Impact of SGLT2 inhibitors on major clinical events and safety outcomes in heart failure patients: a meta-analysis of randomized clinical trials

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ABSTRACT

BACKGROUND Sodium-glucose co-transporter-2 inhibitors (SGLT2i) significantly reduce the risk of cardiovascular (CV) and renal adverse events in patients with diabetes mellitus, heart failure (HF) and/or chronic kidney disease. We performed a meta-analysis to explore the impact of several different SGLT2i on all-cause mortality, CV mortality, HF hospitalizations and the combined outcome CV death/HF hospitalization in HF patients across the spectrum of left ventricular ejection fraction (LVEF) phenotypes.

METHODS A systematic search in MEDLINE database and Cochrane library through March 2021 was performed without limitations. Randomized clinical trials that provided data about the impact of SGLT2i on all-cause mortality, CV mortality, HF hospitalizations or the combined outcome of CV death/HF hospitalization in HF patients were included. A random effects model was used for calculating the effect estimates.

RESULTS Nine studies (n = 16,723 patients, mean age: 65.9 years, males: 70.7%) were included in the quantitative synthesis. Compared to placebo, SGLT2i use was associated with 14% lower risk of all-cause mortality [hazard ratio (HR) = 0.86, 95% CI: 0.78–0.94, I² = 0, P = 0.0008], 32% lower risk of HF hospitalizations (HR = 0.68, 95% CI: 0.62–0.74, I² = 0, P < 0.001), 14% lower risk of CV mortality (HR = 0.86, 95% CI: 0.77–0.95, I² = 0, P = 0.003) and 26% lower risk of CV death/HF hospitalization (HR = 0.74, 95% CI: 0.68–0.80, I² = 0, P < 0.001). Regarding the safety outcomes, our data revealed no significant differences between SGLT2i and placebo groups in drug related discontinuations, amputations, severe hypoglycemia, hypotension, volume depletion, ketoacidosis and genital infections. By contrast, a protective role of SGLT2i against placebo was found for serious adverse events and acute kidney injury.

CONCLUSIONS In patients with HF, regardless of LVEF phenotype, all SGLT2i had an excellent safety profile and significantly reduced the risk of all-cause mortality, CV mortality, HF hospitalizations and CV deaths/HF hospitalizations compared to placebo.

Impact of SGLT2 inhibitors on major clinical events and safety outcomes in heart failure patients: a meta-analysis of randomized clinical trials

Sodium-glucose co-transporter-2 inhibitors (SGLT2i) is an antidiabetic class category that acts by blocking glucose resorption in the proximal tubule of the kidney promoting glucosuria.[¹] Randomized clinical trials have shown the beneficial role of SGLT2i in cardiovascular (CV) and renal outcomes in patients with or without diabetes mellitus (DM), including patients with heart failure (HF) and/or chronic kidney disease (CKD).[²–⁸] According to current guidelines, empagliflozin,
canagliflozin and dapagliflozin are recommended in patients with type 2 DM (T2DM) and CV disease, or at very high/high CV risk to reduce CV events, while empagliflozin is also recommended in patients with T2DM and CV disease to reduce the risk of death. The protective role of SGLT2i on CV events is mainly driven by the reduction in HF hospitalizations. For that reason, SGLT2i (empagliflozin, canagliflozin and dapagliflozin) are also recommended to lower risk of HF hospitalization in patients with DM. Recent studies and meta-analyses have shown that empagliflozin and dapagliflozin can further improve CV and renal outcomes in HF patients with reduced left ventricular ejection fraction [LVEF, especially HF with reduced ejection fraction (HFrEF)], regardless of the presence of DM. In addition, the American College of Cardiology has already recommended SGLT2i for the treatment of HFrEF. However, there are still unanswered questions as to whether the observed favorable outcomes in efficacy and safety constitute a class effect of SGLT2i or an effect confined to specific agents and whether the benefit also extends to HF with preserved LVEF [especially HF with preserved ejection fraction (HFpEF)]. The aim of this meta-analysis is to shed some light on these open issues by pooling data from randomized controlled trials (RCTs) on all clinically available SGLT2i, while examining the effects of SGLT2i across the spectrum of LVEF phenotypes.

METHODS

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement).

Search Strategy

Two independent investigators performed a systematic search in MEDLINE database and Cochrane library through to March 2021 without any limitations. The reference lists of the relevant research studies as well as the relevant review studies and meta-analyses were also searched. We used the following algorithm to retrieve all relevant studies: “sodium-glucose transporter-2 inhibitors” (Pharmacological Action) OR “sodium-glucose transporter-2 inhibitors” (MeSH Terms) OR “sodium-glucose transporter-2 inhibitors” (All Fields) OR “[SGLT2” (All Fields) AND “inhibitor” (All Fields)] OR “[SGLT2 inhibitor” (All Fields) AND “heart failure” (MeSH Terms)] OR “[heart” (All Fields) AND “failure” (All Fields)] OR “heart failure“ (All Fields)

We first screened the titles and abstracts of each study and in case of considering a study as relevant then we went through the full text. Disagreements were resolved by a third investigator.

Eligibility Criteria

We considered eligible placebo RCTs that enrolled patients > 18 years with HF of ischemic or non-ischemic etiology and also provided data about the impact of SGLT2i on all-cause mortality, CV mortality, HF hospitalizations and the combined outcome of CV death/HF hospitalizations. We excluded studies that did not provide data about the HF status, observational studies and studies written in a different language than English.

Data Collection

The following data were extracted for each included study: first author, journal of publication, trial acronym, year of publication, number of patients in each group, duration of follow-up, gender, age, mean ejection fraction, comorbidities (DM, hypertension), HF etiology, safety outcomes and the point estimate and confidence intervals for the outcomes of interest (all-cause mortality, CV mortality, HF hospitalizations and the combined outcome of CV death/HF hospitalizations). The data extraction was performed by two independent investigators.

Statistical Analysis

Data analysis was conducted using RevMan 5.4 (Cochrane Training, London, United Kingdom). Separate analyses for the primary outcomes (all-cause mortality, CV mortality, HF hospitalizations and CV deaths/HF hospitalizations) and safety outcomes [drug related discontinuations, amputations, severe hypoglycaemia, serious adverse events and acute kidney injury (AKI)] were performed. Hazard ratio (HR) estimates were pooled from different studies for the primary outcomes, while risk ratio (RR) was pooled from crude event rates for safety
outcomes. The extent of statistical heterogeneity was assessed using the I² index, with values of 25% (I² = 25), 50% (I² = 50) and 75% (I² = 75) representing low, medium and high level of heterogeneity, respectively. Funnel plots were used to assess publication bias. Cochrane collaboration’s tool was used for assessing risk of bias. A random effects model was used for the analyses. Two-sided P-value < 0.05 were considered statistically significant.

RESULTS

Quality Assessment of Studies and Patients

The search strategy identified 810 studies (Figure 1). Of these studies, 756 studies were excluded at the title/abstract level while 45 studies were excluded at the full-text level. As a result, nine studies [8,11,16–22] (n = 16,723 patients, mean age: 65.9 years, males: 70.7%) were included for further analysis (Table 1). The SGLT2i that were used in the analyses included: canagliflozin (two studies), dapagliflozin (two studies), empagliflozin (three studies), erugenflazin (one study), and sitagliptin (one study). Regarding the quality assessment, all studies were rated as having low quality in all assessed domains (Figure 2).

Table 1  Baseline characteristics and major outcomes of the included studies.

| Authors                  | Trial       | Year   | SGLT2i | n  | SGLT2i group | Placebo group | Age, yrs, % | Males, % | Diabetes mellitus, % | All-cause mortality events | Placebo group | SGLT2i group | Placebo group | SGLT2i group | Placebo group | Cardiovascular deaths events |
|--------------------------|-------------|--------|--------|----|--------------|---------------|-------------|----------|----------------------|--------------------------|---------------|--------------|---------------|--------------|---------------|-----------------------------|
| Rådholm K, et al.[15]    | CANVAS      | 2018   | 1,461 | 803| 658 63.8 56 | 100 84 92 | 41 67 | 70 75                |                          |               |              |               |              |               |                              |
| Fitchett D, et al.[17]   | EMPAREG     | 2016   | 706   | 462| 244 64.5 70 | 100 56 35 | 48 30 | 38 27                |                          |               |              |               |              |               |                              |
| Packer M, et al.[11]     | EMPEROR     | 2020   | 3,730 | 1,863| 1,867 66.9 76 | 49.8 249 266 | 246 342 | 187 202              |                          |               |              |               |              |               |                              |
| McMurray JJV, et al.[8]  | DAPA-HF     | 2019   | 4,744 | 2,373| 2,371 66.4 77 | 41.8 276 329 | 231 318 | 227 273              |                          |               |              |               |              |               |                              |
| Cosentino F, et al.[18]  | VERTIC      | 2020   | 1,958 | 1,286| 672 64.4 68 | 100 150 81 | 69 55 | 116 64               |                          |               |              |               |              |               |                              |
| Bhatt DL, et al.[10]     | SOLOIST     | 2021   | 1,222 | 608| 614 69.5 66 | 100 65 76 | 194 297 | 51 58                |                          |               |              |               |              |               |                              |
| Kato ET, et al.[20]      | DECLARE     | 2019   | 1,987 | 980| 1,007 64.0 71 | 100 122 149 | 92 130 | 79 85                |                          |               |              |               |              |               |                              |
| Nassif ME, et al.[21]    | DEFINE-HF   | 2019   | 263   | 131| 132 61.3 73 | 63.1 1 1 | 10 8 | 1 1                  |                          |               |              |               |              |               |                              |
| Sarraju A, et al.[22]    | CREDENCE2020| 2018  | 652   | 329| 323 65.2 61 | 100 45 44 | 34 36 | – –                 |                          |               |              |               |              |               |                              |

SGLT2i: sodium-glucose co-transporter-2 inhibitors.
Impact of SGLT2i on HF Hospitalizations in HF Patients

We found nine studies\(^{[8,11,16-22]}\) that provided data about the impact of SGLT2i on HF hospitalizations. The quantitative synthesis showed that SGLT2i are related with 32% lower risk of HF hospitalizations compared to placebo (10.9% vs. 16.3%, HR = 0.68, 95% CI: 0.62–0.74, \( \hat{r} = 0, P < 0.001 \)) (Figure 5). Only two studies\(^{[18,20]}\) provided data on the impact of SGLT2i on HF hospitalizations according to LVEF status. Compared to placebo, the quantitative synthesis showed that SGLT2i have a beneficial role in reducing HF hospitalizations in both LVEF ≤ 45% subgroup (HR = 0.62, 95% CI: 0.46–0.85, \( \hat{r} = 0, P = 0.003 \)) and > 45% subgroup (HR = 0.71, 95% CI: 0.52–0.97, \( \hat{r} = 0, P = 0.03 \)) and there is no statistically significant difference between the two subgroups (\( P = 0.55 \)) (Figure 6).

Impact of SGLT2i on CV Mortality in HF Patients

Seven studies\(^{[8,11,16-20]}\) provided data about the impact of SGLT2i on CV mortality. The quantitative synthesis showed that SGLT2i are related with 14% lower risk of CV mortality compared to placebo (9.2% vs. 10.6%, HR = 0.86, 95% CI: 0.77–0.95, \( \hat{r} = 0, P = 0.003 \)) (Figure 7). Compared to placebo, the quantitative synthesis of the two studies\(^{[18,20]}\) that provided separate data according to LVEF status showed a non-significant association of SGLT2i with CV mortality in both the LVEF ≤ 45% subgroup (12.4% vs. 15.1%, HR = 0.72, 95% CI: 0.42–1.24, \( \hat{r} = 58\%\), \( P = 0.24 \)) and > 45% subgroup (7.2% vs. 5.8%, HR = 1.24, 95% CI: 0.85–1.81, \( \hat{r} = 0, P = 0.27 \)) (Figure 8).

Impact of SGLT2i on CV Deaths/HF Hospitalizations in HF Patients

We found eight studies\(^{[8,11,16-20,22]}\) that provided data about the impact of SGLT2i on the combined outcome CV deaths/HF hospitalizations. The quantitative synthesis showed that SGLT2i are related with 26% lower risk of CV deaths/HF hospitalizations compared to placebo (17.7% vs. 23.8%, HR = 0.74, 95% CI: 0.68–0.80, \( \hat{r} = 0, P < 0.001 \)) (Figure 9). We found four studies\(^{[8,11,18,20]}\) that provided data regarding the impact of SGLT2i on CV deaths/HF hospitalizations according to LVEF status. Compared to placebo, the quantitative synthesis showed a beneficial role of SGLT2i in reducing the combined outcome in the LVEF ≤ 45% subgroup (four studies: 18% vs. 23.1%, HR = 0.74, 95% CI: 0.67–0.81, \( \hat{r} = 0, P < 0.001 \)) without reaching a statistical significance in the LVEF > 45% subgroup (two studies: 11.5% vs. 14.1%, HR = 0.84, 95% CI: 0.65–1.10, \( \hat{r} = 0, P = 0.20 \)), and there is no statistically signif-

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**Figure 3** Impact of SGLT2i on all-cause mortality in heart failure patients. HR: hazard ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

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**Table 1**

| Study or subgroup | Log (HR) | SE | Weight, % | HR (95% CI) | HR (95% CI) |
|------------------|----------|----|-----------|-------------|-------------|
| Bhatt DL, et al.\(^{[19]}\) (SOLOIST WHF) | -0.1985 | 0.168 | 7.6 | 0.82 (0.59–1.14) | |
| Cosentino F, et al.\(^{[16]}\) (VERTIS CV) | -0.0408 | 0.1328 | 12.2 | 0.96 (0.74–1.25) | |
| Fitchett D, et al.\(^{[17]}\) (EMPERAREG) | -0.2357 | 0.2134 | 4.7 | 0.79 (0.52–1.20) | |
| Kato ET, et al.\(^{[20]}\) (DECLARE TIMI-58) | -0.2357 | 0.2759 | 2.8 | 0.79 (0.46–1.36) | |
| McMurray JV, et al.\(^{[19]}\) (DAPA HF) | -0.1863 | 0.0797 | 33.8 | 0.83 (0.71–0.97) | |
| Packer M, et al.\(^{[11]}\) (EMPEROR REDUCED) | -0.0834 | 0.0908 | 26.0 | 0.92 (0.77–1.10) | |
| Rådholm K, et al.\(^{[20]}\) (CANVAS) | -0.3567 | 0.1616 | 8.2 | 0.70 (0.51–0.96) | |
| Sarraj A, et al.\(^{[22]}\) (CREDENCE) | -0.0726 | 0.2152 | 4.6 | 0.93 (0.61–1.42) | |
| Total (95% CI) | | | 100 | 0.86 (0.78–0.94) |

Heterogeneity: Tau² = 0, Chi² = 3.52, df = 7 (\( P = 0.83 \)), \( \hat{r} = 0 \)

Test for overall effect: Z = 3.35 (\( P = 0.0008 \))
significant difference between the two subgroups \((P = 0.36)\) (Figure 10). Subgroup analysis according to the DM status was provided in eight studies.\(^{8,11,16-20,22}\) Compared to placebo, the quantitative synthesis showed a beneficial role of SGLT2i in reducing the combined outcome in both diabetic patients (eight studies: \(18.7\%\) vs. \(25.9\%\), \(HR = 0.73, 95\% CI: 0.67–0.80, I^2 = 0, P < 0.001\)) and non-diabetic patients (two studies: \(14.9\%\) vs. \(19.1\%\), \(HR = 0.75, 95\% CI: 0.66–0.87, I^2 = 0, P < 0.001\)), and there is no statistically signi-
significant difference between the two subgroups ($P = 0.69$) (Figure 11).

**Safety Outcomes**

Regarding safety outcomes, events on drug-related discontinuations, amputations, severe hypoglycemia, serious adverse events and AKI were extracted from the different studies. Specifically, our data revealed no significant differences between SGLT2i and placebo groups in drug-related discontinuations (six studies: $RR = 0.94$, 95% CI: 0.83–1.07, $I^2 = 0$, $P = 0.36$) (Figure 12), amputations (six studies: $RR = 1.42$, 95% CI: 1.00–2.03, $I^2 = 0$, $P = 0.05$) (Figure 13), severe hypoglycemia (six studies: $RR = 0.93$, 95% CI: 0.75–1.16, $I^2 = 0$, $P = 0.53$) (Figure 14), hypotension (three studies: $RR = 1.09$, 95% CI: 0.90–1.31, $I^2 = 0$, $P = 0.37$) (Figure 15), diabetic ketoacidosis (two studies: $RR = 1.40$, 95% CI: 0.11–17.30, $I^2 = 56\%$, $P = 0.79$) (Figure 16), volume depletion (six studies: $RR = 1.09$, 95% CI: 0.96–1.24, $I^2 = 0$).

| Study or subgroup                  | Log (HR) | SE   | Weight, % | HR (95% CI)         | HR (95% CI)         |
|-----------------------------------|----------|------|-----------|---------------------|---------------------|
| Bhatt DL, et al.\(^{[19]}\) (SOLOIST WHF) | -0.074  | 0.189 | 7.4       | 0.84 (0.58–1.22)    |                     |
| Cosentino F, et al.\(^{[14]}\) (VERTIS CV) | -0.0513 | 0.1558 | 10.9      | 0.95 (0.70–1.29)    |                     |
| Fitchett D, et al.\(^{[15]}\) (EMPAREG) | -0.3425 | 0.2559 | 4.0       | 0.71 (0.43–1.17)    |                     |
| Kato ET, et al.\(^{[30]}\) (DECLARE TIMI-58) | -0.0619 | 0.1578 | 10.6      | 0.94 (0.69–1.28)    |                     |
| McMurray JV, et al.\(^{[30]}\) (DAPA HF) | -0.1985 | 0.0881 | 34.1      | 0.82 (0.69–0.97)    |                     |
| Packer M, et al.\(^{[11]}\) (EMPEROR REDUCED) | -0.0834 | 0.1042 | 24.4      | 0.92 (0.75–1.13)    |                     |
| Rådholm K, et al.\(^{[20]}\) (CANA\(_V\)S) | -0.3285 | 0.1739 | 8.6       | 0.72 (0.51–1.02)    |                     |
| Total (95% CI)                    |          |      |           | 0.2          | 0.86 (0.77–0.95)    |

Heterogeneity: $\tau^2 = 0$, $\chi^2 = 3.03$, df = 6 ($P = 0.81$), $P = 0$

Test for overall effect: $Z = 3.01$ ($P = 0.003$)

**Figure 7** Impact of SGLT2i on cardiovascular mortality in heart failure patients. HR: hazard ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

| Study or subgroup | Log (HR) | SE   | Weight, % | HR (95% CI) | HR (95% CI) |
|-------------------|----------|------|-----------|-------------|-------------|
| LVEF ≤ 45%        |          |      |           |             |             |
| Cosentino F, et al.\(^{[10]}\) (VERTIS CV) | -0.0408 | 0.266 | 24.9      | 0.96 (0.57–1.62) |             |
| Kato ET, et al.\(^{[30]}\) (DECLARE TIMI-58) | -0.3978 | 0.2454 | 26.5      | 0.55 (0.34–0.89) |             |
| Subtotal (95% CI) |          |      |           |             |             |
| Heterogeneity: $\tau^2 = 0$, $\chi^2 = 2.37$, df = 1 ($P = 0.12$), $P = 58\%$ | | | | | |
| Test for overall effect: $Z = 1.18$ ($P = 0.24$) | | | | | |
| LVEF > 45%        |          |      |           |             |             |
| Cosentino F, et al.\(^{[10]}\) (VERTIS CV) | 0.077 | 0.267 | 24.8      | 1.08 (0.64–1.82) |             |
| Kato ET, et al.\(^{[30]}\) (DECLARE TIMI-58) | 0.3646 | 0.2811 | 23.8      | 1.44 (0.83–2.50) |             |
| Subtotal (95% CI) |          |      |           |             |             |
| Heterogeneity: $\tau^2 = 0$, $\chi^2 = 0.55$, df = 1 ($P = 0.46$), $P = 0$ | | | | | |
| Test for overall effect: $Z = 1.10$ ($P = 0.27$) | | | | | |
| Total (95% CI)    |          |      |           |             |             |
| Heterogeneity: $\tau^2 = 0.10$, $\chi^2 = 7.32$, df = 3 ($P = 0.06$), $P = 59\%$ | | | | | |
| Test for overall effect: $Z = 0.31$ ($P = 0.76$) | | | | | |
| Test for subgroup differences: $\chi^2 = 2.56$, df = 1 ($P = 0.11$), $P = 60.9\%$ | | | | | |

**Figure 8** Impact of SGLT2i on cardiovascular mortality according to LVEF status. HR: hazard ratio; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

| Study or subgroup | Log (HR) | SE   | Weight, % | HR (95% CI) | HR (95% CI) |
|-------------------|----------|------|-----------|-------------|-------------|
| Bhatt DL, et al.\(^{[19]}\) (SOLOIST WHF) | -0.4005 | 0.1293 | 9.4       | 0.67 (0.52–0.86) |             |
| Cosentino F, et al.\(^{[14]}\) (VERTIS CV) | -0.1744 | 0.1308 | 9.2       | 0.84 (0.65–1.09) |             |
| Fitchett D, et al.\(^{[15]}\) (EMPAREG) | -0.3285 | 0.1864 | 4.5       | 0.72 (0.50–1.04) |             |
| Kato ET, et al.\(^{[30]}\) (DECLARE TIMI-58) | -0.3011 | 0.1703 | 5.4       | 0.74 (0.53–1.03) |             |
| McMurray JV, et al.\(^{[30]}\) (DAPA HF) | -0.2877 | 0.073 | 29.5      | 0.75 (0.65–0.87) |             |
| Packer M, et al.\(^{[11]}\) (EMPEROR REDUCED) | -0.2877 | 0.073 | 29.5      | 0.75 (0.65–0.87) |             |
| Rådholm K, et al.\(^{[20]}\) (CANA\(_V\)S) | -0.4943 | 0.144 | 7.6       | 0.61 (0.46–0.81) |             |
| Sarraju A, et al.\(^{[33]}\) (CREDENCE) | -0.2107 | 0.1793 | 4.9       | 0.81 (0.57–1.15) |             |
| Total (95% CI)    |          |      |           |             |             |
| Heterogeneity: $\tau^2 = 0$, $\chi^2 = 3.67$, df = 7 ($P = 0.82$), $P = 0$ | | | | | |
| Test for overall effect: $Z = 7.63$ ($P < 0.00001$) | | | | | |

**Figure 9** Impact of SGLT2i on cardiovascular deaths/heart failure hospitalizations in HF patients. HR: hazard ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.
$P = 0.16$) (Figure 17) and genitalia infection (four studies: RR = 1.90, 95% CI: 0.34–10.45, $I^2 = 43\%$, $P = 0.46$) (Figure 18). On the other hand, a protective role of SGLT2i against placebo was found for serious adverse events (seven studies: RR = 0.89, 95% CI: 0.86–0.93, $I^2 = 0$, $P < 0.001$) (Figure 19) and AKI (four studies: RR = 0.67, 95% CI: 0.52–0.87, $I^2 = 0$, $P = 0.003$) (Figure 20).

**Publication Bias**

Funnel plots revealed no significant publication bias in any of the performed analyses (data not shown).

**DISCUSSION**

The initiation of SGLT2i has been associated with a lower risk of CV events across a broad range of outcomes and patient characteristics. The present meta-analysis showed that in patients with HF, SGLT2i significantly reduce all-cause mortality, CV mortality, HF hospitalizations and the combined outcome of CV deaths/HF hospitalizations compared to placebo, regardless of the presence of DM, while having an excellent safety profile. Important strengths of this analysis compared to previous meta-analyses include the fact that it addressed outcomes of all clinically available SGLT2i inhibitors.

![Figure 10](http://www.jgc301.com) Impact of SGLT2i on cardiovascular deaths/heart failure hospitalizations according to LVEF status. HR: hazard ratio; LVEF: left ventricular ejection fraction; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

![Figure 11](http://www.jgc301.com) Impact of SGLT2i on cardiovascular deaths/heart failure hospitalizations according to diabetes mellitus status. HR: hazard ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.
showing consistent results across the whole drug category, thus indicating a class effect of SGLT2i in HF. Furthermore, it addressed the effects of SGLT2i across the spectrum of LVEF phenotypes, an important aspect, given the lack of effective therapies in HFpEF and the long-expected results of RCTs on empagliflozin/dapagliflozin in these patients. Finally, it assessed important safety concerns, including volume depletion, hypotension, severe hypoglycemia, diabetic ketoacidosis and genital infections.

The results of this meta-analysis confirms the results of individual studies. DAPA-HF trial assigned 4,744 patients with NYHA II-IV and LVEF ≤ 40% regardless of the presence of DM that were randomized to receive either dapagliflozin or placebo. Dapagliflozin was related with a 26% reduction in the risk of the composite outcome consisted of worsening HF or CV death. Similarly, EMPEROR-Reduced trial recruited 3,730 patients with NYHA II-IV and LVEF ≤ 40% with or without DM. The authors found that the empagliflozin group had a lower risk of CV death/HF hospitalization compared to the placebo group, regardless of DM status.

Table 1

| Study or subgroup | Log (RR) | SE  | Weight, % | RR (95% CI) | RR (95% CI) |
|------------------|----------|-----|-----------|-------------|-------------|
| Bhatt DL, et al.[9] (SOLOIST WHF) | 0.067 | 0.333 | 3.6 | 1.07 (0.59–2.05) | 1.07 (0.59–2.05) |
| Fitchett D, et al.[10] (EMPAREG) | -0.1704 | 0.1413 | 20.0 | 0.84 (0.64–1.11) | 0.84 (0.64–1.11) |
| McMurray JV, et al.[11] (DAPA HF) | -0.0441 | 0.1256 | 23.8 | 0.96 (0.74–1.23) | 0.96 (0.74–1.23) |
| Nasser ME, et al.[12] (DEFINE-HF) | -0.0794 | 0.3988 | 2.5 | 0.92 (0.42–2.02) | 0.92 (0.42–2.02) |
| Packer M, et al.[13] (EMPORER REDUCED) | -0.0533 | 0.106 | 35.6 | 0.95 (0.77–1.17) | 0.95 (0.77–1.17) |
| Rådholm K, et al.[14] (CANDY) | -0.0392 | 0.1668 | 14.4 | 1.04 (0.75–1.44) | 1.04 (0.75–1.44) |
| Total (95% CI) | 100 | 0.94 (0.83–1.07) | |

Figure 12  Impact of SGLT2i on drug-related discontinuations. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

Figure 13  Impact of SGLT2i on amputations. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

Figure 14  Impact of SGLT2i on severe hypoglycemia. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

Figure 15  Impact of SGLT2i on hypotension. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.
recent meta-analysis of DAPA-HF and EMPEROR-Reduced trials showed that SGLT2i were associated with a 13\% reduction in all-cause death and 14\% reduction in CV death compared to placebo group.\[^{10}\] SOLOIST-WHF trial recruited 1,222 patients with recent worsening HF who were randomized to receive sitagliptin or placebo.\[^{19}\] This study showed that sitagliptin therapy if initiated shortly after an episode of worsening HF, resulted in a significantly lower total number of CV deaths and HF hospitalizations and urgent visits compared to placebo.\[^{19}\] These findings were consistent in patients with mid-range and reduced ejection fraction and in patients with preserved ejection fraction. However, the results of DECLARE TIMI-58 trial showed that dapagliflozin reduced the risk of CV death or HF hospitalization to a greater extent in patients with HFrEF than in those without.\[^{20}\] Similarly, dapagliflozin significantly reduced all-cause mortality in patients with HFrEF but not in those without.\[^{20}\] In the clinical setting of acute decompensated HF, a pilot multi-center study showed that treatment with empagliflozin was safe, increased urinary output and reduced a combined end-

| Study or subgroup | Log (RR) | SE   | Weight, % | RR (95% CI) | RR (95% CI) |
|------------------|----------|------|-----------|-------------|-------------|
| Bhatt DL, et al.\[^{10}\] (SOLOIST WHF) | -0.6833 | 0.8641 | 61.1 | 0.50 (0.09-2.75) | 0.68 (0.09-2.75) |
| McMurray JV, et al.\[^{10}\] (DAPA HF) | 1.9459 | 1.5116 | 38.9 | 7.00 (0.36-135.45) | 7.00 (0.36-135.45) |
| Total (95\% CI) | 100 | 1.40 (0.11-17.30) | 100 | 1.40 (0.11-17.30) | 100 |

Heterogeneity: Tau\(^2\) = 1.94, Chi\(^2\) = 2.28, df = 1 (P = 0.13), I\(^2\) = 56\% Test for overall effect: Z = 0.26 (P = 0.79)

**Figure 16** Impact of SGLT2i on ketoacidosis. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

| Study or subgroup | Log (RR) | SE   | Weight, % | RR (95% CI) | RR (95% CI) |
|------------------|----------|------|-----------|-------------|-------------|
| Bhatt DL, et al.\[^{10}\] (SOLOIST WHF) | 0.0639 | 0.181 | 12.6 | 1.07 (0.75-1.52) | 1.07 (0.75-1.52) |
| McMurray JV, et al.\[^{10}\] (DAPA HF) | 0.1054 | 0.1076 | 35.6 | 1.11 (0.90-1.37) | 1.11 (0.90-1.37) |
| Nasisse ME, et al.\[^{10}\] (DEFINE-HF) | 0.5466 | 0.4593 | 2.0 | 1.73 (0.70-4.25) | 1.73 (0.70-4.25) |
| Packer M, et al.\[^{10}\] (EMPEROR REDUCED) | 0.0883 | 0.0971 | 43.7 | 1.07 (0.89-1.30) | 1.07 (0.89-1.30) |
| Radhokh K, et al.\[^{10}\] (CANVAS) | 0.5247 | 0.4721 | 1.8 | 1.69 (0.67-4.26) | 1.69 (0.67-4.26) |
| Sarraju A, et al.\[^{10}\] (CREDENCE) | -0.1508 | 0.3083 | 4.3 | 0.86 (0.47-1.57) | 0.86 (0.47-1.57) |
| Total (95\% CI) | 100 | 1.09 (0.96-1.24) | 100 | 1.09 (0.96-1.24) | 100 |

Heterogeneity: Tau\(^2\) = 0, Chi\(^2\) = 2.54, df = 5 (P = 0.77), I\(^2\) = 0 Test for overall effect: Z = 1.39 (P = 0.16)

**Figure 17** Impact of SGLT2i on volume depletion. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

| Study or subgroup | Log (RR) | SE   | Weight, % | RR (95% CI) | RR (95% CI) |
|------------------|----------|------|-----------|-------------|-------------|
| Bhatt DL, et al.\[^{10}\] (SOLOIST WHF) | 1.6193 | 1.0939 | 30.3 | 5.05 (0.59-43.09) | 5.05 (0.59-43.09) |
| Kato ET, et al.\[^{10}\] (DECLARE TIMI-58) | 2.05 | 1.5099 | 21.2 | 7.77 (0.40-149.81) | 7.77 (0.40-149.81) |
| McMurray JV, et al.\[^{10}\] (DAPA HF) | 2.1972 | 1.4904 | 21.5 | 0.11 (0.01-2.06) | 0.11 (0.01-2.06) |
| Packer M, et al.\[^{10}\] (EMPEROR REDUCED) | 0.6931 | 1.2244 | 27.0 | 2.00 (0.18-22.04) | 2.00 (0.18-22.04) |
| Total (95\% CI) | 100 | 1.90 (0.34-10.45) | 100 | 1.90 (0.34-10.45) | 100 |

Heterogeneity: Tau\(^2\) = 1.31, Chi\(^2\) = 5.28, df = 3 (P = 0.15), I\(^2\) = 43\% Test for overall effect: Z = 0.73 (P = 0.46)

**Figure 18** Impact of SGLT2i on genitalia infections. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

| Study or subgroup | Log (RR) | SE   | Weight, % | RR (95% CI) | RR (95% CI) |
|------------------|----------|------|-----------|-------------|-------------|
| Bhatt DL, et al.\[^{10}\] (SOLOIST WHF) | 0.056 | 0.0704 | 8.8 | 0.95 (0.82-1.09) | 0.95 (0.82-1.09) |
| Fitchet D, et al.\[^{10}\] (EMPAREG) | 0.1664 | 0.0614 | 6.6 | 0.85 (0.72-0.99) | 0.85 (0.72-0.99) |
| Kato ET, et al.\[^{10}\] (DECLARE TIMI-58) | 0.0262 | 0.0703 | 8.8 | 0.97 (0.85-1.12) | 0.97 (0.85-1.12) |
| McMurray JV, et al.\[^{10}\] (DAPA HF) | 0.1049 | 0.0358 | 34.0 | 0.90 (0.84-0.97) | 0.90 (0.84-0.97) |
| Nasisse ME, et al.\[^{10}\] (DEFINE-HF) | 0.2307 | 0.2445 | 0.7 | 1.26 (0.78-2.03) | 1.26 (0.78-2.03) |
| Packer M, et al.\[^{10}\] (EMPEROR REDUCED) | 0.1468 | 0.0366 | 32.6 | 0.86 (0.80-0.93) | 0.86 (0.80-0.93) |
| Rådholm K, et al.\[^{10}\] (CANVAS) | 0.1985 | 0.0881 | 5.6 | 0.82 (0.69-0.97) | 0.82 (0.69-0.97) |
| Sarraju A, et al.\[^{10}\] (CREDENCE) | 0.1278 | 0.1241 | 2.8 | 0.88 (0.69-1.12) | 0.88 (0.69-1.12) |
| Total (95\% CI) | 100 | 0.89 (0.86-0.93) | 100 | 0.89 (0.86-0.93) | 100 |

Heterogeneity: Tau\(^2\) = 0, Chi\(^2\) = 6.44, df = 7 (P = 0.49), I\(^2\) = 0 Test for overall effect: Z = 5.50 (P < 0.000,01)

**Figure 19** Impact of SGLT2i on severe adverse events. RR: risk ratio; SGLT2i: sodium-glucose co-transporter-2 inhibitors.
point of worsening HF, HF rehospitalization or death at 60 days.[28] However, larger studies are needed to further explore the role of SGLT2i in acute HF patients. Our findings showed a beneficial role of SGLT2i compared to placebo in reducing the combined outcome of CV deaths/HF hospitalizations without a significant interaction between patients with reduced and preserved LVEF. This later finding is consistent with the results of the SOLOIST-WHF trial on sotagliflozin,[19] while the ongoing EMPEROR-Preserved[29] and DELIVER (NCT 03619213) trials on empagliflozin and dapagliflozin, respectively, will provide more solid evidence on the role of SGLT2i in the HFrEF patients. Our meta-analysis did not assess the impact of SGLT2i on clinical outcomes according to the etiology of HF due to the lack of data. However, EMPEROR-Reduced trial showed that SGLT2i significantly reduced the composite outcome of CV death/HF hospitalization in patients with either ischemic or non-ischemic cause of HF.[11] VERTIS CV (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes) trial assigned 8,246 patients with T2DM and atherosclerotic CV disease that were randomized to receive ertugliflozin or placebo.[18] The results showed that ertugliflozin significantly reduced the risk for HF hospitalization while did not significantly reduce the risk for first CV death/HF hospitalization, while previous HF status did not modify the risk of first HF hospitalization.[18] Subgroup analyses from VERTIS-CV trial on risk for first composite of CV death/HF hospitalization, CV mortality, or all-cause mortality based on pretrial LVEF showed no significant interactions.[18] In a recent meta-analysis of six trials, SGLT2i were associated with a reduced risk of major adverse CV events in patients with T2DM while the largest benefit across the class was for an associated reduction in risk for HF hospitalizations and kidney outcomes.[30] Regarding the potential mechanisms that explain the beneficial role of SGLT2i in HF patients, several mechanisms have been proposed including diuresis/natriuresis, blood pressure reduction, erythropoiesis, improved cardiac energy metabolism, inflammation reduction and prevention of ischemia/reperfusion injury among others.[31] A recent study showed that empagliflozin significantly improves left ventricular volumes, mass and systolic function independently of the glycemic status.[32,33] Other small mechanistic clinical trials or preclinical studies have pointed towards diverse mechanisms but no solid evidence is yet available.

The role of SGLT2i in kidney outcomes has been well studied. In this regard, this meta-analysis showed that a protective role of SGLT2i against placebo in AKI. Data from the EMPAREG OUTCOME trial showed that in patients with T2DM at high CV risk, empagliflozin as compared to placebo was associated with slower progression of kidney disease and lower rates of clinically relevant renal events.[34] Furthermore, the CREDEENCE trial showed that in patients with T2DM and CKD, the risk of kidney failure and CV events was lower in the canagliflozin group than in the placebo group.[5] The DAPA-CKD trial enrolled patients with CKD.[6] The authors found that the risk of the composite outcome consisted of sustained decline in the estimated glomerular filtration rate of at least 50%, end-stage kidney disease, or death from renal or CV causes was significantly lower with dapagliflozin than with placebo independently of the diabetes status.[6] A recent meta-analysis showed that in patients with T2DM, SGLT2i reduced the risk of dialysis, transplantation, or death due to kidney disease while provided protection against AKI.[35] In addition, another recent meta-analysis showed that SGLT2i reduced the risk of progression of renal disease by 45%.[36] This association remained consistent regardless the history of
atherosclerotic CV disease while the magnitude of benefit of SGLT2i varied with baseline renal function, with lesser reductions in progression of renal disease in patients with more severe kidney disease at baseline.\cite{36} Results of a meta-analysis that included RCTs and observational studies showed that SGLT2i reduced the odds of suffering AKI with and without hospitalization in randomized trials and the real-world setting.\cite{37} Moreover, it has been found that in patients with HF and T2DM, empagliflozin in combination with diuretics caused a significant increase in urine volume compared with placebo, as well as a significant increase in electrolyte free water clearance.\cite{38} All these data highlights the role of this drug category in the management of patients with HF and CKD, two clinical entities that often coexist. These findings are in accordance with our secondary analysis which showed a protective role of SGLT2i compared to placebo in reducing the risk of AKI in HF patients.

**LIMITATIONS**

A subgroup analysis according to DM status and etiology of HF (ischemic and non-ischemic) could not be performed for all-cause mortality, CV mortality and HF hospitalizations outcomes due to lack of data. Only two studies\cite{18,20} provided data about the impact of SGLT2i on the primary outcomes of interest according to LVEF status. Furthermore, in one study, LVEF status was retrieved from medical records and not from measurements at the patient enrollment.\cite{18} This consist a major limitation for this analysis and as a result, more data are needed to elucidate the role of SGLT2i in different LVEF categories. Furthermore, in the analysis of regarding the combined CV death/HF hospitalization outcome, in the reduced ejection fraction subgroup defined as ≤ 45%, we also included two studies\cite{6,11} that provided data from patients with LVEF ≤ 40% which consists a limitation of this analysis. However, by removing these two studies, the results did not significantly change [LVEF ≤ 45% (two studies: HR = 0.67, 95% CI: 0.52–0.86, \( P = 0.002 \) and LVEF > 45% (two studies: HR = 0.84, 95% CI: 0.65–1.10, \( P = 0.20 \))], and there is no statistically significant difference between the two subgroups (\( P = 0.22 \)).

Regarding the safety outcome analysis of genital infections, one of the included studies provided data about genital mycotic infections\cite{19} while another one provided data about epididymitis and Fournier gangrene.\cite{8}

**CONCLUSIONS**

In patients with HF, SGLT2i showed an excellent safety profile and significantly reduced all-cause mortality, CV mortality, HF hospitalizations and CV deaths/HF hospitalizations compared to placebo. These beneficial effects are independent of the presence of DM, while they seem to extent to the whole SGLT2i class and to patients with HFpEF.

**DISCLOSURE**

Dr. Dimitrios Farmakis reports speaker honoraria and/or consultation fees from Abbott Laboratories, Bayer, Boehringer-Ingeheim, Leo, Menarini, Novartis, Orion and Roche Diagnostics, outside this work. The rest of the authors had no conflicts of interest to disclose.

**REFERENCES**

[1] Kalra S. Sodium glucose co-transporter-2 (SGLT2) inhibitors: a review of their basic and clinical pharmacology. *Diabetes Ther* 2014; 5: 355–366.
[2] Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
[3] Neal B, Perkovic V, Matthews DR, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 2099.
[4] Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357.
[5] Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306.
[6] Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; 383: 1436–1446.
[7] Cherney DZI, Zinman B, Inzucchi SE, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2017; 5: 610–621.
[8] McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; 381: 1995–2008.
[9] Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2020; 41: 255–323.

[10] Zannad F, Ferreira JP, Pocock SJ, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet 2020; 396: 819–829.

[11] Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020; 383: 1413–1424.

[12] Writing Committee, Maddox TM, Januzzi JL Jr, et al. 2021 Update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021; 77: 772–810.

[13] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.

[14] Huedo-Medina TB, Sánchez-Meca J, Marin-Martínez F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychol Methods 2006; 11: 193–206.

[15] Fellow J, Altman DG. Assessing Risk of Bias in Included Studies, Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. A John Wiley & Sons, Ltd., Publication: the Atrium, Southern Gate, Chichester, West Sussex PO19 8SQ, England, 2008: 187–241.

[16] Rådholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS Program. Circulation 2018; 138: 458–468.

[17] Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J 2016; 37: 1526–1534.

[18] Cosentino F, Cannon CP, Cherney DZI, et al. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: results of the VERTIS CV trial. Circulation 2020; 142: 2205–2215.

[19] Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021; 384: 117–128.

[20] Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019; 139: 2526–2536.

[21] Nassif ME, Windsor SL, Tang F, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. Circulation 2019; 140: 1463–1476.

[22] Sarraju A, Li J, Cannon CP, et al. Effects of canagliflozin on cardiovascular, renal, and safety outcomes in participants with type 2 diabetes and chronic kidney disease according to history of heart failure: results from the CRESCENDO trial. Am Heart J 2021; 233: 141–148.

[23] Kosiborod M, Lam CSP, Kohsaka S, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. J Am Coll Cardiol 2018; 71: 2628–2639.

[24] Li D, Liu Y, Hidru TH, et al. Protective effects of sodium-glucose transporter 2 inhibitors on atrial fibrillation and atrial flutter: a systematic review and meta-analysis of randomized placebo-controlled trials. Front Endocrinol (Lausanne) 2021; 12: 619586.

[25] Kumar K, Kheiri B, Simpson TF, et al. Sodium-glucose cotransporter-2 inhibitors in heart failure: a meta-analysis of randomized clinical trials. Am J Med 2020; 133: e625–e630.

[26] Chambberg-Michilot D, Tauma-Arrué A, Loli-Guevara S. Effects and safety of SGLT2 inhibitors compared to placebo in patients with heart failure: a systematic review and meta-analysis. Int J Cardiol Heart Vasc 2020; 32: 100690.

[27] Li X, Zhang Q, Zhu L, et al. Effects of SGLT2 inhibitors on cardiovascular, renal, and major safety outcomes in heart failure: a meta-analysis of randomized controlled trials. Int J Cardiol 2021; 332: 119–126.

[28] Damman K, Beusekamp JC, Boorsma EM, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail 2020; 22: 713–722.

[29] Anker SD, Butler J, Filippatos G, et al. Baseline characteristics of patients with heart failure with preserved ejection fraction in the EMPEROR-Preserved trial. Eur J Heart Fail 2020; 22: 2383–2392.

[30] McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021; 6: 148–158.

[31] Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. JACC Basic Transl Sci 2020; 5: 632–644.

[32] Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, et al. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. J Am Coll Cardiol 2021; 77: 243–255.

[33] Farmakis D, Butler J, Filippatos G. Sodium-glucose co-transporter 2 inhibitors: a tale of two sisters”, diabetes and heart failure. Eur J Heart Fail 2020; 22: 1259–1262.

[34] Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016; 375: 323–334.

[35] Neuen BL, Young T, Heerspink HJL, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019; 7: 845–854.

[36] Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome...
trials. Lancet 2019; 393: 31–39.

[37] Menne J, Dumann E, Haller H, et al. Acute kidney injury and adverse renal events in patients receiving SGLT2-inhibitors: a systematic review and meta-analysis. PLoS Med 2019; 16: e1002983.

[38] Mordi NA, Mordi IR, Singh JS, et al. Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure: the RECEDE-CHF trial. Circulation 2020; 142: 1713–1724.

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