

# Side effects and treatment initiation barriers of sodium–glucose cotransporter 2 inhibitors in heart failure: a systematic review and meta-analysis

Davor Vukadinović<sup>1\*</sup>, Amr Abdin<sup>1</sup>, Stefan D. Anker<sup>2</sup>, Giuseppe M.C. Rosano<sup>3</sup>, Felix Mahfoud<sup>1</sup>, Milton Packer<sup>4,5</sup>, Javed Butler<sup>6</sup>, and Michael Böhm<sup>1</sup>

<sup>1</sup>Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Universität des Saarlandes, Homburg/Saar, Germany; <sup>2</sup>Department of Cardiology & Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK), partner site Berlin, Charité-Universitätsmedizin Berlin (Campus CVK), Berlin, Germany; <sup>3</sup>Centre for Clinical and Basic Research, IRCCS San Raffaele Roma, Rome, Italy; <sup>4</sup>Baylor Heart and Vascular Institute, Baylor University Medical Center, Dallas, TX, USA; <sup>5</sup>Imperial College London, London, UK; and <sup>6</sup>Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

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## Aims

Physicians are sometimes reluctant to initiate guideline-directed therapy in patients with heart failure and reduced ejection fraction (HFrEF) due to concerns of adverse events. We explored the risk of hypotension, volume depletion, and acute kidney injury (AKI) on sodium–glucose cotransporter 2 (SGLT2) inhibitors in HFrEF populations.

## Methods and results

We determined summary risk ratios (RRs) by conducting a meta-analysis on reported aforementioned adverse events on SGLT2 inhibitors from randomized controlled trials. We explored robustness of meta-analyses by computing fragility and/or reverse fragility index (FI or RFI) and its corresponding fragility quotient (FQ or RFQ) for each outcome. A total of 10 050 patients with HFrEF entered the final meta-analysis. Hypotension was reported in 4.5% (219/4836) on SGLT2 inhibitors and in 4.1% (202/4846) on placebo (RR 1.09, 95% confidence interval [CI] 0.91–1.31,  $p = 0.36$ ). An RFI of 21 and RFQ of 0.002 suggest robust findings for hypotension. Volume depletion occurred in 9.4% (473/5019) on SGLT2 inhibitors and in 8.7% (438/5031) on placebo (RR 1.07, 95% CI 0.95–1.21,  $p = 0.25$ ), respectively. RFI of 19 and RFQ of 0.001 suggest moderately robust findings for volume depletion. AKI was reported in fewer patients (1.9% [95/4888]) on SGLT2 inhibitors than on placebo (2.8% [140/4899]) providing lower incidence of AKI (RR 0.69, 95% CI 0.51–0.93,  $p = 0.02$ ). FI of 14 and RFQ of 0.001 suggest moderately robust findings for AKI.

## Conclusion

Sodium–glucose cotransporter 2 inhibitor therapy is not associated with a clinically relevant risk of hypotension and volume depletion. Its use reduces the risk of AKI. This analysis supports current guideline recommendations on early use of SGLT2 inhibitors.

## Keywords

Sodium–glucose cotransporter 2 inhibitors • Heart failure • Adverse events • Renal function

## Introduction

The beneficial effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors on outcomes of patients with cardiovascular diseases with type 2 diabetes mellitus (DM) have been established in

randomized controlled clinical trials.<sup>1,2</sup> As heart failure hospitalizations were reduced in DM,<sup>1,2</sup> the efficacy of SGLT2 inhibitors have also been explored in patients with heart failure and reduced ejection fraction (HFrEF) with and without DM.<sup>3,4</sup> These studies established SGLT2 inhibitors as a cornerstone in HFrEF treatment

\*Corresponding author. Universität des Saarlandes, Homburg/Saar, Saarland University, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Kirrberger Strasse, D-66421 Homburg, Germany. Email: davor.vukadinovic@uks.eu

as recommended by the current guidelines of the European Society of Cardiology.<sup>5</sup> SGLT2 inhibitors induce glucosuria associated with water and sodium excretion, leading to blood pressure (BP) reduction in hypertensive patients with diabetes.<sup>6</sup> Subsequently, lower BP in HFrEF patients could result in reduced renal perfusion and accordingly worsening of renal function. Of note, HFrEF patients with low BP have increased risk of death and hospitalization compared with those with higher BP.<sup>7–9</sup> Concerns have been expressed that SGLT2 inhibitors may further reduce BP and kidney perfusion by sodium excretion in HFrEF patients, who frequently present with low BP, may discourage physicians to administer these drugs in patients at risk due to concerns of side effects, mainly low BP or acute kidney injury (AKI) despite unequivocal evidence of risk reduction concerning mortality and heart failure hospitalization. We focused on frequent cardiovascular barriers to implement therapy such as hypotension, AKI and volume depletion. Hence, we explored systematically the rate, risk and robustness of the occurrence of these effects, that is, hypotension, volume depletion and AKI, in HFrEF patients from randomized controlled clinical trials with SGLT2 inhibitors.

## Methods

### Search strategy and selection criteria

We conducted a systematic review of the published randomized controlled trials (RCTs) in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses statement.<sup>10</sup> The analysis was registered in INPLASY (doi: [10.37766/inplasy2022.2.0012](https://doi.org/10.37766/inplasy2022.2.0012)). The search strategy was developed in MEDLINE and Embase via OVID® (online supplementary Figure S1), using the following keywords and Medical Subject Headings (MeSH) terms: (SGLT2 inhibitor OR empagliflozin OR dapagliflozin OR canagliflozin OR ertugliflozin OR sotagliflozin AND heart failure OR left ventricular dysfunction AND RCT). We included the main publications of major studies. The search was restricted to full-text articles published in English language between 6 November 2015 and 31 October 2021. Of note, 6 November 2015 was chosen as it corresponds to the publication of one of the landmark trials EMPA-REG OUTCOME.<sup>1</sup> Two reviewers (D.V. and A.A.) reviewed the full-texts and used the same template to extract data relevant to the analysis. Furthermore, we screened the reference list of the European Association of Cardiology guidelines for diabetes, acute myocardial infarction and heart failure. Randomized, placebo-controlled, event-driven, cardiovascular or renal outcome clinical trials that investigated the effects of SGLT2 inhibitors in patients with heart failure with or without type 2 DM were considered eligible for inclusion. There was no limit regarding the number of patients in potentially acceptable studies. Finally, data from non-randomized trials, registries or patients with type 1 DM were not considered eligible for inclusion. The decision to include articles in the final analysis was made after consultation with a third investigator (M.B.). We used reference manager software (Zotero) for duplicate removal and data management.

### Data analysis

Two authors (D.V., A.A.) extracted all relevant data according to a previously established pattern and evaluate the risk of bias at the study level applying the Cochrane risk-of-bias tool.<sup>11</sup> A publication bias was assessed using Funnel plot by plotting the standard error of each trial

against log risk ratio (RR) in case outcome of interest was reported in minimum four studies. The following data were extracted: (i) baseline characteristics (study design, primary outcome, duration of follow-up, sample size, included population); and (ii) rate of hypotension, volume depletion and AKI.

We performed a study-level, pairwise meta-analysis based on the intention-to-treat analysis of the summary data exploring the risk of hypotension, volume depletion and AKI on SGLT2 inhibitors in the HFrEF population. Differences in events rates for specific outcome were determined and presented as RRs with corresponding 95% confidence intervals (CIs) for each study. We used RR as a measure of relative risk. The data from each trial were pooled using random-effects (DerSimonian–Laird) model. Heterogeneity between the trials was assessed using Cochran's Q test and  $I^2$  statistic. Relevant statistical heterogeneity was considered in case Cochran's Q-test  $p < 0.05$  and  $I^2$  greater than 50%. Study-specific and summary RRs with corresponding 95% CIs and  $p$ -value were visualized using Forest plots.

We explored the robustness of the meta-analysis findings by determination of the fragility index (FI) for significant outcomes and reversed FI (RFI) for non-significant outcomes. We computed FI and RFI by applying the calculator available online [http://clincalepidemio.fr/fragility\\_ma/](http://clincalepidemio.fr/fragility_ma/).<sup>12</sup> FI indicates the number of specific events-status modification (events added or subtracted in the treatment or placebo group) needed to turn the statistically significant to statistically non-significant results. RFI indicates the number of specific events-status modification needed to turn the statistically non-significant to significant results. Furthermore, we calculated the fragility quotient (FQ) and reversed FQ (RFQ) by dividing FI or RFI, respectively, with the sample size to account for different sample sizes. FQ represents the proportion of events, which need to be moved to change the significance of results. For example, meta-analysis A had FI of two and sample size of 500 participants while meta-analysis B had FI of two and sample size of 1000. Albeit FI is the same in both analyses, FQ can reveal us which analysis is relatively more fragile. Analysis A had FQ of 0.004 indicating that four events per 1000 patients will be needed to change the results significance, while analysis B has FQ of 0.002 indicating that two events per 1000 patients will be needed to change the results significance. Accordingly, FQ suggests us that results of trial B are more fragile.

Lower FI or RFI suggests less statistical robustness although there are no standardized cut-off values that defines robustness or fragility. For the purpose of this analysis, FI and RFI  $\leq 10$  was considered as fragile, FI and RFI 10–20 was considered as moderately robust, and FI or RFI  $\geq 20$  as robust findings.

Furthermore, we computed for every event of interest (hypotension, volume depletion and AKI) the difference in rates between treatment and placebo group. Difference was stated as excess on SGLT2 inhibitors and/or placebo depending in which group the rate of specific adverse events was higher and presented with Dot plot. For every adverse event we computed corresponding number needed to treat for benefit (NNT-B) or number needed to treat for harm (NNT-H) as appropriate. Within benefit–risk assessment we presented the difference of incidence per 1000 patients using Forest plot between efficacy/benefit (outcome where excess on placebo was reported) and safety/risk (outcome where excess on SGLT2 inhibitors was reported) endpoints and computed benefit–risk ratio as appropriate (NNT-H/NNT-B). Benefit–risk ratio  $> 1$  indicates a favourable benefit–risk balance.<sup>13</sup> This exploratory analysis was based on the assumption that incidence of adverse events on placebo reflects a spontaneous rate of specific adverse events in the investigated population.

All statistical analyses were performed using RevMan 5.4 and Graph-Pad Prism 6. All *p*-values were two-sided, with *p* < 0.05 considered as significant.

## Results

The study selection strategy is visualized in online supplementary Figure S1. We initially identified 864 studies. After removal, the duplicates of 650 studies were screened manually, out of which 49 studies were full-text reviewed. Finally, five studies met the pre-defined inclusion criteria and entered the meta-analysis (online supplementary Figure S1) comprising of 10 050 patients.<sup>3,4,14–16</sup> Baseline study characteristics used for the purpose of meta-analysis are summarized in Table 1. All of the included studies were regarded as high-quality trials (online supplementary Figure S2). Hypotension was defined in all trials according to the preferred terminology by the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0. It was reported in 4.5% (219/4836) on SGLT2 inhibitors and in 4.1% (202/4846) of patients on placebo (RR 1.09, 95% CI 0.91–1.31, *p* = 0.36) (Figure 1A) (*p* for heterogeneity = 0.42, *I*<sup>2</sup> = 0%). The results were robust (RFI = 21, RFQ = 0.002) (online supplementary Table S1). The excess of hypotension on SGLT2 inhibitors was 0.4% over placebo, indicating that approximately one of 250 patients on treatment with SGLT2 inhibitors develops symptomatic hypotension as a consequence of SGLT2 inhibitor therapy (Figure 1B).

Volume depletion was defined as the presence of one of the following: dehydration, hypovolaemia or hypotension. It was reported in 9.4% (473/5019) on SGLT2 inhibitors and in 8.7% (438/5031) of patients on placebo (RR 1.07, 95% CI 0.95–1.21, *p* = 0.25) (Figure 2A) (*p* for heterogeneity = 0.80, *I*<sup>2</sup> = 0%). The results were moderately robust (RFI = 19, RFQ = 0.001) (online supplementary Table S1). The excess of volume depletion on SGLT2 inhibitors was 0.7% over placebo, indicating that approximately one out of 143 patients on treatment with SGLT2 inhibitors would develop signs of volume depletion as a consequence of SGLT2 inhibitor therapy (Figure 2B). According to the Funnel plot, there were no signs of publication bias (online supplementary Figure S4).

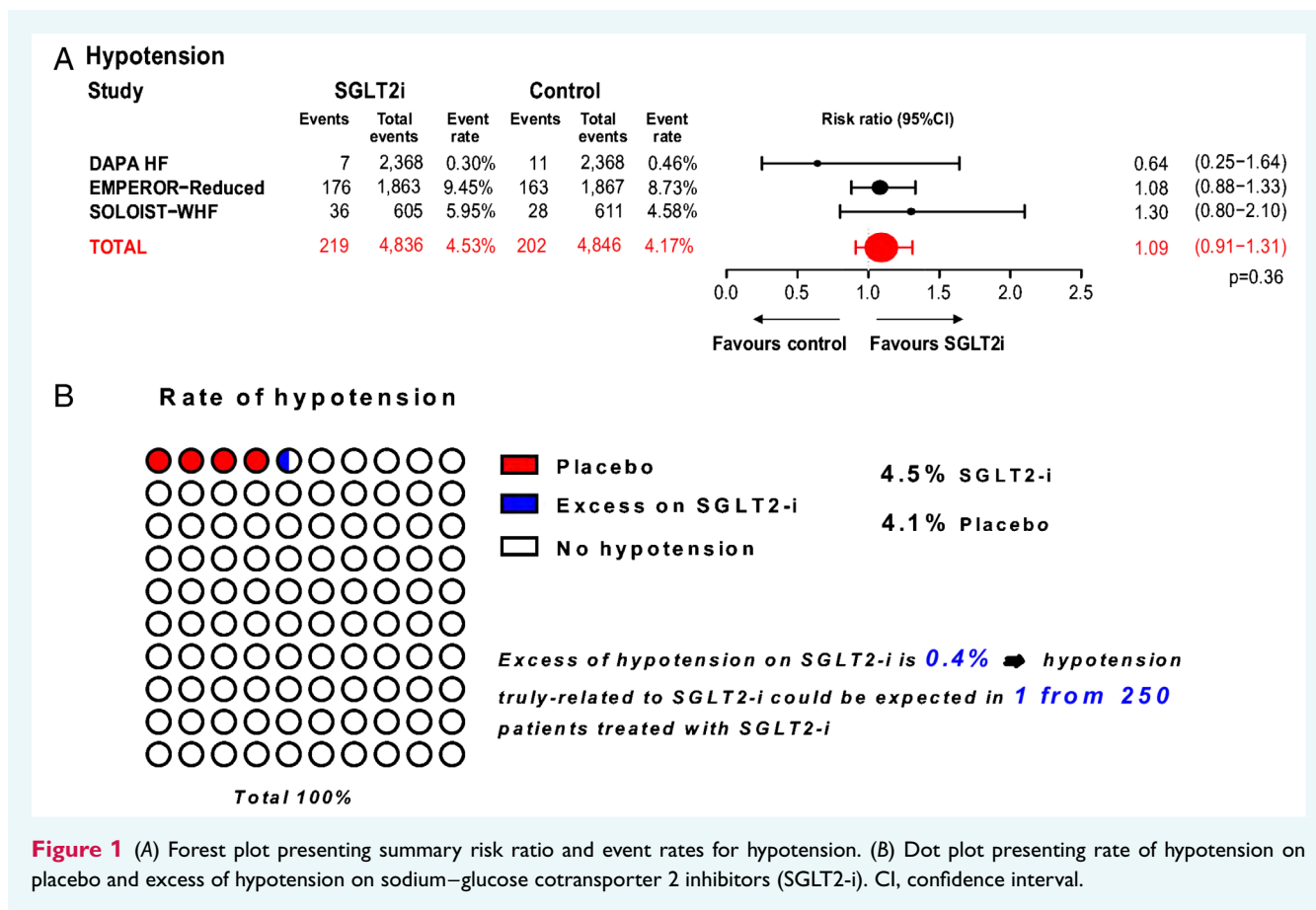
Acute kidney injury was defined according to the preferred terminology by the MedDRA, version 23.0 in three<sup>3,14,15</sup> trials and in one<sup>4</sup> as doubling of baseline serum creatinine values. It was reported in 1.9% (95/4888) on SGLT2 inhibitors and in 2.8% (140/4899) of patients on placebo (RR 0.69, 95% CI 0.51–0.93, *p* = 0.02) (Figure 3A) (*p* for heterogeneity = 0.30, *I*<sup>2</sup> = 19%). FI for AKI was 14 and FQ was 0.001, indicating modest robustness of the observed effect (online supplementary Table S1). The excess of AKI on placebo over SGLT2 inhibitors was 0.9% and the corresponding NNH was 111, indicating that 111 patients should be treated with SGLT2 inhibitors to avoid one AKI event (Figure 3B). According to the Funnel plot, there was no signs of publication bias (online supplementary Figure S3).

Benefit–risk assessment suggests that treating 1000 patients with SGLT2 inhibitors is associated with nine fewer AKI events at a cost of four more hypotension and seven volume depletion events (Figure 4). The benefit–risk ratio between AKI and hypotension was 2.25 and between AKI and volume depletion 1.28, reflecting

**Table 1** Baseline characteristics of analysed trials

Study	Drug	Population	Exclusion criteria for kidney function	Follow-up	Primary outcome
DAPA-HF	Dapagliflozin 10 mg	HFrEF; EF <40%, with or without type 2 DM	eGFR <30 ml/min/1.73 m <sup>2</sup>	18.2 months (median)	Worsening of HF or death from CV causes
DEFINE-HF	Dapagliflozin 10 mg	HFrEF; EF <40%, with or without type 2 DM	eGFR <30 ml/min/1.73 m <sup>2</sup>	3 months (median)	Mean NT-proBNP, proportion of patients with >5 point increase on the KCCQ score
EMPEROR-Reduced	Empagliflozin 10 mg	HFrEF; EF <40%, with or without type 2 DM	eGFR <20 ml/min/1.73 m <sup>2</sup>	16 months (median)	CV death or HFrEF
SOLOIST-WHF	Sotagliflozin 200 mg	HF; type 2 DM	eGFR <30 ml/min/1.73 m <sup>2</sup>	9 months (median)	HHF and/or CV death
SUGAR-DM-HF	Empagliflozin 10 mg	HFrEF; type 2 DM	eGFR <30 ml/min/1.73 m <sup>2</sup>	9 months (median)	Left ventricular end-systolic volume and global longitudinal strain

CV, cardiovascular; DM, diabetes mellitus; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalization for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide.



in both cases a larger magnitude of treatment benefit for AKI than risk for hypotension and volume depletion (Figure 4).

## Discussion

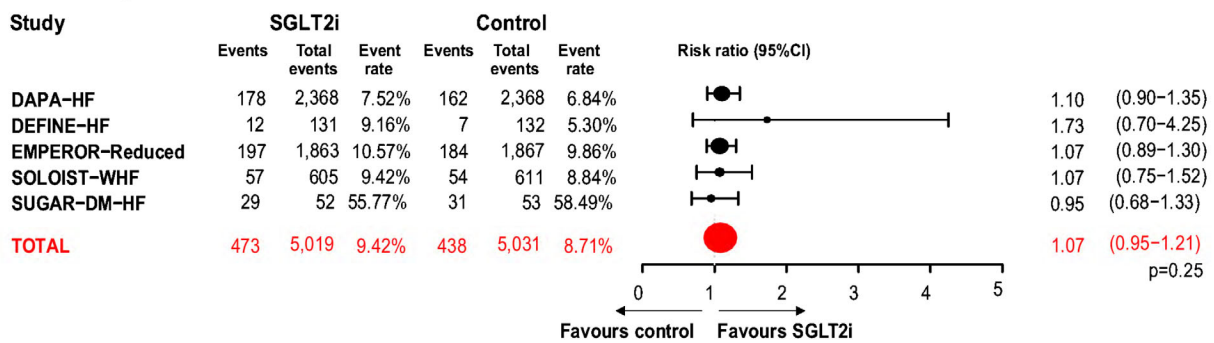
The main findings of the present analysis are that treatment with SGLT2 inhibitors appears not to be associated with an increased risk of hypotension and volume depletion, while it provided a relative risk reduction of 32% for AKI in HFrEF patients.

The European Society of Cardiology recommends in the current heart failure guidelines a therapy with four life-saving drugs such as angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, mineralocorticoid receptor antagonist, beta-blocker, neuroendocrine modulator (angiotensin receptor–neprilysin inhibitor) and SGLT2 inhibitors as foundational therapy in patients with heart failure.<sup>5</sup> These drugs should be initiated promptly and up-titrated later to doses used in clinical trials,<sup>17</sup> as the early treatment initiation has been recognized to improve the prognosis.<sup>18</sup> This approach of prompt and simultaneous initiation of various drug classes often causes concern of tolerability among physicians because of adverse drug effects, such as hypotension, hypovolemia or AKI. Early after discharge after recompensation, patients receive high doses of loop diuretics for treatment of hypervolaemia and maintenance of normovolaemia. These patients are sometimes on high diuretic doses but under-treated with

outcome-modifying drugs<sup>19</sup> and are regarded as a vulnerable population.<sup>20</sup> Thus, relative hypovolaemia, hypotension and volume depletion are perceived as problems especially in this population. According to the one post-hoc analysis from PARADIGM-HF trial, treatment with sacubitril/valsartan may reduce the need for loop diuretics in comparison with enalapril.<sup>21</sup> A post-hoc analysis of the EMPEROR-Reduced trial showed that use of empagliflozin was associated with less intensification of diuretic therapy versus placebo,<sup>22</sup> while another post-hoc analysis of the DAPA-HF trial showed more frequent decrease ( $p < 0.001$ ) of diuretic dose with dapagliflozin (10.4% of patients) versus placebo (7.3% of patients).<sup>23</sup>

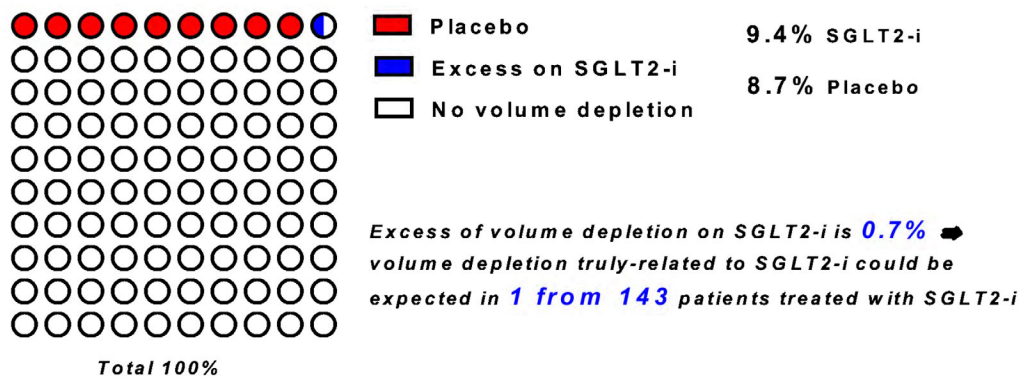
There is evidence that SGLT2 inhibitors reduce BP in patients with DM, arterial hypertension<sup>6</sup> or cardiovascular diseases<sup>24</sup> and this BP lowering appears to be a class effect of all SGLT2 inhibitors.<sup>25</sup> While the baseline BP was higher and the drop of BP smaller in those trials, we report that in the overall population of major heart failure trials, their use is not associated with a significantly or clinically relevant increased risk of hypotension and volume depletion. Results from a post-hoc analysis of the EMPA-REG OUTCOME trial have suggested that although empagliflozin reduced systolic BP (SBP) in patients with history of heart failure, its effect on BP was small at low SBP ( $< 110$  mmHg). The beneficial effects on heart failure outcomes, however, were observed irrespective of baseline SBP and SBP decline.<sup>24</sup> Of note,

## A Volume depletion



## B

## Rate of volume depletion



**Figure 2** (A) Forest plot presenting summary risk ratio and event rates for volume depletion. (B) Dot plot presenting rate of volume depletion on placebo and excess of volume depletion on sodium–glucose cotransporter 2 inhibitors (SGLT2-i). CI, confidence interval.

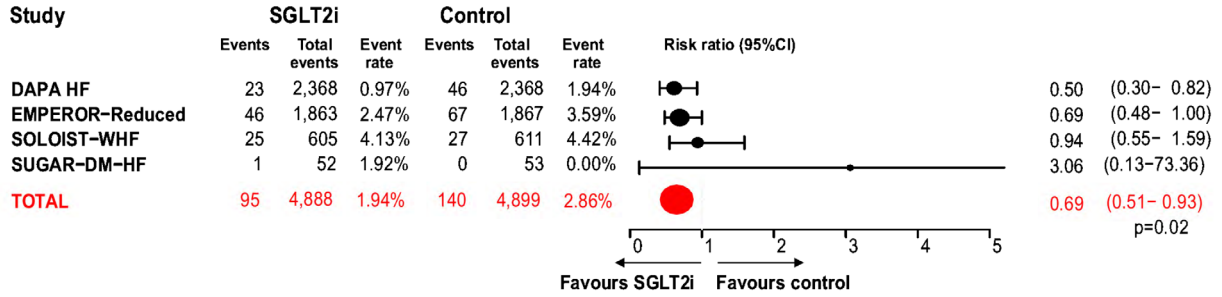
patients with high baseline SBP had a more extensive BP reduction, while patients with low baseline SBP had rather a small increase in SBP.<sup>24</sup> Similar effects according to baseline BP were observed in EMPEROR-Reduced,<sup>8</sup> DAPA-HF<sup>9</sup> and PARADIGM-HF<sup>26</sup> but the drop by sacubitril/valsartan was more pronounced than by SGLT2 inhibitors. Patients with low baseline SBP, in whom reluctance of physicians to apply drugs occurs frequently (i.e. <110 mmHg), had clinically negligible reductions of SBP following SGLT2 inhibitor initiation<sup>9</sup> but there was no increase in hypotension rates after use of dapagliflozin or empagliflozin in EMPEROR-Reduced<sup>8</sup> and DAPA-HF.<sup>9</sup> In line with these findings, the rate of discontinuation of dapagliflozin was relatively low and comparable to those on placebo in participants with SBP <110 mmHg.<sup>9</sup> Nevertheless, the treatment effect of empagliflozin or dapagliflozin was independent of baseline SBP and time-updated SBP during the trials.<sup>8,9</sup>

Chronic kidney disease is a highly prevalent comorbidity and represents a major independent predictor of mortality in patients with heart failure.<sup>27</sup> Therefore, it is imperative to avoid sustained decline of renal function during treatment of heart failure. While SGLT2 inhibitors in heart failure preserve the decline of estimated glomerular filtration rate (eGFR) over time,<sup>3,4</sup> we extend these findings by demonstrating that SGLT2 inhibitors also reduce the risk of AKI. In DAPA-HF, AKI was defined as doubling of baseline

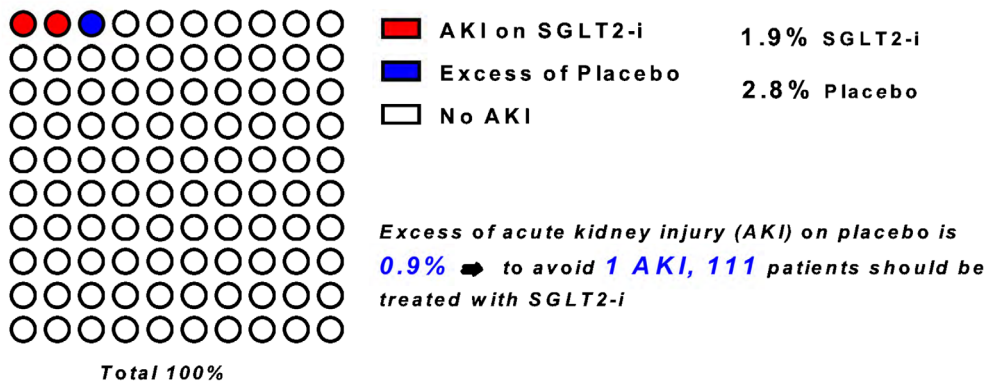
serum creatinine levels that approximates a 57% decline in renal function.<sup>28</sup> Our results are in accordance with already known intermediate and long-term beneficial effects of SGLT2 inhibitors on major kidney outcomes (eGFR decline, end-stage renal disease with dialysis, kidney transplantation and death due to kidney disease), including also lower rates of AKI as shown in a large meta-analysis in patients with type 2 DM.<sup>29</sup> In the randomized, placebo-controlled DAPA-CKD trial, use of dapagliflozin in patients with chronic kidney disease irrespective of the presence or absence of diabetes, reduced the risk of composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes in comparison with placebo.<sup>30</sup>

We also explored the robustness of the observed safety outcomes and found that the results for hypotension were indeed robust (RFI of 21, i.e. 21 events of hypotension added to the empagliflozin group or subtracted from the placebo needed to render the results positive for hypotension, and RFQ of 0.002, i.e. indicating two events per 1000 patients added in the empagliflozin group needed to render the results positive for hypotension), and moderately robust for volume depletion (RFI of 19, i.e. 19 events of volume depletion added to the empagliflozin or subtracted from the placebo group needed to render the results positive, and RFQ of 0.001, i.e. indicating one event per 1000 patients added in the

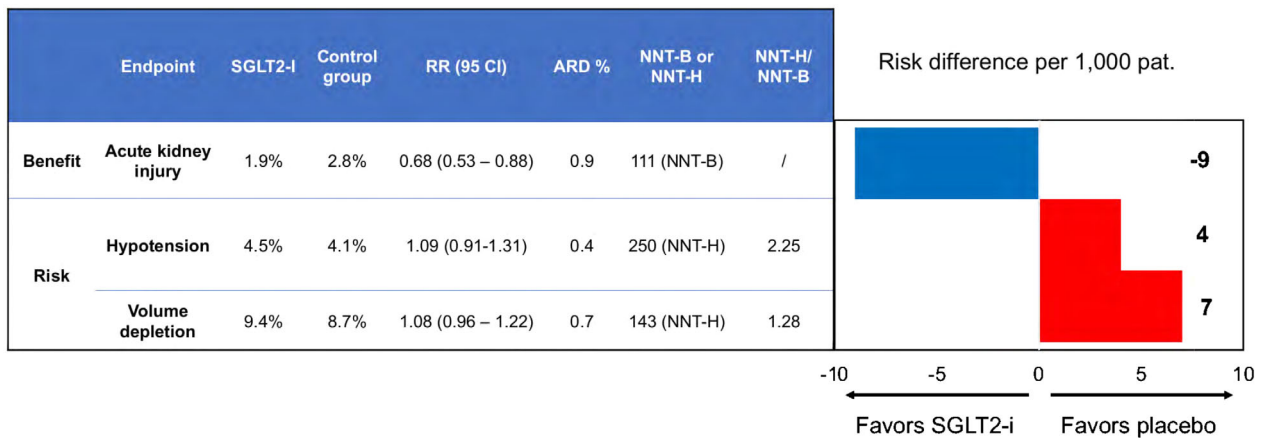
**A Acute Kidney Injury**



**B Rate of acute kidney injury**



**Figure 3** (A) Forest plot presenting summary risk ratio and event rates for acute kidney injury (AKI). (B) Dot plot presenting rate of AKI on sodium–glucose cotransporter 2 inhibitors (SGLT2-i) and excess of AKI on placebo. CI, confidence interval.



**Figure 4** Key benefit–risk summary table with embedded risk difference forest plot per 1000 patients. ARD, absolute risk difference; CI, confidence interval; NNT-B, number needed to treat for benefit; NNT-H, number needed to treat for harm; RR, risk ratio; SGLT2-i, sodium–glucose cotransporter 2 inhibitor.

empagliflozin group needed to render the results positive for volume depletion) and AKI (FI of 14, i.e. 14 events of AKI added to the empagliflozin or subtracted from the placebo group needed to render the results neutral, and FQ of 0.001, i.e. indicating one event per 1000 patients added in the empagliflozin group needed to render the results neutral for AKI).

Benefit–risk assessment exhibited a favourable benefit–risk balance of SGLT2 inhibitors between beneficial effects regarding reduction of AKI and negative effects regarding increase in hypotension and volume depletion cases. The benefit–risk ratio was favourable ( $>1$ ) in both cases (between AKI and hypotension as between AKI and volume depletion), thus showing that beneficial effects regarding reduction of AKI overwhelm the increased risk of hypotension and volume depletion. However, although the benefit–risk ratio is considered as a quantitative measure, it should be interpreted rather as descriptive as SGLT2 inhibitors reduced the risk of AKI (RR 0.69,  $p = 0.02$ ) whereas the risk of hypotension and volume depletion were comparable between groups.

## Limitations

The outcomes of interest were not available from all included trials, which may have affected the results. The analysed side effects were non-adjudicated, investigator-reported adverse events which may vary to some extent across the included trials. We included the data from SOLOIST-WHF although this trial included patients with both reduced and preserved ejection fraction. As the number of patients lost to follow-up from the landmark trials (DAPA-HF:  $n = 36$ ; EMPEROR-Reduced:  $n = 42$ ; SOLOIST-WHF:  $n = 43$ ) included in this meta-analysis was higher than FI/RFI for all outcomes, the findings of the meta-analysis should be interpreted with caution. Nevertheless, the included trials randomized a large number of patients. In most studies, the included populations were rather homogeneous across the trials with respect to heart failure classification and background medication.

## Conclusion

Our findings should encourage clinicians not to withhold evidence-based and guideline-recommended therapy with SGLT2 inhibitors in HFrEF patients. The heart failure population with low BP or impaired kidney function at presentation should not be undertreated due to unfounded concerns as use of SGLT2 inhibitors is not associated with clinically relevant risk of hypotension and volume depletion. SGLT2 inhibitors reduce the risk of AKI and preserve eGFR in concert with the reduction of heart failure outcomes.

## Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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