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João Pedro Ferreira, Ana Cristina Oliveira, Francisca Saraiva, Francisco
Vasques-Nóvoa, Adelino Leite-Moreira

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

2

3 Authors:

4 João Pedro Ferreira, MD, PhD^{1,2}; Ana Cristina Oliveira, Msc²; Francisca A. Saraiva, Msc²;

5 Francisco Vasques-Nóvoa, MD, Msc²; Adelino Leite-Moreira, MD, PhD²

6

7 Affiliations :

8 ¹ Université de Lorraine, Inserm, Centre d'Investigations Cliniques, - Plurithématique 14-33,

9 and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists),

10 Nancy, France.

11 ² Cardiovascular Research and Development Center, Department of Surgery and Physiology,

12 Faculty of Medicine of the University of Porto, Porto, Portugal.

13

14 Contact to:

15 Dr João Pedro Ferreira

16 Centre d'Investigation Clinique 1433 module Plurithématique

17 CHRU Nancy - Hopitaux de Brabois, Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu

18 4 rue du Morvan, 54500 Vandoeuvre les Nancy

19 Tel : +33 (0) 3 83 15 73 15

20 Fax : +33 (0) 3 83 15 73 24

21 Mail: j.ferreira@chru-nancy.fr

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 (I² =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 (I² =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 interaction P=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 (I²
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 (I² =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 interaction P=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 death¹. 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)²⁻⁴. 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^{5, 6}.

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 diabetes⁷⁻¹¹. The reduction
63 of hospitalisations due to HF is particularly striking with these agents^{12, 13}. 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 episodes¹⁴⁻²⁰.

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 guideline²¹. 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 22nd 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^{22, 23}. 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)⁷; 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)⁸; 3) the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the
95 Incidence of Cardiovascular Events (DECLARE-TIMI 58)⁹; 4) the Cardiovascular Outcomes
96 Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular
97 Disease (VERTIS-CV)²⁴; 5) the Effect of Sotagliflozin on Cardiovascular Events in Patients
98 With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF)²²; 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)²³. 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^{12, 13, 25}. The Evaluation of the Effects of
105 Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic
106 Nephropathy (CREDENCE)¹⁰, 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 ²⁶. 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 tool²⁷. 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 (I² =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^{28, 29}. Furthermore, insulin-treatment may lead to
196 weight gain, fluid retention, higher blood pressure, and increase the risk of hypoglycemia
197 without reducing cardiovascular complications³⁰⁻³². 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^{4, 33}. 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^{7-9, 22-24}. 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 levels²⁵. 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 pressure¹⁵.
229 Similar findings were observed with dapagliflozin and empagliflozin in patients with
230 inadequately controlled T2D on basal insulin^{16, 18} and obese difficult-to-treat patients with
231 T2D requiring high doses of insulin¹⁷. It should be noted, that SGLT2i also reduced insulin
232 requirements without increased risk of hypoglycemia¹⁷⁻¹⁹.

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**

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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.