiovascular death. Furthermore, SGLTi  
67 may help controlling blood pressure, weight, and sodium retention, thus counteracting the  
68 deleterious effects associated with insulin-treatment without increasing the risk of  
69 hypoglycemic episodes<sup>14-20</sup>.

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

73

## 74 **Methods**

## 75 **Search strategy and selection criteria**

76 This meta-analysis was conducted in accordance with the Preferred Reporting Items for  
77 Systematic Reviews and Meta-analyses (PRISMA) reporting guideline<sup>21</sup>. We defined both  
78 MeSH terms (controlled language) and free text terms to express each component of PICO  
79 expression: P) Population, patients with diabetes; I) Intervention, SGLT inhibitors; C)  
80 Comparison, placebo and O) Outcomes, MACEs. The search query included the following  
81 and it was last searched on 22<sup>nd</sup> of November 2020: ("Diabetes Mellitus"[Mesh] OR  
82 diabetes) AND ("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR sglit inhibitors) AND  
83 ("Placebos"[Mesh] OR placebo) AND ("Randomized Controlled Trial" [Publication Type] OR  
84 randomized controlled trial) AND (cardiovascular death OR cardiovascular events). We did  
85 not restrict the search by language, date or publication status. Additionally, we have  
86 included recently published trials that were not displayed on PubMed at the time<sup>22, 23</sup>. One  
87 hundred fifteen studies were initially identified, of which 108 were excluded because of  
88 inadequate study design, outcomes or topic of interest. Then we have assessed whether the  
89 identified trials displayed subgroup analyses in patients with and without background insulin  
90 treatment, resulting in 6 selected RCTs: 1) Empagliflozin Cardiovascular Outcome Event Trial  
91 in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)<sup>7</sup>; 2) the CANVAS-Program,  
92 consisting of the Canagliflozin Cardiovascular Assessment Study (CANVAS) and A Study of  
93 the Effects of Canagliflozin on Renal Endpoints in Adult Participants With Type 2 Diabetes  
94 Mellitus (CANVAS-R)<sup>8</sup>; 3) the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the  
95 Incidence of Cardiovascular Events (DECLARE-TIMI 58)<sup>9</sup>; 4) the Cardiovascular Outcomes  
96 Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular  
97 Disease (VERTIS-CV)<sup>24</sup>; 5) the Effect of Sotagliflozin on Cardiovascular Events in Patients  
98 With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF)<sup>22</sup>; and the 6) Effect of

99 Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and  
100 Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED)<sup>23</sup>. Trial eligibility was  
101 confirmed by 2 independent reviewers (J.P.F., A.C.O.), data extraction was performed by  
102 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  
103 also cross-checked the RCTs selected to the present analysis with other recently published  
104 meta-analyses and the concordance was perfect<sup>12, 13, 25</sup>. The Evaluation of the Effects of  
105 Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic  
106 Nephropathy (CREDENCE)<sup>10</sup>, which was primarily a kidney outcomes trial, did not report  
107 treatment effects in insulin subgroups and was not included in the analysis. A detailed  
108 description of each individual trial is provided in the respective main reports as above  
109 referenced.

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

## 112 **Outcomes**

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

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

### 131 **Statistical analysis**

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



147 trim-and-fill method. The statistical analyses were performed using Stata® software version  
148 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp  
149 LLC.) and the package *meta*. The risk of bias in randomised trials was assessed with the RoB  
150 2 tool<sup>27</sup>. Two-sided P values <0.05 were considered significant.

151

## 152 **Results**

153 The characteristics of the patients from the RCTs included in this analysis are depicted in the  
154 *Table 2*. A total of 54374 patients with T2D were included in the analysis, of which 26551  
155 (48.8%) were treated with insulin. The mean age of all trial participants was 66 years, 19702  
156 (36.2%) were women, and 43806 (80.6%) were Caucasian. The number of participants per  
157 trial ranged from 1222 in SOLIST-WHF to 17160 in DECLARE-TIMI 58. The median follow-up  
158 ranged from 0.8 years in SOLIST-WHF to 4.2 years in DECLARE-TIMI 58 (*Table 2*). The  
159 assessment of risk of bias by visual inspection of funnel plots and quantitative assessment  
160 suggested no indication of publication bias. The risk of bias in randomized trials as assessed  
161 by the RoB 2 tool was low.

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

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

167 For the composite outcome of myocardial infarction, stroke or cardiovascular death  
168 in patients without insulin treatment, the HR (95%CI) for the effect of SGLTi vs. placebo was  
169 0.93 (0.81-1.05), with moderate heterogeneity (I<sup>2</sup> =49.2%, Q statistic P =0.11). In insulin-  
170 treated patients, the HR (95%CI) for the effect of SGLTi vs. placebo was 0.88 (0.82-0.95),

171 without evidence of heterogeneity ( $I^2 = 0.0\%$ , Q statistic  $P = 0.91$ ). The pooled effect  
172 evidenced a 10% reduction of 3P-MACE with SGLTi (HR 0.90, 95%CI 0.85-0.96), without  
173 significant interaction between subgroups of insulin (yes vs. no), interaction  $P = 0.53$ . *Figure*  
174 *1, panel A*.

175 For the composite outcome of HF hospitalisation or cardiovascular death  
176 (cardiovascular death alone in the EMPA-REG OUTCOME trial) in patients without insulin  
177 treatment, SGLTi reduced the event rate by 23% (HR 0.77, 95%CI 0.61-0.92) but the  
178 treatment effect was heterogeneous ( $I^2 = 66.8\%$ , Q statistic  $P = 0.02$ ). In insulin-treated  
179 patients, SGLTi significantly reduced HF hospitalisation or cardiovascular death (HR 0.77,  
180 95%CI 0.68-0.86) without significant heterogeneity ( $I^2 = 31.7\%$ , Q statistic  $P = 0.25$ ). The  
181 pooled effect evidenced a 23% reduction of HF hospitalisations or cardiovascular death with  
182 SGLTi (HR 0.77, 95%CI 0.68-0.85), without significant interaction between subgroups of  
183 insulin (yes vs. no), interaction  $P = 0.98$ . *Figure 1, panel B*.

184

## 185 **Discussion**

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

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

195 hypoglycemic episodes and mortality<sup>28, 29</sup>. Furthermore, insulin-treatment may lead to  
196 weight gain, fluid retention, higher blood pressure, and increase the risk of hypoglycemia  
197 without reducing cardiovascular complications<sup>30-32</sup>. Patients with T2D who require insulin,  
198 usually have a poor glycemic and metabolic control, and have a high risk of cardiovascular  
199 complications, including HF hospitalisations and death from cardiovascular causes<sup>4, 33</sup>. For  
200 these reasons, there is an urgent need to reduce the risk profile of insulin-treated patients,  
201 while also improving their metabolic components, reduce weight, and decrease the burden  
202 of hospitalisations and adverse cardiovascular outcomes. Inhibitors of the sodium glucose  
203 co-transporter have many beneficial effects beyond glucose control, and, indeed, may help  
204 to reduce weight, control blood pressure, limit sodium retention, reduce hospitalisations  
205 (HF-related in particular) and cardiovascular death, counteracting the negative effects of  
206 insulin. As shown in the present study, SGLTi reduce cardiovascular complications regardless  
207 of insulin treatment. However, the treatment effect was more homogeneous among insulin-  
208 treated patients leading to consistent reductions of cardiovascular complications,  
209 comprising HF hospitalisations and cardiovascular death across multiple populations with  
210 T2D, including patients with chronic kidney disease and worsening heart failure<sup>7-9, 22-24</sup>. This  
211 effect was seen regardless of the type of SGLTi i.e., the SGLT1/2 inhibitor sotagliflozin and  
212 the remainder SGLT2 inhibitors had similar effects to reduce cardiovascular events  
213 regardless of insulin treatment, but with a more homogeneous effect among insulin-treated  
214 patients.

215           A recently published meta-analysis showed that in placebo-controlled RCTs SGLT2i  
216 reduced cardiovascular events and HF hospitalisations, independently of the presence of  
217 atherosclerotic cardiovascular disease, kidney function, and glycated hemoglobin levels<sup>25</sup>. It  
218 is likely that insulin-treated patients also had higher burden of cardiovascular disease, worse

219 kidney and higher glycated hemoglobin levels; however, beyond the higher cardiovascular  
220 risk (with potentially larger treatment benefit), insulin-treated patients may experience a  
221 more consistent benefit from SGLTi due to the effects and mechanisms associated with  
222 insulin administration, such as weight gain and sodium retention that may be  
223 counterbalanced by SGLTi. Supporting this hypothesis, smaller “mechanistic” studies testing  
224 the effects of SGLT2i among insulin-treated patients also showed a beneficial effect of these  
225 agents. For example, a subsample of patients enrolled in the CANVAS-Program and receiving  
226 insulin at baseline were randomized to receive placebo (n =690), canagliflozin 100 mg (n  
227 =692), or canagliflozin 300 mg (n =690). Compared with the placebo both canagliflozin doses  
228 reduced glycated hemoglobin, fasting plasma glucose, body weight and blood pressure<sup>15</sup>.  
229 Similar findings were observed with dapagliflozin and empagliflozin in patients with  
230 inadequately controlled T2D on basal insulin<sup>16, 18</sup> and obese difficult-to-treat patients with  
231 T2D requiring high doses of insulin<sup>17</sup>. It should be noted, that SGLT2i also reduced insulin  
232 requirements without increased risk of hypoglycemia<sup>17-19</sup>.

### 233 **Limitations**

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

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

250

### 251 **Conclusions**

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

256

### 257 **Disclosures**

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

260

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381 Figure 1. Treatment effects by insulin treatment subgroups

382 (A) Myocardial infarction, stroke or cardiovascular death

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384 (B) Heart failure hospitalisation or cardiovascular death

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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.