Updated Meta-analysis Assessing the Effect of Sodium-Glucose Co-transporter-2 Inhibitors on Surrogate End points in Patients With Heart Failure With Reduced Ejection Fraction

Type 2 diabetes mellitus (T2DM) represents a major health problem,[1] contributing to 11.3% of deaths globally.[2] Cardiovascular disease still affects a large proportion of patients,[3] despite the fact that incidence rates of cardiovascular outcomes have decreased over the last 2 decades.[4] Heart failure (HF) is a main contributor of cardiovascular morbidity and mortality in patients with T2DM,[5] who feature an almost two-fold increase in the risk of HF, with women having a greater risk compared with men.[6] HF with reduced ejection fraction >(HFrEF), defined as the presence of left ventricular ejection fraction lower than 40%, is associated with significant 5-year mortality equal to 75.3%, along with high re-admission rates for any cardiovascular event or worsening of HF and a median survival time of 2.1 years.[7] According to recent observational data, prevalence of T2DM in patients with HFrEF is estimated to be 40.2%, representing an independent risk factor for 1-year all-cause mortality and HF re-admission.[8] Therefore, it may be deduced that this concomitance requires appropriate therapeutic management and meticulous follow-up.

Sodium-glucose co-transporter 2 (SGLT-2) inhibitors, a novel class of antidiabetic drugs, has revolutionized the management of patients with T2DM and cardiovascular disease during the last decade, after the publication of the hallmark cardiovascular outcome trials, namely the Empagliflozin Cardiovascular Outcome Event Trial in T2DM Patients−Removing Excess Glucose (EMPA-REG OUTCOME),[9] the Canagliflozin Cardiovascular Assessment Study (CANVAS),[10] and the Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 (DECLARE−TIMI 58) trial.[11] Of course, we have to admit that the most recently published trial, VERTIS CV, utilizing ertugliflozin, failed to show any benefit regarding the prespecified primary composite cardiovascular outcome, raising some questions on the so-called "class effect."[12] Significantly, SGLT-2 inhibitors have recently provided significant cardiovascular benefits in patients with HFrEF irrespective of T2DM status, as demonstrated in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and the EMPEROR-Reduced trials.[13, 14] Therefore, we sought to determine the effect of SGLT-2 inhibitors on surrogate end points in patients with HFrEF with or without concomitant T2DM.

We identified the hallmark cardiovascular outcome trials and we searched the 2 major electronic databases, PubMed and Cochrane Central Register of Controlled Trials, for subanalyses of these trials according to HF status of enrolled participants at baseline.

Two independent reviewers (D.P. and C.P.) extracted the data from the eligible reports, by using a pilot tested, data extraction form. We assessed the following surrogate end points: hospitalization for HF (primary efficacy outcome), cardiovascular death, all-cause death ,and the composite of hospitalization for HF or cardiovascular death. We did not assess safety outcomes. We preferred utilizing data from intention-to-treat analyses.

As we assessed only dichotomous variables, differences were calculated with the use of odds ratio (OR), with 95% confidence interval (CI), after implementation of the Mantel-Haenszel random effects formula. Statistical heterogeneity in studies was assessed by using I^2 statistics. Heterogeneity was considered to be low if I^2 was between 0% and 25%, moderate if I^2 was between 25% and 50%, or high if I^2 was greater than 75%.[15] All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.3 software.[16]

Two independent reviewers (D.P. and A.K.) assessed the quality of the included RCTs, by using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) for the primary efficacy outcome.[17] Discrepancies between reviewers were solved by discussion, consensus or arbitration by a third senior reviewer (M.D.).

Besides the dedicated HFrEF trials, only researchers of the DECLARE-TIMI 58 trial provided data regarding the effect of dapagliflozin on "hard" outcomes in patients with HFrEF.[18] Unfortunately, trialists of the EMPA-REG OUTCOME trial and the CANVAS program did not perform subgroup analyses according to HFrEF or HF with preserved ejection fraction (HFpEF) status at baseline.[19, 20] Therefore, we pooled data from the DAPA-HF and the EMPEROR-Reduced trials, along with data from the subanalysis of the DECLARE-TIMI 58 trial in a total of 9,145 patients with HFrEF. Risk of bias is considered as low across all included studies.

SGLT-2 inhibitor treatment resulted in a significant decrease in the odds for HF hospitalization compared with placebo, equal to 31% (OR = 0.69, 95% CI; 0.61 to 0.78, $I^2 = 0\%$), as shown in Figure 1. In addition, SGLT-2 inhibitor treatment decreased the odds for cardiovascular death by 18% (OR = 0.82, 95% CI; 0.68 to 0.99, $I^2 = 40\%$), as shown in Figure 1. Odds for the composite outcome of cardiovascular death or HF hospitalization was significantly decreased by 28% with SGLT-2 inhibitor treatment (OR = 0.72, 95% CI; 0.65 to 0.80, $I^2 = 0\%$), as depicted in Figure 1. Finally, SGLT-2 inhibitor treatment resulted in marginally nonsignificant decrease in the odds for all-cause death by 17% (OR = 0.83, 95% CI; 0.68 to 1.00, $I^2 = 53\%$), as shown in Figure 1.

Our meta-analysis confirms the results reported by Zannad et al.[21] in their recent meta-analysis of the DAPA-HF and the EMPEROR-Reduced trials. However, the latter meta-analysis did not include data from the HFrEF arm of the DECLARE-TIMI 58 trial, which were incorporated in our updated meta-analysis.

In conclusion, SGLT-2 inhibitor treatment provides substantial cardiovascular benefits in patients with HFrEF, decreasing the odds for HF hospitalization and cardiovascular death, while it might reduce the odds for all-cause death, compared with placebo. These significant findings provide new insights into the therapeutic management of this sensitive population regardless of T2DM status and might influence treatment decisions, as reflected in a recent position paper by the European Society of Cardiology and the Heart Failure Association.[22]

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have

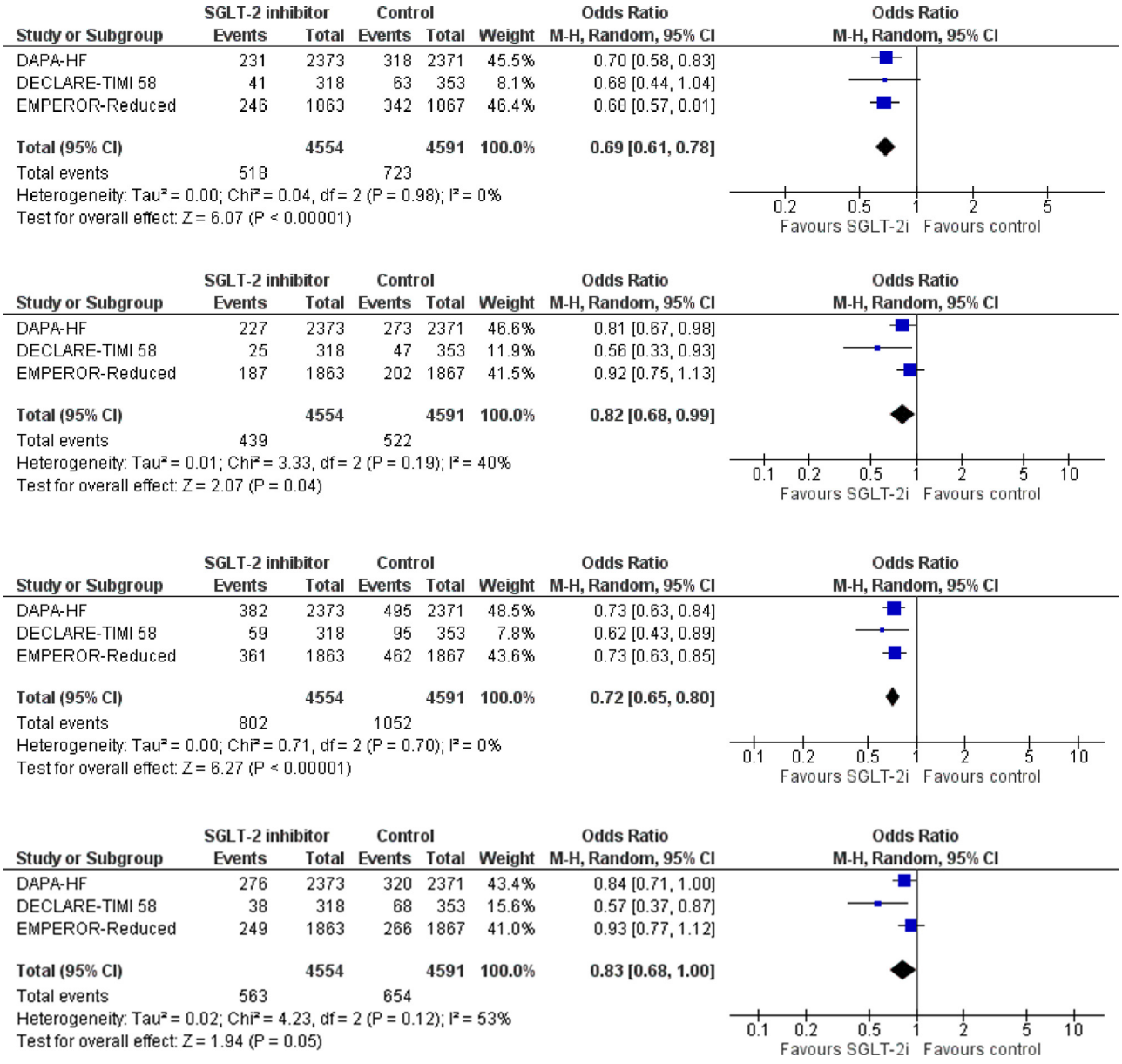

Figure 1. Effect of SGLT-2 inhibitors compared to control on: (A) hospitalization for heart failure, (B) cardiovascular death, (C) hospitalization for heart failure or cardiovascular death, and (D) all-cause death.

appeared to influence the work reported in this study.

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Next-Generation Primary Atherosclerotic Cardiovascular Risk Prediction Tool. Are Nonmodifiable Risk Factors Relevant in the Equation?

Atherosclerotic cardiovascular disease (ASCVD) continues to be a major cause of morbidity and mortality especially in developed countries. Most of these ASCVD events occur in individuals without prior history of the disease. As documented by Dr Geoffrey Rose, a large number of individuals exposed to low risk will generate more cases than a small number of individuals exposed to high risk. Thus a focus on primary ASCVD prevention, which contributes mostly to our annual ASCVD events, has been emphasized in societal documents and guidelines. Current guidelines recommend behavioral and lifestyle changes and medications to minimize ASCVD risk.[1]

The targeting and treatment of traditional ASCVD risk factors including age, male gender, race/ethnicity, blood pressure, lipids levels, diabetes mellitus, and cigarette smoking forms the basis of primary ASCVD prevention and in recent times have been incorporated into risk prediction tools for assessing an individual's future risk of having a clinical ASCVD event.[2] Clinicians are advised to use these risk prediction tools to calculate the 10-year ASCVD risk, discuss this risk with their patients and then come up with a plan to minimize this risk. Current data show that these risk prediction tools have suboptimal discrimination for predicting future ASCVD events.[3] Hence other nontraditional risk factors have been suggested to help refine the calculated ASCVD risk using the risk prediction tools. Even though current data show that targeting some of the ASCVD risk factors results in a reduction in future ASCVD events. It is fair to say that till date the efficacy of an approach that employs these ASCVD risk prediction tools and other nontraditional risk factors to reduce primary ASCVD events has not been tested. In addition, the role and contribution of nonmodifiable ASCVD risk factors such as age, male gender, race/ethnicity, and their possible interactions with the known treatment effects of modifiable risk factors is less known.

In communicating ASCVD risk during the recommended clinician-patient discussion by current guidelines, clinicians often communicate the calculated 10-year risk to the patient without clearly articulating how much of the calculated risk is actually modifiable with interventions. This makes the clinician-patient discussion incomplete. Data from one of the well-