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Effects and safety of SGLT2 inhibitors compared to placebo in patients with heart failure: A systematic review and meta-analysis

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ABSTRACT

Background: Heart failure (HF) prognosis without therapy is poor, however introduction of a range of drugs has improved it. We aimed to perform a systematic review on the effects and safety of sodium-glucose transporter 2 inhibitors (SGLT2i) in HF patients.
Methods: We carried out a systematic review of randomized controlled trials (RCTs) on SGLT2i compared to placebo for HF patients. We searched in PubMed, Scopus, Web of Science and EMBASE, with no language restriction, from inception to 31 August 2020. We included nine RCTs comprising three arms (empagliflozin, dapagliflozin and placebo). Effects sizes for continuous variables were expressed as mean differences (MDs) and 95% confidence intervals (CIs). Effects sizes for dichotomous variables were expresses as risk ratio (RR) and 95% CIs. We used random-effect models with the inverse variance method. We performed subgroup meta-analyses by intervention drug and follow-up period.
Results: SGLT2i significantly reduced all-cause mortality (RR: 0.88, 95%CI 0.79–0.98, I2 = 0%), cardiovascular mortality (RR: 0.87, 95%CI 0.77–0.99, I2 = 0%), HF hospitalization (RR: 0.73, 95%CI 0.66–0.81, I2 = 0%) and emergency room visits due to HF (RR: 0.40, 95%CI 0.21–0.76, I2 = 0%), as well as composite outcomes including the previous ones. Besides, it significantly improved the score of the Kansas City Cardiomyopathy Questionnaire (KCCQ, MD: 1.70, 95%CI 1.67–1.73, I2 = 54%). SGLT2i reduced any serious adverse events, blood pressure and weight. However, it increased hematocrit and creatinine. The meta-analysis of RCTs of > 12 weeks of follow-up showed that SGTL2i significantly reduced NT-proBNP.
Conclusions: SGLT2i showed to improve critical outcomes in HF patients, and it is apparently safe.
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1. Introduction

Heart failure (HF) prevalence increases with aging [1–3]. Moreover, HF is the main cause of hospitalization in older adults in the United States, and accounts for 9.3% of total deaths due to cardiovascular diseases [4]. It was reported that approximately 6.2 million American adults suffered from HF between 2013 and 2016 [4]. HF represents a growing problem for public health and economic burden, and studies estimate 8 million cases in 2030 [1].

HF with reduced ejection fraction (HFrEF) is associated with worse clinical symptoms and frequent hospitalization [5]. The current pharmacological management of HFrEF relies on a triple neurohormonal blockade based on angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), beta-blockers and mineralocorticoid receptor antagonists, with recommendations in specific clinical patient's conditions [6–8].

The prognosis of HF without therapy is poor, however the introduction of a range of pharmacological treatments has improved it [6,9,10]. New drugs have been studied looking for better outcomes, such as neprilysin inhibitors and ivabradin, and some of them have been incorporated in guidelines [9].

Sodium-Glucose Transporter 2 inhibitors (SGLT2i) increase the urinary excretion of glucose, allowing a reduction of glycaemia, and are recommended in patients with type 2 diabetes (T2D) [11]. Currently, some studies have described potential protective effects against progressive renal events and hospitalization rates due to HF [12]. Some authors have proposed that SGLT2i promotes the fasting transcriptional paradigm, and increases ketone bodies,

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which changes the myocardial metabolism and raises antioxidant and anti-inflammatory effects [13,14].

Randomized controlled trials (RCTs) have evaluated the effects of SGLT-2i in patients with HF for improving symptoms, mortality, hospitalization, and biomarkers, however results are heterogeneous [15,16]. It is relevant to synthesize the current evidence in order to improve the evidence-based decision making in clinical practice. Therefore, we aimed to perform a systematic review on the effects and safety of SGLT2i in patients with HF.

2. Methods

This systematic review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [17], and the Cochrane Handbook for Systematic Reviews of Interventions [18]. The protocol was registered in PROSPERO (CRD42020206969) and Figshare [19].

2.1. Search strategy

We searched evidence up to 31 August 2020 in the following databases: PubMed, Scopus, Web of Science and EMBASE. The search strategies are available in **Supplementary material 1**. We did not limit the search by publication date or language.

2.2. Inclusion criteria

We included all RCTs that assessed the effects and safety of any SGLT2i compared to placebo in adults with HF. We excluded secondary analyses of RCTs (i.e.: results from a RCT that was originally performed in patients with diabetes regardless of HF), case reports, case series, cross-sectional studies, cohorts, case-control studies, reviews, letters to the editor, congress or conference abstracts, editorials, interviews, comments, and newspaper articles.

2.3. Study selection

One author (D.C.M.) downloaded all references to an EndNote document to eliminate duplicates. Then, the author exported those references to the Rayyan QCRI webpage (https://rayyan.qcri.org/). Two reviewers (D.C.M., A.T.A.) independently screened titles and abstracts. Those reviewers assessed the full-text version of selected articles to determine eligibility. This selection was performed using a pre-piloted Microsoft Excel sheet. Any disagreement was resolved by consensus with a third author (S.L.G.). The kappa coefficient between the two reviewers was 0.825.

2.4. Data extraction

Two reviewers (A.T.A., S.L.G.) independently extracted data of interest. Any disagreement was resolved by consensus with a third reviewer (D.C.M.). For dichotomous outcomes, we extracted absolute and relative frequencies. For continuous outcomes, we extracted baseline and follow-up measurements, as well as the change between them. The extraction was performed using a pre-piloted Microsoft Excel sheet.

2.5. Primary and secondary outcomes and subgroup analyses

Composite outcomes including cardiovascular mortality, HF hospitalization or emergency room visits due to HF (HF urgent visit); NT-proBNP, the Kansas City Cardiomyopathy Questionnaire (KCCQ), changes in dyspnea visual analogue, diuretic response, 24-hour urinary volume change, left ventricular end-systolic volume, and natriuresis were the primary outcomes in this systematic review since they were stated as it in the RCTs. Secondary outcomes were specific and serious adverse events, discontinuation due to adverse events, weight, systolic blood pressure (SBP), diastolic blood pressure, hematocrit, glycated hemoglobin, beta-hydroxybutyrate, estimated glomerular filtration rate (eGFR), creatinine, left ventricular ejection fraction (LVEF), and indexed left atrial volume.

2.6. Risk of bias

We assessed the risk of bias using the version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2). This tool has five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results) and the overall score. Each domain can be judged as follows: low risk of bias, some concerns, and high risk of bias [18].

2.7. Data synthesis

Meta-analyses were performed using random-effect model with the inverse variance method. We used the Paule-Mandel estimator and Hartung-Knapp-Sidik-Jonkman method for τ^2 and 95% confidence intervals (95% CIs) calculation, respectively [20,21].

For dichotomous outcomes, we used relative risks (RRs) with their 95% CIs. For continuous outcomes, we calculated the mean difference (MD) by subtracting the baseline mean from mean at the last follow-up in a group. Standard deviation (SD) of MD was calculated as follows: $SDc = \sqrt{SD^2b + SD^2f - (2xCorrxSDbxSDf)}$, where *SDc, SDb, SDf* and *Corr* are SD change, baseline SD, follow-up SD, and correlation coefficient, respectively [18]. We assumed a *Corr* of 0.5 [22]. If *SDb* and *SDf* were not available, we used the following formula: $SDc = SEx\sqrt{n}$, where *SE* and *n* are standard error and sample size, respectively. SE was calculated as follows: $(UL - LM)/3.92$, where UL and LM are the upper and lower limits of 95% CI [18]. If a continuous outcome was expressed in median *(m)* instead of mean *(X)*, we used the following formula: $X = \frac{q1+m+q3}{3}$, where *q1 and q3* are first and third quartiles, respectively [18,23]. Then, in case of sample sizes *(n) of* ≤ 201, we used the following formula to calculate SD: $SD = \frac{q3-q1}{\eta(n)}$, whose $\eta(n)$ values are reported in a published methodology [23]. In case of larger sample sizes, we used: $SD = \frac{q3-q1}{2\alpha^{-1}(\frac{0.75n-0.125}{n+0.25})}$ [18,23]. Note that the denominator converges to 1.34898 as *n* tends to infinity [23]. Standardized mean difference (SMD) was calculated if the scale or units of continuous variables were heterogeneous among studies.

Heterogeneity was described with the I^2 statistic [24]. An $I^2 < 30\%$, I^2 30–60%, and $I^2 > 60\%$ defined low, moderate and high heterogeneity, respectively. We pooled outcomes only if occurring in at least two studies. If one or more outcomes could not be extracted from a study, it was removed from the analysis.

We performed subgroup analyses of primary outcomes by intervention drug and follow-up ($\leq$12 weeks and > 12 weeks). Two-sided p-values ≤ 0.05 were considered statistically significant for all tests. Meta-regressions could not be performed due to insufficient number of studies per meta-analysis. We did not assess publication bias due to the low number of studies [25]. We conducted the analyses using *metabin*, *metacount* and *metareg* functions of the meta library of R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

2.8. Recommendations

We used the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) to rate the quality of

evidence of the pooled primary outcomes. The domains of assessment are risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect. The quality ratings are very low, low, moderate or high [26].

3. Results

3.1. Eligible studies

We identified 1863 publications. After removing duplicates and screening phase, we selected 26 articles for full-text screening. Finally, nine RCTs were included in this systematic review [15,16,27–33] (Fig. 1).

3.2. Characteristics of studies included in the systematic review

Seven studies were parallel-group RCTs, and two studies were crossover RCTs. One RCT was in phase 2, three RCTs were in phase 2, two RCTs in phase 3, and three RCTs in phase 4. Interventions consisted on dapagliflozin or empagliflozin. One study presented five arms: empagliflozin, licogliflozin (2.5 mg, 10 mg, and 50 mg) and placebo. We found two studies whose sample size were the largest among the others: McMurray's RCT (dapagliflozin, n = 4744) and Packer's RCT (empagliflozin, n = 3730). Intervention sample size ranged from 12 to 2373 patients among studies. Follow-up periods ranged from six weeks to 38 months. Eight RCTs included adults with stable HF (seven studies: HFrEF), and one RCT

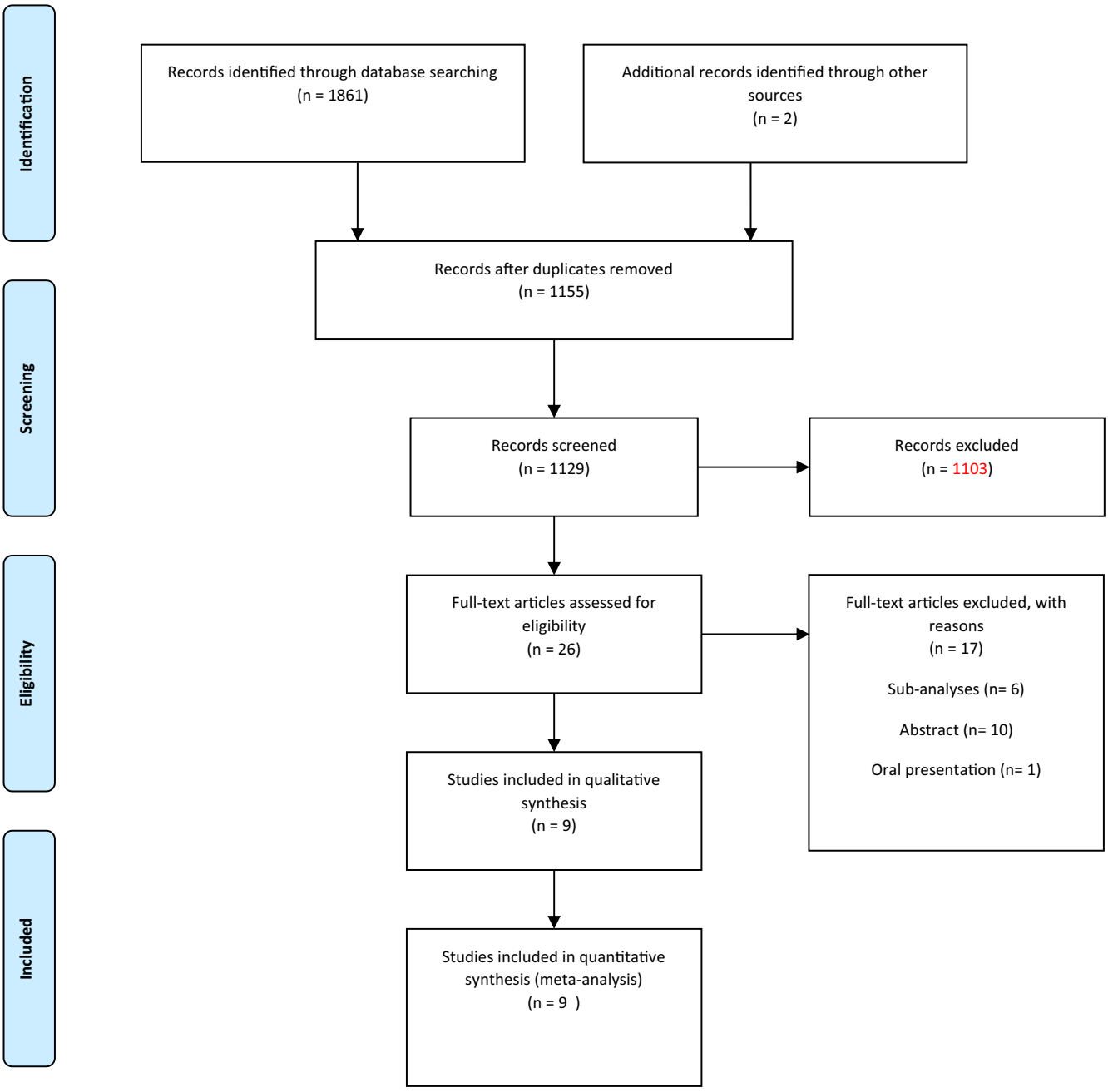


Fig. 1. PRISMA Flowchart of selection.

included only patients with decompensated HF. The cut-off of LVEF to determine HFrEF was 40% in eight studies, and 50% in one study. The majority of studies required patients to receive a standard HF drug or device therapy. Considered primary outcomes were composite outcomes that included cardiovascular death, HF hospitalization, and emergency room visits due to HF (two RCTs), NT-proBNP (four RCTs), KCCQ (one RCT), changes in dyspnea visual analogue scale (one RCT), diuretic response (one RCT), length of stay (one RCT), 24-hour urinary volume (one RCT), left ventricular end-systolic volume (LVESV, one RCT), and natriuresis (one RCT) (Table 1).

3.3. Characteristics of studies' population

The mean/median age ranged from 60 to 80 years. In all RCTs, sex male proportion was higher than 50%. Four studies included exclusively patients with HF and T2D. NYHA II group was the most frequent HF classification among studies. Baseline mean/median NT-proBNP ranged from 399 to 6168 pg/ml. In the majority of RCTs, the most frequent prior therapies were ACEis, ARBs and loop diuretics (Table 2).

3.4. Risk of bias assessment

Seven out of nine RCTs had overall low risk of bias. Two studies presented some concerns in selection of the reported results **(**Fig. 2**).**

3.5. Meta-analyses of primary outcomes

A meta-analysis of five RCTs showed that, compared to placebo, SGLT2i decreased all-cause mortality (RR: 0.88, 95%CI 0.79–0.98, I^2 = 0%) **(**Fig. 3**A).** A similar effect was found in cardiovascular mortality **(**Fig. 3**B).** Moreover, meta-analyses showed that SGLT2i decreased HF hospitalization (RR: 0.73, 95%CI 0.66–0.81, I^2 = 0%), emergency room visits due to HF (RR: 0.40, 95%CI 0.21–0.76, I^2 = 0%), and HF hospitalization or emergency room visits due to HF (RR: 0.73, 95%CI 0.65–0.81, I^2 = 0%) **(**Fig. 3**C-E).** Regarding the composite outcomes, we found that SGLT2i decreased 1) cardiovascular mortality or HF hospitalization (RR: 0.78, 95%CI 0.71–0.85, I^2 = 0%) **(**Fig. 3**F),** and 2) cardiovascular mortality, HF hospitalization or emergency room visits due to HF (RR: 0.78, 95%CI 0.71–0.85, I^2 = 0%) **(**Fig. 3**G).** Finally, a meta-analysis of three RCTs showed that SGLT2i improved the KCCQ score (MD: 1.70, 95%CI 1.67–1.73, I^2 = 54%) **(**Fig. 3**I).**

We used the empagliflozin and placebo arms of De Boer's RCT in order to keep homogeneity in the intervention, furthermore, the other arms [licogliflozin at different doses (2.5 mg, 10 mg, and 50 mg)] were not included since they are not SGLT2i, but SGLT1/2i. We did not include results of Damman's RCT in composite outcomes because they did not report cardiovascular mortality. We did not meta-analyze Nassif's and Griffin's results due to insufficient information: lack of baseline means and sample size per group in the full-text paper, respectively.

3.6. Meta-analyses of secondary outcomes and subgroups

Meta-analyses showed that SGLT2i reduced any serious adverse events (RR: 0.89, 95%CI 0.84–0.94, I^2 = 4%), SBP (MD: −0.70, 95%CI −0.73 to −0.68, I^2 = 48%), and weight (MD: −0.81, 95%CI −0.82 to −0.80, I^2 = 47%). Nevertheless, SGLT2i increased hematocrit (MD: 1.38, 95%CI 0.02–2.74, I^2 = 100%) and creatinine (MD: 2.65, 95%CI 2.63–2.67, I^2 = 0%) **(Supplementary material 2).**

We performed subgroup meta-analyses by study drug and follow-up. SGLT2i significantly decreased all-cause mortality, cardiovascular mortality, and emergency room visits due to HF in the dapagliflozin group, but not in the empagliflozin group. In the meta-analysis of RCTs that reported a follow-up > 12 weeks, SGLT2i was significantly associated with NT-proBNP reduction **(Supplementary material 2).**

3.7. Non meta-analyzed results

Damman's RCT, which assessed patients with decompensated HF, found no effect of empagliflozin in dyspnea, diuretic response, length of stay or NT-proBNP. Mordi's RCT found that empagliflozin increased 24-hour urinary volume without increasing urinary sodium. Singh's RCT was unable to detect and effect on LVESV. Griffin's RCT, which was the only phase 1 study, found that empagliflozin caused significant natriuresis, especially when it was combined with loop diuretics **(**Table 1**).**

3.8. GRADE summary of findings

Among the pooled primary outcomes, composite outcomes including cardiovascular mortality, HF hospitalization or emergency room visits due to HF showed high certainty of evidence. Effect in KCCQ and NT-proBNP had moderate and low certainty, respectively **(**Table 3**).**

4. Discussion

4.1. Main findings

Through this systematic review with meta-analyses, we found that SGLT2i compared to placebo mainly improved mortality, HF hospitalization, emergency room visits due to HF, NT-proBNP, KCCQ, and reduced serious adverse events. Nevertheless, it increased hematocrit and creatinine. Primary outcomes had high certainty of evidence, and the majority of trials presented overall low risk of bias.

4.2. What is known in literature about SGLT2i?

Prior RCTs have evidenced that SGLT2i have beneficial effects on hospitalization and cardiovascular events, including mortality [34,35]. Indeed, a meta-analysis of the largest RCTs showed that SGLT2i reduced by 23% the risk of cardiovascular death or HF hospitalization in patients with diabetes [12]. A sub-analysis suggested a significant effect of SGLT2i in patients with HF at baseline [36]; besides, a post hoc analysis showed greater benefit in diabetic patients with very high cardiovascular risk [37]. These findings encouraged the research of SGLT2i benefits in patients with HF.

SGLT2i mechanism of action in HF patients has not been completely elucidated. Despite its well-known effect as a glycosuric agent, there are other proposed explanations for benefits. Some of them are metabolic changes, such as more ketone body production, activation of anti-inflammatory and anti-oxidative pathways, and reduction of advanced glycation end-products mediated effects [38–41]. SGLT2i reduces Nod-like receptor protein 3 (NLRP3) inflammasome activation, reducing IL1-β in macrophages, which is associated with less development of atherosclerotic plaques [42]. Preclinical studies have described an improvement of cardiac contraction and coronary microvascular function [39,43]. Additionally, SGLT2i inhibit the sodium/hydrogen exchanger 1 and 3, lowering the levels of sodium and calcium in the heart and kidney, respectively. Those exchangers are associated with fibrosis, hypertrophy and sodium retention in the heart [38–

Table 1
Characteristics of included studies.

Author	Year	Study design	Main inclusion criteria	Main exclusion criteria	Sample size (I/P)	Intervention	Dose	Comparator	Follow-up period	Primary outcome	Conclusion
McMurray	2019	Paralell-group phase 3 RCT	Adults with HFrEF*, NYHA II-IV, NT-proBNP $\geq$ 600 pg/ml, receiving drug and device therapies	Recent SGLT2i use or adverse events, T1D, hypotension, eGFR < 30 ml/min/1.73 m2	2373/2371	Dapagliflozin	10 mg once daily	Placebo	24 months	CV death or HF hospitalization or HF urgent visit for HF	Dapagliflozin reduces the risk of primary outcome regardless of diabetes
De Boer	2019	Paralell-group phase 2A RCT	Adults with HFrEF*, NYHA II-IV, T2D, HbA1c 6.5–10%, BMI $\geq$ 22 kg/m^2, eGFR $\geq$ 45 ml/min/1.73 m^2, NT-proBNP > 300 pg/ml	T1D, monogenic diabetes, secondary diabetes, DKA, prior MI or CV intervention, hypotension	Five arms: 15/16/31/30/33	Licogliflozin 2.5 mg Licogliflozin 10 mg Licogliflozin 50 mg Empagliflozin 25 mg All: once daily.		Placebo	12 weeks	NT-proBNP	Licogliflozin shows a potential benefit in reducing NT-proBNP
Nassif	2019	Paralell-group phase 4 RCT	Adults with HFrEF*, NYHA II-III	Recent HF hospitalization, eGFR < 30 ml/min/1.73 m^2, T1D	131/132	Dapagliflozin	10 mg once daily	Placebo	12 weeks	NT-proBNP and KCCQ	Dapagliflozin did not affect NT-proBNP, but increases clinically improvements, especially in non-diabetics.
Jensen	2020	Paralell-group phase 2 RCT	Adults with HFrEF*, NYHA I-III, receiving drug therapy	CRT < 90 days, >85 years, dementia, HF hospitalization < 30 days, hypotension	95/95	Empagliflozin	10 mg once daily	Placebo	12 weeks	NT-proBNP	Empagliflozin did not reduce NT-proBNP
Packer	2020	Paralell-group phase 3 RCT	Adults with HFrEF*, NYHA II-IV, receiving appropriate therapy	Diseases or treatments modifying the clinical course or drug tolerability	1863/1867	Empagliflozin	10 mg once daily	Placebo	38 months	CV death or HF hospitalization	Empagliflozin reduces the risk of the primary outcome regardless of diabetes
Damman	2020	Paralell-group phase 2 RCT	Adults with decompensated HF, NT-proBNP > 1400 pg/ml, eGFR $\geq$ 30 ml/min/1.73 m^2, treated with loop diuretics	T1D, dyspnea due to other causes, ACS or coronary intervention in the 30 days, DKA, pregnancy	40/39	Empagliflozin	10 mg once daily	Placebo	30 days‡	Changes in dyspnea VAS, diuretic response, length of stay, NT-proBNP	Empagliflozin had no effect on primary outcomes
Mordi	2020	Crossover-group phase 4 RCT	Adults with HFrEF†, NYHA II-III, T2D, stable dose of loop diuretic, no hospitalization in the last 3 months	Hypotension, HbA1c < 6%, eGFR < 45 ml/min/1.73 m^2, taking thiazide, chronic liver disease or high liver enzymes	12/11	Empagliflozin	25 mg once daily	Placebo	6 weeks	24-hour urinary volume	Empagliflozin increases urinary volume without increasing urinary sodium
Singh	2020	Paralell-group phase 4 RCT	Adults with HFrEF*, T2D, eGFR of $\geq$ 45 ml/min/1.73 m^2, receiving drug therapy	Severe hepatic disease, CKD > 3b, hypotension, life-threatening diseases	28/28	Dapagliflozin	10 mg once daily	Placebo	12 months	LVESV	Unable to detect effect on LV remodelling
Griffin	2020	Crossover-group phase 1 RCT	Adults with HF, T2D, no hospitalization in the last 60 days, stable HF medication, eGFR of $\geq$ 45 ml/min/1.73 m^2	Medication titration, DKA, hypoglycemia, use of another SGLT2i or adverse events, use of non-loop diuretics, prior heart transplant, valvular or congenital heart diseases	20	Empagliflozin	10 mg once daily	Placebo	4 weeks§	Natriuretic effect	Empagliflozin causes significant natriuresis, particularly when combined with loop diuretics

RCT: randomized controlled trial. HF: heart failure. HFrEF: HF with reduced ejection fraction. NYHA: New York Heart Association. I/P: intervention/placebo. NR: not reported. SGLT2i: sodium-glucose cotransporter-2 inhibitors. T1D: type 1 diabetes mellitus. T2D: type 2 diabetes mellitus. eGFR: estimated glomerular filtration rate. HbA1c: glycated hemoglobin. LV: left ventricle. LVEF: left ventricular ejection fraction. LVESV: left ventricular end-systolic volume. BMI: body mass index. DKA: diabetic ketoacidosis. MI: myocardial infarction. CV: cardiovascular: CVD: cardiovascular disease. ACS: acute coronary syndrome. VAS: visual analogue scale. KCCQ: Kansas City Cardiomyopathy Questionnaire.

† In this study, HFrEF was defined as LVEF < 50%.

‡ In this study, primary outcome were assessed at the day 4.

§ Outcomes were assessed at 2 weeks.

* HFrEF was defined as LVEF < 40%.

Table 2
Characteristics of population of included studies.

Author	Year	Study groups	Age	Male (%)	NYHA	Diabetes (%)	CAD (%)	CKD (%)	History of HF hospitalization (%)	Baseline LVEF (%)	Baseline NT-proBNP pg/ml	Baseline eGFR ml/min/1.73 m^2	Prior pharmacological therapy	Device therapy
McMurray	2019	Dapagliflozin	66.2 (11)	76.2	II: 67.7% III: 31.5% IV: 0.8%	41.8	55.5	NR	47.4	31.2 (6.7)	1428 (857–2655) †	66.0 (19.6)	ACEi: 56.1% ARB: 28.4% ARNI: 10.5% MRA: 71.5% Diuretics: 93.4% Biguanide: 50.8% Insulin: 27.6%	ICD: 26.2% CRT: 8.0%
		Placebo	66.5 (10.8)	77	II: 67.4% III: 31.7% IV: 1.0%	41.8	57.3	NR	47.5	30.9 (6.9)	1446 (857–2641) †	65.5 (19.3)	ACEi: 56.1% ARB: 26.7% ARNI: 10.9% MRA: 70.6% Diuretics: 93.5% Biguanide: 51.7% Insulin: 26.9%	ICD: 26.1% CRT: 6.9%
De Boer	2019	Empagliflozin 25 mg	68.5 (62–74) †	66.7	II: 73.3% III: 26.7% IV: 0%	100	20	6.7	NR	53.9 (45.4–63.7) †	978.5 (649–1292) †	63.5 (56.9–73.1) †	ACEi: 0% ARB: 3.3% Diuretics: 0% ARNI: 0% Metformin: 6.7% Insuline: NR	NR
		Placebo	71 (59–74) †	57.6	II:75.8% III: 24.2% IV: 0%	100	12.1	6.1	NR	55.4 (43.4–61.8) †	894 (477–1447)	66.5 (55.5–78.8) †	ACEi: 0% ARB: 0% Diuretics: 3.3% ARNI: 3.3% Metformin: 21.2% Insuline: NR	NR
Nassif	2019	Dapagliflozin 10 mg	62.2 (11)	72.5	II: 69.5% III: 30.5%	61.8	53.4	NR	77.1	27.2 (8)	1136 (668–2465) †	66.9 (21.1)	ACEI or ARB: 58% ARNI: 35.9% MRA: 58.0% Loop diuretics: 87.0% Insulin: 51.9% Metformin: 35.8%	ICD: 67.2% CRT: 32.8%
		Placebo	60.4 (12)	74.2	II: 62.1% III: 37.9%	64.4	52.3	NR	81.8	25.7 (8.2)	1136 (545–2049) †	71.2 (23.1)	ACEI or ARB: 60.6% ARNI: 28.8% MRA: 63.6% Loop diuretics: 84.1% Insulin: 52.9% Metformin: 38.8%	ICD: 56.8% CRT: 18.9%
Jensen	2020	Empagliflozin 10 mg	64 (57–73) †	83	I: 5.3% II: 76% III: 19%	20	53	Stage 3: 12	52	30 (25–35)	582 (304–1020) †	73 (57–89) †	ACE or ARB or ARNI: 95% ARNI: 33% MRA: 65% Loop diuretics: 65% Insulin: 46% Metformin: 91%	ICD: 47% CRT: 19%
		Placebo	63 (55–72) †	87	I: 7.4% II: 81% III: 12%	15	56	13	53	30 (25–35) †	605 (322–1070) †	74 (60–89) †	ACE or ARB or ARNI: 97% ARNI: 28% MRA: 66% Loop diuretics: 62% Insulin: 23% Metformin: 54%	ICD: 48% CRT: 19%
Packer	2020	Empagliflozin 10 mg	67.2 (10.8)	76.5	II: 75.1% III: 24.4% IV: 0.5%	49.8	52.8	NR	31	27.7 (6)	1887 (1077–3429) †	61.8 (21.7)	ACEi or ARB without: 70.5% ACEi or ARA with ARNI: 18.3% MRA: 70.1%	ICD: 31% CRT: 11.8%

Table 2 (*continued*)

Author	Year	Study groups	Age	Male (%)	NYHA	Diabetes (%)	CAD (%)	CKD (%)	History of HF hospitalization (%)	Baseline LVEF (%)	Baseline NT-proBNP pg/ml	Baseline eGFR ml/min/1.73 m^2	Prior pharmacological therapy	Device therapy
		Placebo	66.5 (11.2)	75.6	II: 75% III: 24.4% IV: 0.6%	49.8	50.7	NR	30.7	27.2 (6.1)	1926 (1153–3525) †	62.2 (21.5)	ACEi or ARB without: 68.9% ACEi or ARB with ARNI: 20.7% MRA: 72.6%	ICD: 31.8% CRT: 11.9%
Damman	2020	Empagliflozin 10 mg	79 (73–83) †	60	III/IV: 92%	38	Myocardial infarction: 30%	NR	NR	36 (17)	4406 (2873–6979) †	55 (18)	ACEI: 40% ARB: 5% ARNI: 5% Loop diuretics: 100% Insulin: NR Metformin: NR	ICD: 8% CRT:15%
		Placebo	73 (61–83) †	74	III/IV: 97%	28	Myocardial infarction: 38%	NR	NR	37 (14)	6168 (3180–10489) †	55 (18)	ACEI: 47% ARB: 3% ARNI: 3% MRA: 45% Loop diuretics: 100% Insulin: NR Metformin: NR	ICD: 23% CRT:13%
Mordi	2020	Empagliflozin 25 mg	69.8 (5.7) *	73.9*	NR	100	43.5*	Stage 3a: 26.1*	NR	NR	2381 (1472–7434)*, †	NR	ACEi: 39.1%	NR
		Placebo			NR	100			NR	NR		NR	ARB: 34.8% MRA: 47.8% ARNI: 13% Loop diuretic: 100% Insulin: 21.7% Metformin: 69.6%*	NR
Singh	2020	Dapagliflozin 10 mg	66.9 (7)	64.3	I: 42.9% II: 46.4% III: 10.7%	100	53.6	NR	NR	44.5 (12.4)	NR	67.7 (16.4)	ACEi or ARB: 89.3% MRA: 46.4% Metformin: 60.7% Insulin: 21.4%	NR
		Placebo	67.4 (6.8)	67.9	I: 46.4% II: 39.3% III: 14.3%	100	53.6	NR	NR	46.5 (11.7)	NR	76.2 (21)	ACEi or ARB: 89.3% MRA: 35.7% Metformin: 50% Insulin: 35.7%	NR
Griffin	2020	Empagliflozin 10 mg	60 (12)*	75*	I-II: 70* III: 30*	100*	60*	NR*	NR*	42.9 (15)*	399 (139–2000)*, †	69.1 (19)*	ACEi or ARB or ARNI: 85% MRA: 50% Loop diuretic: 95% Metformin: 60% Insulin: 40%*	ICD: 50% CRT: 10%*
		Placebo												

NYHA: New York Heart Association. CAD: coronary artery disease. CKD: chronic kidney disease. HF: heart failure. LVEF: left ventricular ejection fraction. eGFR: estimated glomerular filtration rate. NR: not reported. ACEi: angiotensin-converting-enzyme inhibitors. ARB: angiotensin II receptor blockers. CRT: cardiac resynchronization therapy. ICD: implantable cardioverter defibrillator. MRA: mineralocorticoid receptor antagonist. ARNI: angiotensin receptor neprilysin inhibitor.

† Interquartile range.

* Reported for the whole cohort.

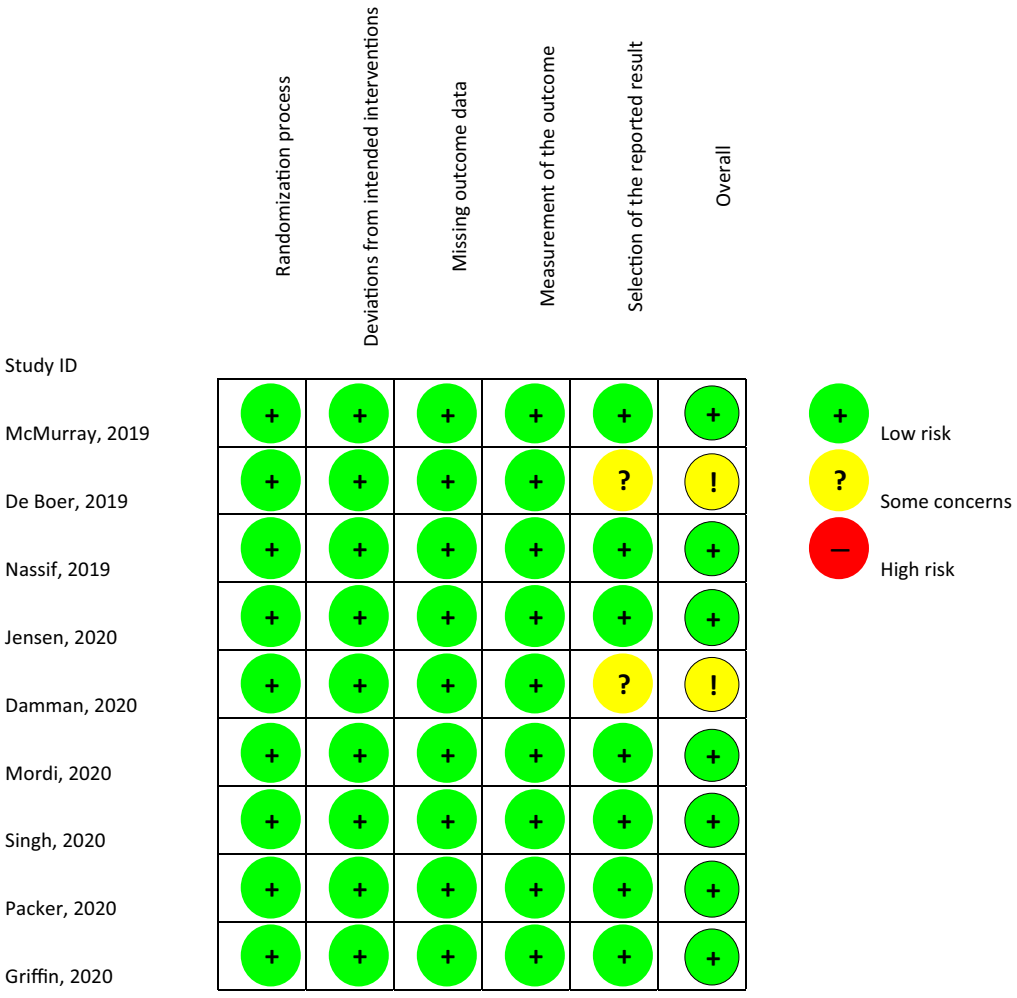


Fig. 2. Risk of bias assessment of included trials.

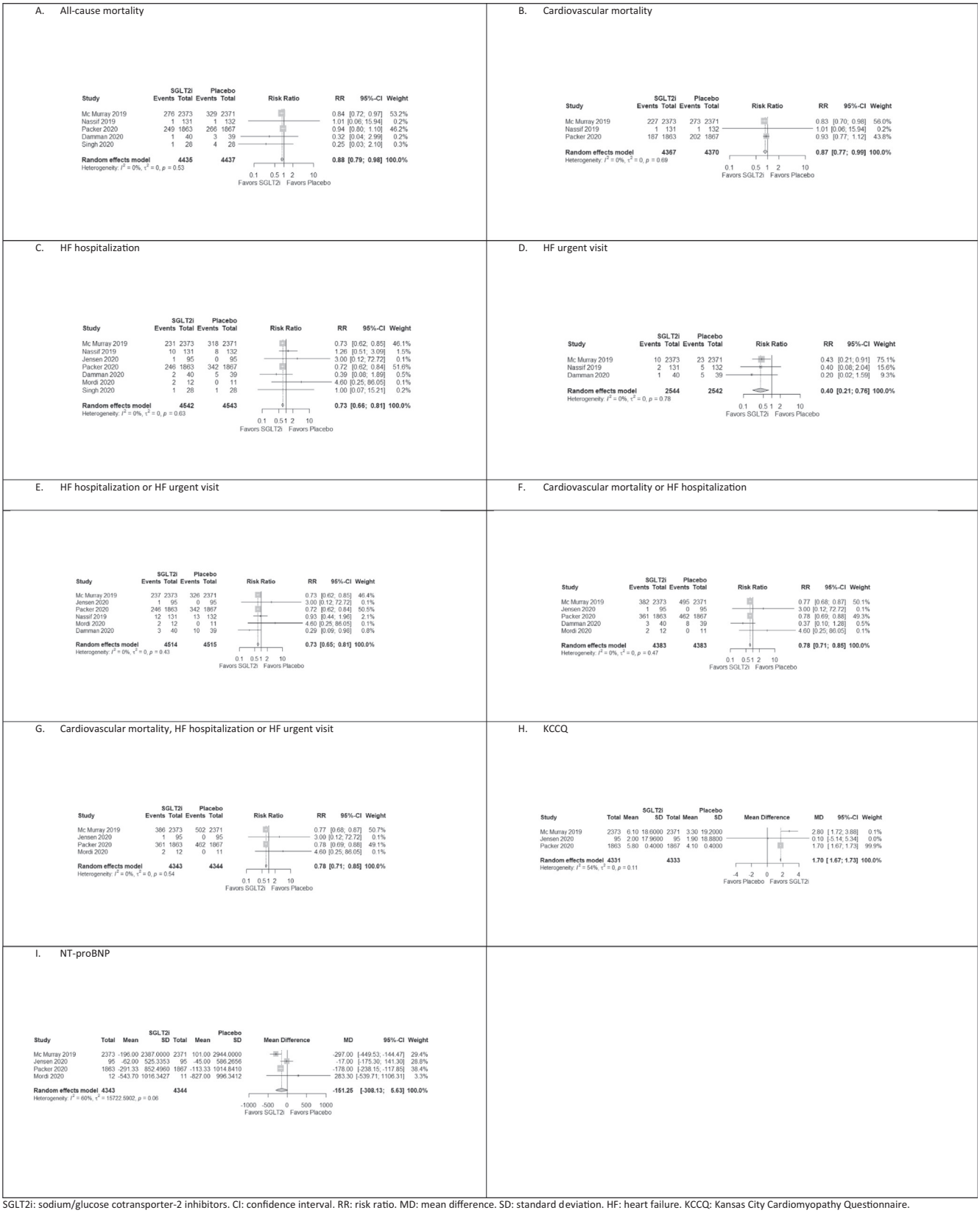
41,44]. Other cardiorenal benefit pathways are reduction in systemic blood pressure and plasma uric acid, and increase in natriuresis and hematocrit [41].

In 2019, the American Diabetes Association updated the 2018 consensus on hyperglycemia, mainly recommending SGLT2i in patients with diabetes and HFrEF [45]. However, since the last year, many trials on HF patients in absence of diabetes have been published.

The DAPA-HF was a placebo-controlled RCT that randomly assigned NYHA II-IV HFrEF patients to dapagliflozin, a SGLT2i, or placebo. Authors concluded that dapagliflozin significantly reduced the risk of the composite outcome (cardiovascular death, HF hospitalization, and emergency room visits due to HF) [15]. Recently, the EMPEROR-Reduced was published. It was a placebo-controlled RCT that randomly assigned NYHA II-IV HFrEF patients to empagliflozin or placebo, concluding that the intervention significantly reduced cardiovascular death or HF hospitalization in absence of diabetes [29]. Other trials in HFrEF patients have shown important results. The DEFINE-HF trial reported that patients randomized to dapagliflozin showed superior clinical improvement, which was measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ), than those in placebo group [16]. De Boer et al [27] published a phase 2 RCT, comparing three doses of licogliflozin, which is a SGLT1/2 inhibitor, empagliflozin and placebo. They observed greater reduce of SBP in the empagliflozin group compared to placebo.

Despite the quantity of new published RCTs, DAPA-HF and EMPEROR-Reduced are the most significant trials for SGLT2i in HF due to its large sample size, which are higher than 3000 patients each one. In this context, Zannad et al [46] meta-analyzed those trials, however they did not perform a systematic review of more trials. They pooled data of 8474 patients, and reported that SGLT2i significantly decreased the risk of all-cause and cardiovascular death, and two composite outcomes (cardiovascular death or HF hospitalization, and cardiovascular death or recurrent hospitalizations), and reduced renal adverse events. Additionally, they showed that the effect was consistent in several subgroups (age, sex, diabetes, treatment with angiotensin receptor neprilysin inhibitor, and baseline eGFR), but it was considerably different in NYHA II patients compared to NYHA III-IV.

A recent systematic review included RCTs and subgroup analyses enrolling HFrEF patients randomized to a SGLT2i [47]. However, there are some debatable issues and differences with our review. Authors included six trials, and two of them were included in our review: DAPA-HF and DEFINE-HF [15,16], where all patients had HFrEF. However, HF prevalence in the other four trials were<15%. This situation is important for interpretation of results, because meta-analyzing data of trials with heterogeneous populations may reduce the value of global estimates. In our systematic review, we included RCTs with HF prevalence of 100%, therefore, compared to the cited review, our results are more homogenous regarding the population.



SGLT2i: sodium/glucose cotransporter-2 inhibitors. CI: confidence interval. RR: risk ratio. MD: mean difference. SD: standard deviation. HF: heart failure. KCCQ: Kansas City Cardiomyopathy Questionnaire.

Fig. 3. Effect of SGLT2i on primary and other outcomes. SGLT2i: sodium/glucose cotransporter-2 inhibitors. CI: confidence interval. RR: risk ratio. MD: mean difference. SD: standard deviation. HF: heart failure. KCCQ: Kansas City Cardiomyopathy Questionnaire.

Table 3
GRADE summary of findings (primary pooled outcomes).

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	**Risk with SGLT2i**			
All-cause mortality	136 per 1000	120 per 1000 (107 to 133)	RR 0.88 (0.79 to 0.98)	8872 (5 RCTSs)	⊕⊕⊕⊕HIGH
Cardiovascular mortality	109 per 1000	95 per 1000 (84 to 108)	RR 0.87 (0.77 to 0.99)	8737 (3 RCTs)	⊕⊕⊕⊕ HIGH
HF hospitalization	148 per 1000	108 per 1000 (98 to 120)	RR 0.73 (0.66 to 0.81)	9085 (7 RCTs)	⊕⊕⊕⊕ HIGH
HF urgent visit	13 per 1000	5 per 1000 (3 to 10)	RR 0.40 (0.21 to 0.76)	5086 (3 RCTs)	⊕⊕⊕⊕ HIGH
HF hospitalization or HF urgent visit	153 per 1000	112 per 1000 (99 to 124)	RR 0.73 (0.65 to 0.81)	9029 (6 RCTs)	⊕⊕⊕⊕ HIGH
Cardiovascular mortality or HF hospitalization	220 per 1000	172 per 1000 (156 to 187)	RR 0.78 (0.71 to 0.85)	8766 (5 RCTs)	⊕⊕⊕⊕ HIGH
Cardiovascular mortality, HF hospitalization or HF urgent visit	222 per 1000	173 per 1000 (158 to 189)	RR 0.78 (0.71 to 0.85)	8687 4 RCTs)	⊕⊕⊕⊕ HIGH
NT-proBNP	–	MD 151.25 pg/ml lower (308.13 lower to 5.63 higher)	–	8687 (4 RCTs)	⊕⊕◯◯ LOW [a,b]
KCCQ	–	MD 1.7 points higher (1.67 higher to 1.73 higher)	–	8664 (3 RCTs)	⊕⊕⊕◯ MODERATE [a]

CI: confidence interval. RR: risk ratio. MD: mean difference. RCT: randomized controlled trial. HF: heart failure. KCCQ: Kansas City Cardiomyopathy Questionnaire. GRADE: Grading of Recommendations Assessment, Development and Evaluation.
GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
a. The I^2 was higher than 40%.
b. Confidence interval crosses the non-effect value.

- To our knowledge, this is the first systematic review of randomized controlled trials that assessed the effects and safety of sodium-glucose transporter 2 inhibitors (SGLT2i) compared to placebo in patients with heart failure regardless of diabetes.
- Compared to placebo, SGLT2i reduced mortality, hospitalization, urgent visits, and improved quality of life (Kansas City Cardiomyopathy Questionnaire).
- SGLT2i showed to improve critical outcomes in patients with heart failure, and it is apparently safe.

4.3. What our study adds to literature?

We assessed more RCTs and outcomes than the two previous meta-analyses. We did not repeat meta-analyses that were already done in Zannad's meta-analysis, such as subgroup analyses by baseline variables (i.e.: sex, age and diabetes) [46]. But we extended the pooled outcomes if new RCTs added information. Our meta-analyses are consistent with Zannad's meta-analyses. Regarding quality of life, which was measured with the KCCQ, SGLT2i showed a statistically significant benefit, but it was not clinically significant; possibly, because patients had compensated HF. Additionally, we performed subgroup analyses by intervention drug and follow-up period. Our results suggest that there might be slight differences in benefit between dapagliflozin and empagliflozin, and assessing outcomes at a longer follow-up showed a benefit in NT-proBNP. Our GRADE approach might be useful when evaluating SGLT2i in future clinical practice guidelines.

Both dapagliflozin and empagliflozin differ in their pharmacokinetics. It could partially explain the differences found in our meta-analyses. Empagliflozin at 10 mg reaches its concentration peak between 1 and 1.5 h in both healthy and diabetic patients, with an a half-life of 9.88 h in healthy subjects, 7.61 h in diabetic young, and 8.8 to 11.9 h in diabetic adults [48–52]. While dapagliflozin, using the same dose, reaches its maximum concentration faster, between 1.0 and 1.3 h, and its half-life is 12.1 h in healthy subjects [53,54].

In relation to safety outcomes, we could not meta-analyze diabetic ketoacidosis (DKA) or acute kidney injury (AKI) due to lack of data. A previous meta-analysis showed a risk two times higher of DKA in patients assigned to SGLT2i compared with the placebo group, however the incidence rate was low [12]. Regarding AKI, a meta-analysis reported that SGLT2i was associated with a reduction of 34% in AKI risk [55]. Furthermore, our results evidenced that SGLT2i increased creatinine and hematocrit. A previous systematic review found that SGLT2i compared to placebo was associated with initial increase of creatinine, but followed by return to baseline levels in patients with renal impairment [56]. We collected information on baseline eGFR, and several RCTs reported values surrounding the cut-off of impaired function (<60 ml/min/1.73 mi n^2), therefore clinicians should consider monitoring renal function in HF patients taking SGLT2i, especially in chronic kidney disease. We found that SGLT2i was associated with increased hematocrit. Despite this event may contribute to better cardiovascular outcomes and previous reviews support beneficial effects [41,57], other reviews suggest that hemoconcentration may increase the risk of thrombosis [58], besides, large cohorts have evidenced an independent associated between high hematocrit, incidence of stroke, and early post-stroke mortality [59,60].

In this way, we recommend that future phase 4 trials must state specific adverse events as primary outcomes. Moreover, Zannad's meta-analyses suggest that there could be better benefit in NYHA II [46], however non-planned baseline differences in groups (NYHA II vs. III-IV) may be increased, leading to statistically significant differences. Therefore we do encourage future trials on NYHA II to confirm those results.

Aside from clinical trials, some studies have estimated the impact of SGLT2i in the real-world setting [61–64]. Arnold et al [61] evaluated patients of the Diabetes Collaborative Registry,

and described that 26.2% of patients met the inclusion criteria for taking SGLT2i, but only 5.2% did it, causing more death and hospitalization rates. Cardiovascular benefits of SGLT2i over other glycosuric-agents has been proven in the real-world setting [65,66]. The largest study included 40 thousand patients from three different countries, reporting that dapagliflozin was associated with 21% lower risk of major adverse cardiovascular events and 38% lower risk of HF hospitalization compared with DPP-4 inhibitors [67]. Another multinational cohort also described that SGLT2i was associated with a significant reduction in new HF events and death compared to other oral hypoglycemic agents [63]. Bassi et al [64] projected that around 69% of patients with HFrEF in the United States will be candidates for using SGTL2i, and this implementation will considerably prevent the number of deaths per year.

A multinational analysis based on DAPA-HF trial evaluated dapagliflozin as an additional treatment for HF, and a positive incremental cost-effectiveness ratio was described [68]. Moreover, a gaining in life-years and quality-adjusted life-years with the implementation of dapagliflozin was also identified [68]. In this way, other analyses based on studies in patients with diabetes found that this drug is cost-effective [69,70]. Canagliflozin has been demonstrated to reduce the cost of HF hospitalization and total healthcare costs in patients with diabetes and established cardiovascular disease [71].

4.4. Limitations

Our study has several limitations. First, despite there are several SGLT2i, we found evidence on only two SGLT2i (dapagliflozin and empagliflozin) that were compared with placebo. Then, only two studies (McMurray's and Packer's RCTs) mainly contributed to meta-analyses due to its large sample size. Nevertheless, we found low heterogeneity in the majority of analyses. Only two studies had safety outcomes (24-hour urinary volume and natriuretic effect) as primary outcomes, besides, they could not be meta-analyzed. Seven out of nine RCTs included only patients with HFrEF, therefore our results should not be applicable for HF with preserved ejection fraction. Finally, due to the low number of studies in each meta-analysis, we could not explore meta-regression between prognostic variables, such as coronary artery disease and diabetes, and RRs.

4.5. Conclusions

To our knowledge, this is the first systematic review of RCTs comparing SGLT2i with placebo in patients with HF. Our meta-analyses demonstrate multiple positive effects and acceptable safety of SGLT2i in critical outcomes in HF.

5. Authors' statement

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100690.

References

[1] F. Ceia, C. Fonseca, T. Mota, H. Morais, F. Matias, A. de Sousa, et al., Prevalence of chronic heart failure in Southwestern Europe: the EPICA study, Eur. J. Heart Fail. 4 (4) (2002) 531–539.
[2] E.J. Benjamin, M.J. Blaha, S.E. Chiuve, M. Cushman, S.R. Das, R. Deo, et al., Heart Disease and Stroke Statistics—2017 Update, Circulation 135 (10) (2017) e146–e603.
[3] G. Savarese, L.H. Lund, Global Public Health Burden of Heart Failure, Card. Fail. Rev. 3 (1) (2017) 7–11.
[4] E.J. Benjamin, P. Muntner, A. Alonso, M.S. Bittencourt, C.W. Callaway, A.P. Carson, et al., Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association, Circulation 139 (10) (2019) e56–e528.
[5] A.L. Bui, T.B. Horwich, G.C. Fonarow, Epidemiology and risk profile of heart failure, Nat. Rev. Cardiol. 8 (1) (2011) 30–41.
[6] P. van der Meer, H.K. Gaggin, G.W. Dec, ACC/AHA Versus ESC Guidelines on Heart Failure: JACC Guideline Comparison, J. Am. Coll. Cardiol. 73 (21) (2019) 2756–2768.
[7] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G.F. Cleland, A.J.S. Coats, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failureThe Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 37 (27) (2016) 2129–2200.
[8] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey, M.M. Colvin, et al., 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, J. Am. Coll. Cardiol. 70 (6) (2017) 776–803.
[9] D. Berliner, J. Bauersachs, Current Drug Therapy in Chronic Heart Failure: the New Guidelines of the European Society of Cardiology (ESC), Korean Circ. J. 47 (5) (2017) 543–554.
[10] H. Burnett, A. Earley, A.A. Voors, M. Senni, J.J.V. McMurray, C. Deschaseaux, et al., Thirty Years of Evidence on the Efficacy of Drug Treatments for Chronic Heart Failure With Reduced Ejection Fraction, Circ. Heart Fail. 10 (1) (2017) e003529.
[11] Kidney Disease Improving Global Outcomes. KDIGO CLINICAL PRACTICE GUIDELINE ON DIABETES MANGEMENT IN CHRONIC KIDNEY DISEASE. 2019 [cited on September 1st 2020]. Available in: https://kdigo.org/wp-content/uploads/2018/03/KDIGO-Diabetes-Management-in-CKD_Public-Review.pdf.
[12] T.A. Zelniker, S.D. Wiviott, I. Raz, K. Im, E.L. Goodrich, M.P. Bonaca, 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, The Lancet. 393 (10166) (2019) 31–39.
[13] Y. Maejima, SGLT2 Inhibitors Play a Salutary Role in Heart Failure via Modulation of the Mitochondrial Function, Front. Cardiovasc. Med. 6 (2020) 186.
[14] M. Packer, SGLT2 Inhibitors Produce Cardiorenal Benefits by Promoting Adaptive Cellular Reprogramming to Induce a State of Fasting Mimicry: A Paradigm Shift in Understanding Their Mechanism of Action, Diab. Care 43 (3) (2020) 508–511.
[15] J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, et al., Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction, N. Engl. J. Med. 381 (21) (2019) 1995–2008.
[16] M.E. Nassif, S.L. Windsor, T. Fengming, K. Yevgeniy, H. Mansoor, S.E. Inzucchi, et al., Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction, Circulation 140 (18) (2019) 1463–1476.
[17] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, BMJ 339 (b2535) (2009).
[18] J.P.T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. Page, V. Welch, (Eds.) Cochrane Handbook for Systematic Reviews of Interventions. (2nd ed.) Wiley-Blackwell, 2019.
[19] Diego Chambergo-Michilot, Astrid Tauma-Arrué, Silvana Loli-Guevara, Figshare-protocol of a systematic review.docx. figshare. Online resource. Available in: https://doi.org/10.6084/m9.figshare.12933833.v3, 2020.
[20] A.A. Veroniki, D. Jackson, W. Viechtbauer, et al., Methods to estimate the between-study 2 variance and its uncertainty in meta-analysis, Res. Synth. Methods 7 (1) (2016) 55–79, 3.
[21] J. IntHout, J.P.A. Ioannidis, G.F. Borm, The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method, BMC Med. Res. Methodol. 14 (2014) 25.
[22] R. Fu, B.W. Vandermeer, T.A. Shamliyan, M.E. O'Neil, F. Yazdi, S.H. Fox, et al. Handling Continuous Outcomes in Quantitative Synthesis. En: Methods Guide for Effectiveness and Comparative Effectiveness Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008. (AHRQ Methods

for Effective Health Care). Available in: http://www.ncbi.nlm.nih.gov/books/NBK154408/.
[23] X. Wan, W. Wang, J. Liu, T. Tong, Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range, BMC Med. Res. Methodol. 14 (2014) 135.
[24] J.P.T. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ 327 (7414) (2003) 557–560.
[25] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a 8 simple, graphical test, BMJ 315 (7109) (1997) 629–634.
[26] G. Guyatt, A.D. Oxman, E.A. Akl, R. Kunz, G. Vist, J. Brozek, et al., GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables, J. Clin. Epidemiol. 64 (4) (2011) 383–394.
[27] R.A. de Boer, J. Núñez, P. Kozlovski, Y. Wang, P. Proot, D. Keefe, Effects of the dual sodium–glucose linked transporter inhibitor, licogliflozin vs placebo or empagliflozin in patients with type 2 diabetes and heart failure, Br. J. Clin. Pharmacol. 86 (7) (2020) 1346–1356.
[28] J. Jensen, M. Omar, C. Kistorp, M.K. Poulsen, C. Tuxen, I. Gustafsson, et al., Twelve weeks of treatment with empagliflozin in patients with heart failure and reduced ejection fraction: A double-blinded, randomized, and placebo-controlled trial, Am. Heart J. 228 (2020) 47–56.
[29] M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, et al., Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2022190.
[30] K. Damman, J.C. Beusekamp, E.M. Boorsma, H.P. Swart, T.D.J. Smilde, A. Elvan, 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. 22 (4) (2020) 713–722.
[31] A. Mordi Natalie, R. Mordi Ify, S. Singh Jagdeep, J. McCrimmon Rory, D. Struthers Allan, C. Lang Chim, 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. 0(0). DOI: https://doi.org/10.1161/CIRCULATIONAHA.120.048739.
[32] J.S.S. Singh, I.R. Mordi, K. Vickneson, A. Fathi, P.T. Donnan, M. Mohan, et al., Dapagliflozin Versus Placebo on Left Ventricular Remodeling in Patients With Diabetes and Heart Failure: The REFORM Trial, Diab. Care 43 (6) (2020) 1356–1359.
[33] Matthew Griffin, S. Rao Veena, Juan Ivey-Miranda, James Fleming, Devin Mahoney, Christopher Maulion, et al. Empagliflozin in Heart Failure. Circulation 142(11) (2020) 1028-1039.
[34] B. Neal, V. Perkovic, K.W. Mahaffey, D. de Zeeuw, G. Fulcher, N. Erondu, et al., Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes, N. Engl. J. Med. 377 (7) (2017) 644–657.
[35] B. Zinman, C. Wanner, J.M. Lachin, D. Fitchett, E. Bluhmki, S. Hantel, et al., Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes, N. Engl. J. Med. 373 (22) (2015) 2117–2128.
[36] D. Fitchett, B. Zinman, C. Wanner, J.M. Lachin, S. Hantel, A. Salsali, 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. 37 (19) (2016) 1526–1534.
[37] S. Verma, A. Sharma, B. Zinman, A.P. Ofstad, D. Fitchett, M. Brueckmann, et al., Empagliflozin reduces the risk of mortality and hospitalization for heart failure across Thrombolysis In Myocardial Infarction Risk Score for Heart Failure in Diabetes categories: Post hoc analysis of the EMPA-REG OUTCOME trial, Diab. Obes. Metab. 22 (7) (2020) 1141–1150.
[38] P. Grubić Rotkvić, M. Cigrovski Berković, N. Bulj, L. Rotkvić, I. Ćelap, Sodium-glucose cotransporter 2 inhibitors' mechanisms of action in heart failure, World J. Diab. 11 (7) (2020) 269–279.
[39] B. Lin, N. Koibuchi, Y. Hasegawa, D. Sueta, K. Toyama, K. Uekawa, et al., Glycemic control with empagliflozin, a novel selective SGLT2 inhibitor, ameliorates cardiovascular injury and cognitive dysfunction in obese and type 2 diabetic mice, Cardiovasc. Diabetol. 13 (2014) 148.
[40] N. Katsiki, D.P. Mikhailidis, M.J. Theodorakis, Sodium-glucose Cotransporter 2 Inhibitors (SGLT2i): Their Role in Cardiometabolic Risk Management, Curr. Pharm. Des. 23 (10) (2017) 1522–1532.
[41] M.R. Cowie, M. Fisher, SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control, Nat. Rev. Cardiol. 1–12 (2020).
[42] S.R. Kim, S.-G. Lee, S.H. Kim, J.H. Kim, E. Choi, W. Cho, et al., SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease, Nat. Commun. 11 (1) (2020) 2127.
[43] L. Uthman, A. Baartscheer, B. Bleijlevens, C.A. Schumacher, J.W.T. Fiolet, A. Koeman, et al., Class effects of SGLT2 inhibitors in mouse cardiomyocytes and hearts: inhibition of Na+/H+ exchanger, lowering of cytosolic Na+ and vasodilation, Diabetologia 61 (3) (2018) 722.
[44] Y.-H. Chan, T.-J. Hsu, C.-L. Wang, Y.-W. Kao, C.-Y. Huang, P.-H. Chu, Sodium glucose cotransporter-2 inhibitor was associated with an improvement in left ventricular systolic function in patients with type 2 diabetes mellitus with impaired left ventricular systolic function, ESC Heart Fail. (2020), https://doi.org/10.1002/ehf2.12877(n/a).
[45] J.B. Buse, D.J. Wexler, A. Tsapas, P. Rossing, G. Mingrone, C. Mathieu, et al. 2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2019. Available in: https://care.diabetesjournals.org/content/early/2019/12/18/dci19-0066.
[46] F. Zannad, J.P. Ferreira, S.J. Pocock, S.D. Anker, J. Butler, G. Filippatos, et al., SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials, The Lancet. 396 (10254) (2020) P819–P829.
[47] K. Kumar, B. Kheiri, T.F. Simpson, M. Osman, H. Rahmouni, Sodium-Glucose Cotransporter-2 Inhibitors in Heart Failure: A Meta-Analysis of Randomized Clinical Trials, Am. J. Med. (2020), https://doi.org/10.1016/j.amjmed.2020.04.006.
[48] A. Sarashina, K. Koiwai, L.J. Seman, N. Yamamura, A. Taniguchi, T. Negishi, et al., Safety, tolerability, pharmacokinetics and pharmacodynamics of single doses of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in healthy Japanese subjects, Drug Metab. Pharmacokinet. 28 (3) (2013) 213–219.
[49] S. Macha, T. Brand, T. Meinicke, J. Link, U.C. Broedl, Pharmacokinetics and Pharmacodynamics of Twice Daily and Once Daily Regimens of Empagliflozin in Healthy Subjects, Clin. Ther. 37 (8) (2015) 1789–1796.
[50] L.M.B. Laffel, W.V. Tamborlane, A. Yver, G. Simons, J. Wu, V. Nock, et al., Pharmacokinetic and pharmacodynamic profile of the sodium-glucose co-transporter-2 inhibitor empagliflozin in young people with Type 2 diabetes: a randomized trial, Diab. Med. 35 (8) (2018) 1096–1104.
[51] T. Heise, E. Seewaldt-Becker, S. Macha, S. Hantel, S. Pinnetti, L. Seman, et al., Safety, tolerability, pharmacokinetics and pharmacodynamics following 4 weeks' treatment with empagliflozin once daily in patients with type 2 diabetes, Diab. Obes. Metab. 15 (7) (2013) 613–621.
[52] T. Heise, L. Seman, S. Macha, P. Jones, A. Marquart, S. Pinnetti, et al., Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Rising Doses of Empagliflozin in Patients with Type 2 Diabetes Mellitus, Diab. Ther. 4 (2) (2013) 331–345.
[53] S. Sha, D. Polidori, K. Farrell, A. Ghosh, J. Natarajan, N. Vaccaro, et al., Pharmacodynamic differences between canagliflozin and dapagliflozin: results of a randomized, double-blind, crossover study, Diab. Obes. Metab. 17 (2) (2015) 188–197.
[54] S. Kasichayanula, M. Chang, M. Hasegawa, X. Liu, N. Yamahira, F.P. LaCreta, et al., Pharmacokinetics and pharmacodynamics of dapagliflozin, a novel selective inhibitor of sodium-glucose co-transporter type 2, in Japanese subjects without and with type 2 diabetes mellitus, Diab. Obes. Metab. 13 (4) (2011) 357–365.
[55] R.E. Gilbert, K.E. Thorpe, Acute kidney injury with sodium-glucose co-transporter-2 inhibitors: A meta-analysis of cardiovascular outcome trials, Diab. Obes. Metab. 21 (8) (2019) 1996–2000.
[56] S. Seidu, S.K. Kunutsor, X. Cos, S. Gillani, K. Khunti, For and on behalf of Primary Care Diabetes Europe. SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment: A systematic review and meta-analysis, Prim. Care Diab. 12 (3) (2018) 265–283.
[57] B.M. Bonora, A. Avogaro, G.P. Fadini, Extraglycemic Effects of SGLT2 Inhibitors: A Review of the Evidence, Diab. Metab. Syndr. Obes. Targets Ther. 13 (2020) 161–174.
[58] M. Guo, J. Ding, J. Li, J. Wang, T. Zhang, C. Liu, et al., SGLT2 inhibitors and risk of stroke in patients with type 2 diabetes: A systematic review and meta-analysis, Diab. Obes. Metab. 20 (8) (2018) 1977–1982.
[59] R. Yang, A. Wang, L. Ma, Z. Su, S. Chen, Y. Wang, et al., Hematocrit and the incidence of stroke: a prospective, population-based cohort study, Ther. Clin. Risk Manag. 14 (2018) 2081–2088.
[60] J.J. Sico, L.J. Myers, B.J. Fenton, J. Concato, L.S. Williams, D.M. Bravata, Association between admission haematocrit and mortality among men with acute ischaemic stroke, Stroke Vasc. Neurol. 3 (3) (2018) 160–168.
[61] S.V. Arnold, S.E. Inzucchi, F. Tang, D.K. McGuire, S.N. Mehta, T.M. Maddox, et al., Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: An NCDR® Research to Practice project, Eur. J. Prev. Cardiol. 24 (15) (2017) 1637–1645.
[62] H.-Y. Chen, J.-Y. Huang, W.-Z. Siao, G.-P. Jong, The association between SGLT2 inhibitors and new-onset arrhythmias: a nationwide population-based longitudinal cohort study, Cardiovasc. Diabetol. 19 (1) (2020) 73.
[63] M.A. Cavender, A. Norhammar, K.I. Birkeland, M.E. Jorgensen, J.P.H. Wilding, K. Khunti, et al., Hospitalization for Heart Failure and Death in New Users of SGLT-2 Inhibitors in Patients With and Without Cardiovascular Disease—CVD Real Study, Can. J. Diab. 41 (5) (2017) S51–S52.
[64] N.S. Bassi, B. Ziaeian, C.W. Yancy, G.C. Fonarow, Association of Optimal Implementation of Sodium-Glucose Cotransporter 2 Inhibitor Therapy With Outcome for Patients With Heart Failure, JAMA Cardiol. 5 (8) (2020) 948–951.
[65] P.B. Ryan, J.B. Buse, M.J. Schuemie, F. DeFalco, Z. Yuan, P.E. Stang, et al., Comparative effectiveness of canagliflozin, SGLT2 inhibitors and non-SGLT2 inhibitors on the risk of hospitalization for heart failure and amputation in patients with type 2 diabetes mellitus: A real-world meta-analysis of 4 observational databases (OBSERVE-4D), Diab. Obes. Metab. 20 (11) (2018) 2585–2597.
[66] M. Kosiborod, M.A. Cavender, A.Z. Fu, J.P. Wilding, K. Khunti, R.W. Holl, et al., Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors), Circulation 136 (3) (2017) 249–259.
[67] F. Persson, T. Nyström, M.E. Jørgensen, B. Carstensen, H.L. Gulseth, M. Thuresson, et al., Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes

(CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: A multinational observational study, Diab. Obes. Metab. 20 (2) (2018) 344–351.

[68] P. McEwan, O. Darlington, J.J.V. McMurray, P.S. Jhund, K.F. Docherty, M. Böhm, et al. Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: a multinational health-economic analysis of DAPA-HF. Eur. J. Heart Fail. 2020. Available in: https://onlinelibrary.wiley.com/doi/abs/10.1002/ejhf.1978.

[69] A. Kansal, O.S. Reifsnider, I. Proskorovsky, Y. Zheng, E. Pfarr, J.T. George, et al., Cost-effectiveness analysis of empagliflozin treatment in people with Type 2 diabetes and established cardiovascular disease in the EMPA-REG OUTCOME trial, Diab. Med. 36 (11) (2019) 1494–1502.

[70] A. Abotaleb, M. Amin, PDB40 - impact of dapagliflozin on reducing economic burden of type 2 diabetes & enhancement patient's outcomes at countries with high incidence of diabetes Egypt case, Value Health. 21 (2018) S124–S125.

[71] Y.-W. Chen, J. Voelker, O. Tunceli, C.D. Pericone, B. Bookhart, M. Durkin, Real-world comparison of hospitalization costs for heart failure in type 2 diabetes mellitus patients with established cardiovascular disease treated with canagliflozin versus other antihyperglycemic agents, J. Med. Econ. 23 (4) (2020) 401–406.