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CORRESPONDENCE

Safety and efficacy of early initiation of sodium-glucose cotransporter-2 inhibitors after an acute coronary syndrome event: a meta-analysis of randomized controlled trials

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Although remarkable progress has been made in the management of acute coronary syndromes (ACS), current rates of adverse cardiovascular events remain high, fuelling the need for new therapies.[1] Sodium-glucose cotransporter-2 inhibitors (SGLT2i) represent a well-established therapy for chronic heart failure (HF) regardless of ejection fraction values and have demonstrated encouraging results even in patients hospitalized for acute HF.[2] Nevertheless, their role in the early phase after ACS remains to be determined. In order to perform a meta-analysis of randomized controlled trials (RCTs) on the latter topic, we systematically reviewed all the available publications according to the current PRISMA guidelines[3] and included studies comparing SGLT2i vs. control in patients with a recent ACS. The Q Cochran test and Higgins I^2 statistics were calculated to estimate heterogeneity among the included studies. Risk ratios (RR) with 95% confidence intervals (CIs) by using random effect model were calculated using Stata 18 (64-bit; StataCorp, College Station, TX). *P*-values <0.05 (two-tailed) were considered statistically significant. Publication bias and meta-regressions were performed if the number of studies was ≥ 10.[3] Efficacy endpoints were all-cause death, death from cardiovascular causes, recurrent myocardial infarction, and total HF hospitalizations. Safety endpoints were serious adverse events, worsening renal failure, volume depletion, urinary and genital tract infections, ketoacidosis, and hypoglycaemia. A total of 11 253 patients from six RCTs were included.[4–9] The timing of initiation of SGLT2i therapy in relation to the ACS episode varied across these studies. In the EMBODY and SOCOGAMI trials,[4,6] SGLT2i were started after 2 weeks and within 6 months from the index event, respectively, while in the other RCTs, the median time of initiation was 3 days [inter-quartile range (IQR) 3–4.5 days].[5,7–9] Four RCTs used empagliflozin and two utilized dapagliflozin. Median follow-up (FUP) was 26 weeks (IQR 18–59 weeks). Early initiation of SGLT2i significantly reduced the rate of total HF hospitalizations (RR 0.74; 95% CI 0.62–0.90; $I^2 = 0\%$) (*Figure 1a*), but not all-cause death (RR 0.99; 95% CI 0.83–1.2; $I^2 = 0\%$) (*Figure 1b*), nor death from cardiovascular causes (5 RCTs; RR 1.03; 95% CI 0.83–1.28; $I^2 = 0\%$), and recurrent myocardial infarction (4 RCTs; RR 1.32; 95% CI 0.83–2.09; $I^2 = 12.27\%$). The benefit of HF hospitalizations remained consistent even considering those RCTs including patients without a previous HF diagnosis and when specifically evaluating the first hospitalization for HF as an endpoint (i.e. DACAMI, DAPA-MI, and EMPACT-MI) (RR 0.79; 95% CI 0.64–0.98; $I^2 = 0\%$). The leave-one sensitivity analysis showed that the effect of SGLT2i on first and total HF hospitalizations was mainly driven by the results of the EMPACT-MI. In terms of safety, early implementation of SGLT2i did not increase the incidence of serious adverse events (RR 1.01; 95% CI 0.93–1.1; $I^2 = 8.71\%$) (*Figure 1c*), worsening renal failure (3 RCTs; RR 0.73; 95% CI 0.5–1.09; $I^2 = 0\%$), volume depletion (3 RCTs; RR 0.88; 95% CI 0.56–1.37; $I^2 = 0\%$), urinary tract infections (4 RCTs; RR 1.7; 95% CI 0.73–3.95; $I^2 = 0\%$), genital infections (3 RCTs; RR 2.58; 95% CI 0.66–10.05; $I^2 = 0\%$), ketoacidosis (3 RCTs; RR 1.51; 95% CI 0.25–9.27; $I^2 = 0\%$), and hypoglycaemia (4 RCTs; RR 0.85; 95% CI 0.27–2.66; $I^2 = 0\%$).

Collectively, the current meta-analysis shows that an early initiation of SGLT2i after ACS is safe and able to reduce the risk of readmissions for HF. However, this finding should be considered hypothesis-generating for several reasons. First, none of the studies included in the analyses had 'HF hospitalization' as the primary endpoint. Second, the pooled estimate of this meta-analysis was mainly driven by a single RCT (i.e. EMPACT-MI) with the longest FUP time (i.e. 71.6 weeks). Notably, compared with DAPA-MI, patients enrolled in EMPACT-MI exhibited a higher burden of cardiovascular risk factors and diseases (i.e. prior myocardial infarction, multi-vessel disease, and type 2 diabetes mellitus), and were more likely to undergo fibrinolysis as first reperfusion strategy,[8,9] resulting in a higher overall rate of HF hospitalizations, which allowed to detect a statistically significant

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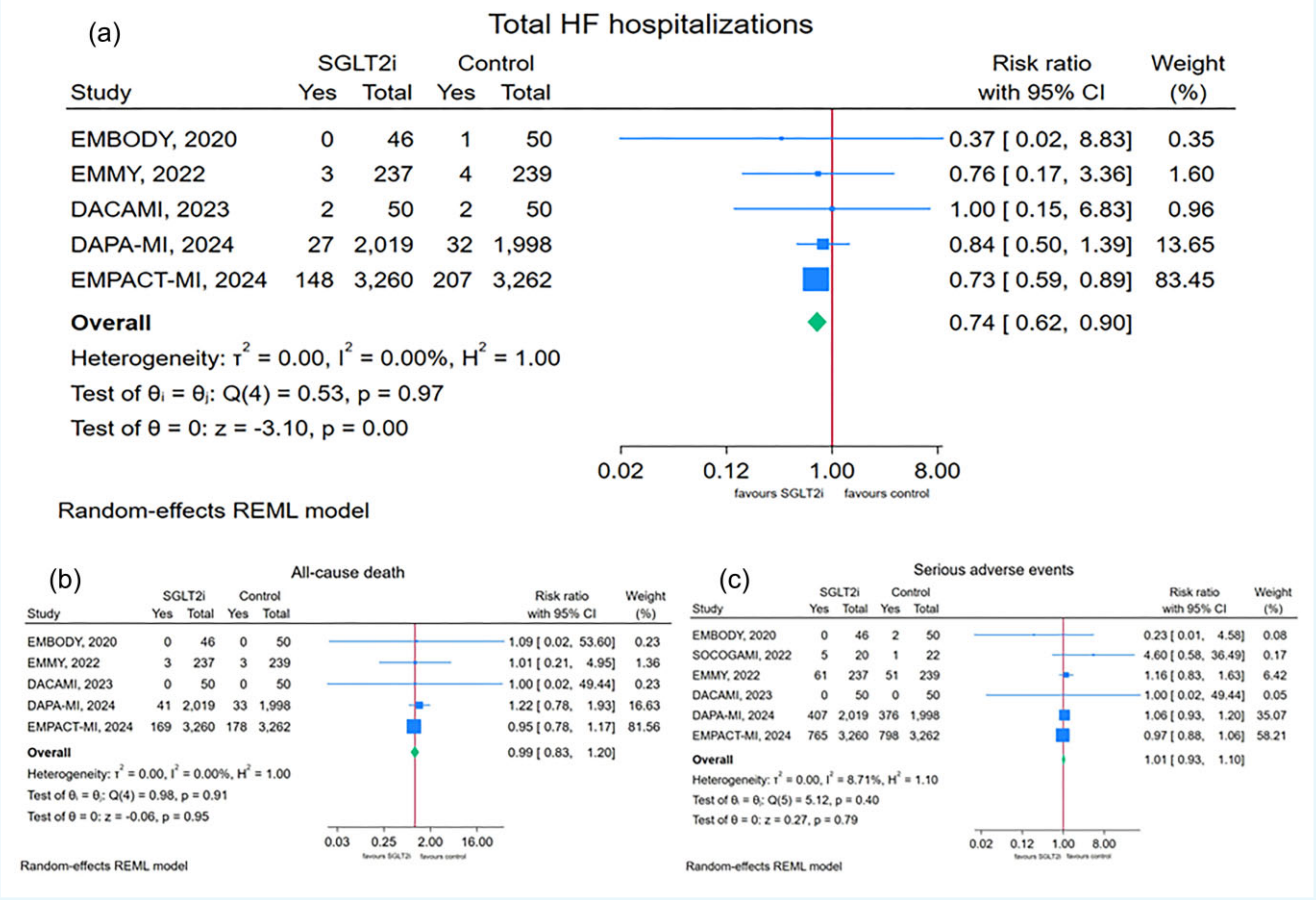

Figure 1 Forest plot for total HF hospitalizations (1a), all-cause death (1b), and serious adverse events (1c). The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% confidence intervals (CIs). The open diamond represents the pooled relative risk, and its width represents its 95% CI. Abbreviations: HF, heart failure.

result. Third, the pathophysiological mechanism by which SGLT2i provides benefit in this clinical setting remains to be elucidated. In some of the included studies, these drugs showed a beneficial effect on post-infarction remodelling, as evidenced by a significant reduction in NT-proBNP levels and an increase in left ventricular ejection fraction, as well as a decrease in body weight, probably related to their natriuretic and glycosuric properties.[4–7] Consistently, the administration of SGLT2i in preclinical animal models of ACS was associated with reduction of the infarct size,[10] eventually explaining the beneficial effects of these compounds on HF occurrence. Another mechanism of action could be represented by the known anti-inflammatory effects of SGLT2i, as inflammation is associated with an increased risk of developing HF after an ischaemic event.[11–13] However, none of the included RCTs assessed the inflammatory status of the patients enrolled.

Nevertheless, it is conceivable that EMPACT-MI patients had more baseline inflammation compared with DAPA-MI patients, due to the higher prevalence of conditions associated with a pro-inflammatory milieu such as diabetes, renal impairment, and previous myocardial infarction. Dedicated post-hoc analyses could address this point. Of note, the absence of benefit in terms of cardiovascular death or recurrent myocardial infarction may reflect a true lack of benefit or, more probably, the fact that available RCTs were underpowered to assess differences for these outcome measures as SGLT2i have been shown to reduce the risk of myocardial infarction and cardiovascular death in other clinical settings.[14,15] The pathophysiological mechanism is not well established, but preclinical and clinical studies demonstrated promising results of SGLT2i in stabilizing or inducing regression of atherosclerotic plaque, unveiling a critical involvement of the SGLT2 pathway in the progression of the atherosclerotic disease.[16–18]

Overall, the data presented in this meta-analysis again underscores how an early administration of SGLT2i in patients with ACS is safe, allowing us to glimpse a new era in the treatment of HF from the earliest stages of disease development. Further studies are needed to fully legitimize the use of these drugs in such a clinical setting.

Conflict of interest: Dr Savarese reports grants and personal fees from CSL Vifor, Boehringer Ingelheim, AstraZeneca, Servier, Novartis, Cytokinetics, Pharmacosmos, and personal fees from Roche, Abbott, Edwards Lifescience, Medtronic, TEVA, INTAS and grants from Boston Scientific, Merck, Bayer, all outside the submitted work. The remaining authors have no conflicts of interest to declare for the present work.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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