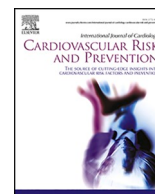




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Meta-analysis addressing the impact of sodium-glucose Co-transporter-2 inhibitors on the risk for atrial fibrillation among individuals with heart failure with preserved ejection fraction

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The formerly published “2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure” suggest that sodium-glucose co-transporter-2 (SGLT-2) inhibitors can be beneficial in reducing heart failure (HF) hospitalizations and cardiovascular mortality among subjects with HF with preserved left ventricular ejection fraction (HFpEF) [class of recommendation: 2a] [1]. In a recently published, updated meta-analysis of the dedicated HF trials across the range of left ventricular ejection fraction it was demonstrated that SGLT-2 inhibitors substantially decrease the risk for cardiovascular death and HF hospitalization, a finding that supports their new role as a foundational therapy in HF [2].

It has been demonstrated that SGLT-2 inhibitors produce a significant decrease in the risk for atrial fibrillation (AF), equal to 38% compared to placebo, among subjects with HF with reduced left ventricular ejection fraction (HFrEF) [3]. AF in individuals with HFpEF has been shown to significantly increase the risk for HF hospitalization, compared to their counterparts without AF [4]. In addition, AF is associated with significantly increased risk for progressive HF death in the same population [5]. Therefore, we sought to determine whether SGLT-2 inhibitors affect the risk for incident AF among subjects with HFpEF, exerting an additional cardiovascular benefit.

We searched PubMed database and clinicaltrials.gov from inception to November 1, 2022, for randomized controlled trials (RCTs) enrolling adult subjects with HFpEF, addressing the cardiovascular efficacy and safety of SGLT-2 inhibitors compared to placebo or active control. We applied the following search strategy: (((((((SGLT-2 inhibitor) OR (empagliflozin)) OR (dapagliflozin)) OR (canagliflozin)) OR (ertugliflozin)) OR (sotagliflozin)) OR (ipragliflozin)) OR (luseogliflozin)) OR (bexagliflozin)) OR (remogliflozin)) OR (tofogliflozin)) OR (licogliflozin) AND (heart failure with preserved ejection fraction) OR (HFpEF).

We did not impose any filter regarding study setting, sample size, study duration or publication language. We set as primary efficacy outcome the effect of SGLT-2 inhibitors compared to control on the risk for incident AF.

Three independent reviewers (D.P., T.M. and A.D.) extracted the data from the eligible reports, by using a pilot tested, data extraction form. As we assessed only a dichotomous variable, difference was

calculated with the use of risk ratio (RR), with 95% confidence interval (CI), after implementation of the Mantel-Haenszel (M – H) random effects formula. Statistical heterogeneity among studies was assessed by using I^2 statistics. Analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.3 software. Publication bias was assessed visually by the inspection of the corresponding funnel plot.

In total, we pooled data from 5 eligible RCTs, 3 of which have already been published [6–10]. SGLT-2 inhibitors, compared to placebo, resulted in a non-significant effect on the risk for incident AF (RR = 1.19, 95% CI; 0.94–1.50, I^2 = 0%, p = 0.14), as depicted in Fig. 1. Subgroup analysis by the type of utilized SGLT-2 inhibitor revealed that neither dapagliflozin (RR = 1.26, 95% CI; 0.87–1.84, I^2 = 0%, p = 0.22) nor empagliflozin (RR = 1.14, 95% CI; 0.85–1.53, I^2 = 0%, p = 0.37) had a significant effect on the risk for AF. Exclusion of the 2 unpublished RCTs did not have a significant impact on the generated effect on the risk for AF (RR = 1.18, 95% CI; 0.94–1.50, I^2 = 0%). Inspection of the corresponding funnel plot did not reveal any asymmetry, indicative of publication bias.

We consider as main limitation of the present analysis the lack of access to individual participants' data, to perform subgroup analyses according to baseline characteristics of interest (medication, medical history, etc.). In addition, 2 out of 5 eligible RCTs are unpublished, and thus may introduce some form of bias. Of course, it has to be admitted that none of the eligible RCTs utilized Holter monitoring for the detection of AF, and thus some cases may have been missed.

In conclusion, the present analysis failed to demonstrate that SGLT-2 inhibitors have a beneficial effect by decreasing the risk for incident AF among individuals with HFpEF, similar to that seen with this drug class in the HFrEF population. Further, dedicated RCTs in the HFpEF population are required to shed further light on this important research question.

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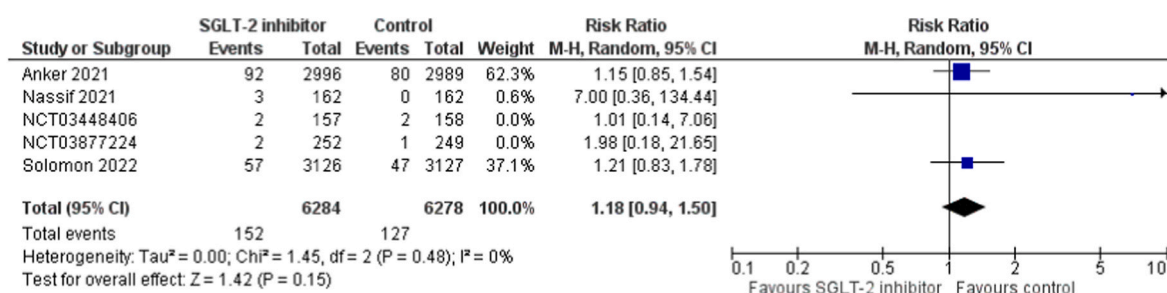


Fig. 1. Effect of SGLT-2 inhibitors compared to control on the risk for AF among individuals with HFpEF.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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