

Systematic Review

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Insufficient evidence regarding benefits from sodium-glucose cotransporter-2 inhibitors in heart failure with preserved ejection fraction

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Abstract

Aim: Sodium-glucose cotransporter-2 (SGLT2)-inhibitors improve survival in adults with reduced ejection fraction. Clinical outcomes in adults with heart failure (HF) with preserved ejection fraction (HFpEF) have not been systematically reviewed.

Methods: We conducted a systematic rapid literature review and appraised the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation methodology.

Results: We identified *post-hoc* subgroup analyses of four randomized controlled clinical trials (RCTs) and unpublished results from 2 RCTs. In 2 RCTs *vs.* placebo, Canagliflozin reduced the risk of fatal or hospitalized HF in adults with HF and documented or assumed left ventricular ejection fraction (LVEF) $\geq 50\%$ (hazard rate ratio, HR = 0.71, 95%CI: 0.52-0.97) but had no effect in a subpopulation with documented LVEF $\geq 50\%$ (HR = 0.83, 95%CI: 0.55-1.25). Dapagliflozin or ertugliflozin did not improve all-cause or cardiovascular death or hospitalization for HF in adults with HF and LVEF $> 45\%$ in two pivotal RCTs *vs.* placebo. Empagliflozin did not improve exercise ability, patient-reported outcomes or congestion, diuretic use and all-cause healthcare resource utilization in unpublished RCT *vs.* placebo. Various definitions of HFpEF, *post-hoc* interaction analyses suggesting outcome improvement



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regardless of heart failure type, small number of events, and probable publication bias hampered the quality of evidence.

Conclusion: Existing evidence is insufficient to support definitive clinical recommendations for use of SGLT2-inhibitors in adults with HFpEF. Future research should employ consistent definitions of HFpEF and examine the effects from SGLT2- Inhibitors in patients with various HFpEF phenotypes and underlying causes.

Keywords: Sodium-glucose cotransporter-2 - inhibitors, heart failure with preserved ejection fraction, cardiovascular mortality, heart failure hospitalization, systematic literature review, grading of recommendations assessment, development and evaluation methodology

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) presents a significant and growing clinical and economic burden in aging populations, specifically with prevalent arterial hypertension and diabetes^[1-4]. Estimated 1-year all-cause mortality rates of 33% and all cause readmission rates of 67% in patients with HFpEF have not improve over the last decade in the US^[3]. Diabetes is a widely recognized risk factor for cardiovascular morbidity and mortality^[5,6]. Although emerging treatments improved cardiovascular outcomes in people with diabetes^[7,8], no treatments have been proven to improve survival and reduce health care utilization in people with HFpEF^[9-14]. Sodium-glucose cotransporter-2 (SGLT2)- inhibitors are found to improve survival in heart failure with reduce ejection fraction and reduce the risk of major cardiovascular events including heart failure hospitalizations in adults with type 2 diabetes^[15-19]. Empagliflozin and canagliflozin have been approved by the US Food and Drug Administration (FDA) to reduce the risk of cardiovascular death in adults with type 2 diabetes and established cardiovascular disease while dapagliflozin has also been approved to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with reduced left ventricular ejection fraction (LVEF \leq 40%)^[20-25]. Recent evidence-based guidelines recommend SGLT2- inhibitors for the improvement in cardiovascular outcomes in adults with type 2 diabetes^[26-29]. However, the evidence regarding the benefits from SGLT2- inhibitors in adults with HFpEF has not been systematically reviewed and appraised. We conducted a systematic rapid literature review of all completed and ongoing clinical studies aimed at patient outcomes in adults with HFpEF.

METHODS

We conducted our review according to the developed priori protocol^[30-32]. We hypothesized that SGLT2-inhibitors improve cardiovascular mortality, morbidity and hospitalizations in adults with HFpEF, with or without diabetes^[33-38].

Eligible interventions included SGLT2- inhibitors regardless of country' approval [Supplementary Table 1] focusing on the availability in the US, for example dapagliflozin, canagliflozin, empagliflozin and ertugliflozin [Supplementary Table 2]. We included studies that compared SGLT2- inhibitors with antidiabetic medications or placebo. We abstracted reported number of events or rates of all-cause and cardiovascular mortality, incident or progressing of heart failure, and hospitalizations for heart failure^[14,39]. We also looked at the reported intermediate outcomes, e.g., exercise tolerability and the quality of life or other patient reported outcomes as defined in the primary studies^[40-45].

We conducted a comprehensive search with MeSH terms and key words in PubMed, Scopus, the Cochrane Library, www.clinicaltrials.gov, the World Health organization International Clinical Trials Registry Platform, Health Technology Assessment databases, and regulatory agencies up to October 2020 to find

systematic reviews, published and unpublished randomized controlled clinical trials (RCTs), and real-world evidence from the high quality nationally representative controlled observational studies^[30,31]. All of the authors looked at the retrieved publications as well as the evidence-based guidelines that provided definitions of HFpEF and recommend treatments for HFpEF. We documented the eligibility of studies in a reference database.

We planned a quantitative direct meta-analysis of similar interventions and outcomes using random effects models in compliance with recommended meta-analytic methods^[46]. We intended to calculate pooled relative risk, absolute risk difference, number needed to treat and number of attributable events per 1000 treated with 95% confidence intervals (CI). We proposed to examine inconsistency in treatment effects with recommended I² statistics (if I² was > 50%)^[30]. We planned pooled analyses regardless of statistically significant heterogeneity^[46]. Instead, we proposed exploring heterogeneity with a priori defined patient characteristics, e.g., definitions of HFpEF, outcomes, and study quality^[46].

Since *post hoc* analyses of statistical power is not recommended^[47-50], we downgraded the quality of evidence for imprecision based on an estimated priori optimal information size in an adequately powered RCT (e.g., ≥ 250 patients with the event)^[51].

We concluded statistical significance at a 95% confidence level using Statistics/Data Analysis, STATA software (StataCorp LP, College Station, Texas).

We judged the risk of bias in primary studies with the Cochrane risk of bias tool^[52-54]. We judged the quality of evidence according to the recommendations by the grading of recommendations assessment, development and evaluation (GRADE) methodology^[55]. We downgraded the quality of evidence from RCTs according to the domains of the risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the probability of the reporting bias^[55]. We assigned low quality of evidence to all nonrandomized studies, upgrading the quality for the evidence of a strong or dose-response association^[56]. We concluded insufficient evidence when valid information about treatment effects was not identified.

RESULTS

We excluded the majority of clinical studies of SGLT2- inhibitors because they did not report patient outcomes in adults with HFpEF (search strings are available in the appendix and the list of excluded publications and registered studies is available by the request from the authors). We identified *post hoc* subgroup individual patient data meta-analysis of the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program that examined canagliflozin when compared with placebo in patients with HFpEF [Table 1]^[57]. We identified *post-hoc* subgroup analysis of the pivotal DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58) RCT that examined dapagliflozin when compared with placebo in patients with HFpEF [Table 1]^[58]. We also identified unpublished results from pivotal EMPERIAL trials that examined empagliflozin when compared with placebo in patients with HFpEF^[59-61]. We identified *post-hoc* subgroup analysis of the pivotal VERTIS CV RCT (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial) that examined ertugliflozin when compared with placebo in patients with HFpEF [Table 1]^[62].

We did not identify observational studies that reported patient outcomes after SGLT2- inhibitors in patients with HFpEF and concluded probable publication bias because several completed registered studies remain unpublished. We downgraded the quality of evidence for high risk of bias in *post-hoc* subgroup analyses, imprecision in treatment effects due to small number of events, and probable publication bias. We concluded that the evidence is insufficient for definitive clinical recommendation to use SGLT2- inhibitors

Table 1. Sodium-glucose cotransporter 2 inhibitors in adults with heart failure with preserved ejection fraction, the results from *post-hoc* subgroup analyses of the randomized controlled clinical trials

Population Definition	Outcome	Treatment effect
Canagliflozin vs. Placebo the CANVAS Program ^[57] * ClinicalTrials.gov/NCT01032629/NCT01989754		
Heart failure event with documented EF of $\geq 50\%$ at the HF admission	Fatal or hospitalized heart failure	HR 0.83 (0.55-1.25)
Heart failure event with documented EF of $\geq 50\%$ or assumed to be $\geq 50\%$	Fatal or hospitalized heart failure	HR 0.71 (0.52-0.97) ¹
Dapagliflozin, 10 mg vs. Placebo DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58) ^[58] ** ClinicalTrials.gov/NCT01730534		
Heart failure with EF of $\geq 45\%$ or without known reduced ejection fraction	Cardiovascular death or hospitalization for heart failure	HR 0.88 (0.66-1.17)
	Hospitalization for heart failure	HR 0.72 (0.5-1.04)
	Cardiovascular death	HR 1.41 (0.93-2.13)
	All-cause mortality	HR 1.02 (0.75-1.38)
Heart failure with EF of $\geq 45\%$	Cardiovascular death or hospitalization for heart failure	HR 0.79 (0.56-1.13)
	Hospitalization for heart failure	HR 0.74 (0.48-1.14)
	Cardiovascular death	HR 1.44 (0.83-2.49)
	All-cause mortality	HR 1.06 (0.71-1.59)
Heart failure with EF 45-< 55%	Cardiovascular death or hospitalization for heart failure	HR 0.83 (0.58-1.2)
	Hospitalization for heart failure	HR 0.76 (0.48-1.19)
	Cardiovascular death	HR 1.18 (0.69-2.01)
	All-cause mortality	HR 0.98 (0.66-1.46)
Ertugliflozin, 5 mg, 15 mg vs. Placebo (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial) ^[62] *** ClinicalTrials.gov/NCT01986881		
Heart Failure with EF > 45%	Cardiovascular death or hospitalization for heart failure	HR 0.92 (0.61-1.39)
	Cardiovascular death	HR 1.08 (0.64-1.8)
	All-cause mortality	HR 1.01 (0.66-1.56)
	Hospitalization for heart failure	HR 0.70 (0.39-1.26)

¹Statistically significant differences at 95% confidence level. *Ejection fraction was assessed during retrospective secondary review of the medical record data by one of the members of the original adjudication committee who was blinded to individual participant treatment assignment; **Prospective baseline assessment of ejection fraction was conducted in all participants; ***Ejection fraction was assessed from medical records when available. EF: ejection fraction; HR: hazard rate ratio

for the reduction in cardiovascular mortality, morbidity or heart failure hospitalizations in patients with HFpEF.

Canagliflozin

Canagliflozin did not reduce the risk of fatal or hospitalized heart failure when compared with placebo in adults with type 2 diabetes and heart failure with documented LVEF of $\geq 50\%$ [Table 1]^[57]. Canagliflozin reduced the risk of fatal or hospitalized heart failure in a subpopulation with heart failure and documented LVEF of $\geq 50\%$ [Table 1]^[57].

The CANVAS RCTs did not examine LVEF at baseline in enrolled adults of ≥ 30 years of age with a history of symptomatic atherosclerotic cardiovascular disease or aged ≥ 50 years with 2 or more risk factors for cardiovascular disease^[44,63]. *Post hoc* subgroup analysis was based on retrospective secondary review of the medical hospitalization record data by one of the members of the original adjudication committee to identify patients with HFpEF defined as heart failure with documented LVEF of $\geq 50\%$ (101 patients)^[57]. The authors conducted a sensitivity analysis assuming that patients with unknown LVEF had HFpEF (61 patients) and found a significant protective effects from canagliflozin in this combined subpopulation^[57].

Based on *post hoc* interaction model and protective effects from canagliflozin in heart failure with reduced ejection fraction (LVEF < 50%), the authors concluded similar canagliflozin benefits in the overall trial population^[57].

Canagliflozin improved diastolic function in patients with type 2 diabetes in two Japanese non-randomized controlled clinical trials^[64,65]. One trial of canagliflozin in outpatients with chronic heart failure and diabetes (CANOSSA trial: prospective, open-label, add-on trial of canagliflozin for diabetes mellitus and stable chronic heart failure) enrolled 94% of patients with HFpEF (exact definition was not provided)^[65]. Canagliflozin improved echocardiographic parameters of diastolic function at 6 and 12 month ($P < 0.001$)^[65]. The second pilot study reported improved left ventricular diastolic function after 3 months of canagliflozin treatment although it did not specify baseline HFpEF^[64].

Dapagliflozin

Dapagliflozin did not improve all-cause or cardiovascular death or hospitalization for heart failure in adults with type 2 diabetes and HFpEF (LVEF $\geq 45\%$) [Table 1]^[58].

DECLARE-TIMI 58 investigators conducted a prospective baseline assessment of ejection fraction in all enrolled patients with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD and with a creatinine clearance ≥ 60 mL/min^[58]. The authors acknowledged the absence of universally accepted definitions of HFpEF and reported outcomes in subpopulations with various baseline LVEF thresholds ($< 45\%$, $\geq 45\%$, and $45\%-55\%$). Based on post hoc interaction model and protective effects from dapagliflozin in heart failure with reduced ejection fraction, the authors concluded similar dapagliflozin benefits in overall trial population^[58].

We identified two RCTs that examined the effects from dapagliflozin on diastolic function in adults with type 2 diabetes^[66,67]. The RCT enrolling patients with heart failure reported that dapagliflozin significantly improved diastolic function in those with baseline LVEF $\geq 45\%$ ^[66]. The second RCT that enrolled patients without prior history of heart failure, reported that dapagliflozin had no effect on diastolic function when compared with placebo^[67].

Ongoing registered studies reported different definitions of HFpEF, exclusion of adults with various thresholds of reduced LVEF (e.g., $< 45\%$ or $< 50\%$) and various definitions of primary and secondary outcomes [Table 2]. Available protocols did not provide details on estimated statistical power and required sample size to detect statistically significant differences in primary outcomes.

Empagliflozin

Empagliflozin did not improve exercise tolerance, patient-reported outcomes related to the quality of life and patient satisfaction, congestion, diuretic use and all-cause healthcare resource utilization in adults with HFpEF enrolled in the pivotal EMPERIAL trials^[59-61]. Trials enrolled adults with heart failure with or without diabetes^[45]. The authors defined HFpEF as symptomatic heart failure with LVEF $> 40\%$ and elevated N-Terminal Pro-Brain Natriuretic Peptide [Table 3]. The unpublished results have been presented in the meeting of the European Society of Cardiology in June 2020^[59,60]. Some positive trends in improving congestion after empagliflozin in HFpEF did not achieve statistical significance, possibly due to insufficient statistical power^[59].

The pivotal Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME Trial) did not examine baseline ejection fraction but reported improvement in diastolic dysfunction as a possible mechanism in the observed reduced cardiovascular mortality and morbidity^[68].

Ongoing registered studies reported different definitions of HFpEF (e.g., LVEF ≥ 40 or $\geq 50\%$), exclusion of adults with various thresholds of the reduced LVEF (e.g., $< 30\%$ or $< 40\%$) and various definitions of primary and secondary outcomes [Table 3]. Available protocols did not provide details on estimated statistical power and required sample size to detect statistically significant differences in primary outcomes.

Table 2. Ongoing registered clinical trials of dapagliflozin in adults with heart failure with preserved ejection fraction

NCT number phase enrollment	Title acronym	Inclusion criteria defining HFpEF	Exclusion by LVEF	Outcome measures
NCT03030235 Phase: Phase 4 Sample: 320	Dapagliflozin in PRESERVED Ejection Fraction Heart Failure PRESERVED-HF	Symptomatic heart failure (NYHA class II-IV) Left Ventricular Ejection Fraction (LVEF) \geq 45% Elevated NT-proBNP (\geq 225 pg/mL) or BNP (\geq 75 pg/mL). For patients with permanent atrial fibrillation (AF) BNP \geq 100 pg/mL or NTproBNP \geq 375 pg/mL	Previous LVEF < 45%	Change from baseline in: NTproBNP and BNP, heart failure related quality of life using the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, 6-min walk test (6MWD)
NCT02751398 Phase: Phase 4 Sample: 60	Impact of dapagliflozin on diastolic dysfunction in type 2 diabetic patients	\geq grade 1 diastolic function (relaxation abnormality) at resting echocardiography	LV ejection fraction < 50%	Subclinical diastolic dysfunction assessed by diastolic stress echocardiography
NCT03619213 JPRN- JapicCTI-184157 EUCTR2018-000802-46-CZ PER-026-18 Phase: Phase 3 Sample: 6100	Dapagliflozin evaluation to improve the LVEs of patients with preserved ejection fraction heart failure. DELIVER	Symptomatic heart failure (NYHA class II-IV) LVEF > 40% and evidence of structural heart disease Elevated NT-pro BNP levels	NR	The first occurrence of any of the components of this composite: (1) CV death; (2) Hospitalization for HF; (3) Urgent HF visit Total number of hospitalizations for HF and CV death; Change from baseline in KCCQ-TSS; All-cause mortality
NCT03877224 EUCTR2018-003441-42-DK JPRN- JapicCTI-194724 Phase: Phase 3 Sample: 500	DETERMINE-preserved - Dapagliflozin Effect on Exercise Capacity using a 6-min walk test in patients with heart failure with preserved ejection fraction	Symptomatic heart failure (NYHA functional class II-IV) LVEF > 40% and evidence of structural heart disease Elevated NT-proBNP levels 6MWD \geq 100 meters and M 425 meters	NR	Change from baseline in: 6MWD, KCCQ-TSS, movement intensity during walking
NCT03794518 Phase: Phase 3 Sample: 648	Effect of Dapagliflozin plus low dose pioglitazone on hospitalization rate in patients with hF and HFpEF	Hospitalized for HFpEF (hospitalization require intravenous diuresis) in the 6 months preceding recruitment. LVEF > 50% Presence of LV diastolic dysfunction in echocardiography	LVEF < 50%	Time to first hospitalization for heart failure after starting intervention; All-cause mortality
JPRN- UMIN000038380 Sample: NR	Yokohama add-on inhibitory efficacy of dapagliflozin on left ventricular filling pressure in patients with acute heart failure with preserved ejection fraction complicated with type 2 diabetes study	Acute heart failure with LVEF \geq 40% and stable hemodynamically	NR	Change from baseline in: diastolic parameters of echocardiography, BNP; CVD events, not specified

BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro b-type natriuretic peptide

Ertugliflozin

The ongoing evaluation of ERTugliflozin efficacy and Safety CardioVascular outcomes trial (VERTIS-CV) enrolled adults with type 2 diabetes and established atherosclerotic cardiovascular disease, did not specify subgroup analysis depending on baseline ejection fraction obtained from medical records but reported that 80.6% of 8,238 randomized patients had HFpEF (LVEF > 40%)^[69]. This RCT was designed to determine non-inferiority of ertugliflozin when compared with placebo on major adverse CV events including death, nonfatal myocardial infarction, or nonfatal stroke^[69]. Preliminary publications defined HFpEF as LVEF > 45% and reported no reduction in patient outcomes in this subpopulation after comparing ertugliflozin vs. placebo [Table 1]. Based on the post hoc interaction model and protective effects from ertugliflozin in heart failure with reduced ejection fraction, the authors concluded similar ertugliflozin benefits in the overall trial population^[62,70].

Table 3. Ongoing registered clinical trials of empagliflozin in adults with heart failure with preserved ejection fraction

NCT number phase enrollment	Title acronym	Inclusion criteria defining HFPEF	Exclusion by LVEF	Outcome measures
NCT02932436 Phase: Phase 4 Sample: 158	Effects of Empagliflozin on left ventricular diastolic function compared to usual care in type 2 diabetics EmDia	Diastolic cardiac dysfunction E/E' ratio ≥ 8	NYHA classification III - IV	Change from baseline in: E/e' ratio, Left end-diastolic volume (LEDV)
NCT03057951 EUCTR2016-002278-11-DE Phase: Phase 3 Sample: 5750	Empagliflozin outcome trial in patients with chronic heart failure with preserved ejection fraction (EMPEROR-Preserved)	Symptomatic heart failure (NYHA class II-IV) LVEF > 40 % NT-proBNP > 300 pg/ml for patients without AF, OR > 900 pg/ml for patients with AF	NR	Composite primary endpoint: CV death or hospitalization for heart failure failure); All hospitalizations for heart failure; All-cause mortality; Change from baseline in KCCQ; All-cause hospitalizations
NCT03448406 Phase: phase 3 sample: 315	Empagliflozin in Patients with chronic heart failure with preserved ejection fraction (HFpEF) EMPERIAL-preserved	6MWT M 350 m Symptomatic heart failure (NYHA class II-IV) LVEF > 40% NT-proBNP > 300 pg/ml for patients without AF, OR > 600 pg/ml for patients with AF	Prior LVEF M 40%	Change from baseline in: 6MWT KCCQ TS, chronic heart failure questionnaire, self-administered standardized format (CHQ-SAS) dyspnea score, patient global impression of severity (PGI-S) of heart failure symptoms, patient global impression of dyspnea severity, patient global impression of change (PGI-C) in heart failure symptoms, patient global impression of change in dyspnea, N-terminal pro-brain natriuretic peptide (NTproBNP)
NCT02998970 Phase: Phase 4 Sample: 97	Effects of Empagliflozin on cardiac structure in patients with type 2 diabetes EMPA-HEART	Previous myocardial infarction ≥ 6 months ago, or previous coronary revascularization ≥ 2 months ago	LVEF < 30% NYHA Class IV or recent hospitalization for decompensated heart failure (HF)	Change from baseline in: Left Ventricular (LV) mass LV end-diastolic volume LVEF Regional LV diastolic function
NCT03753087 Phase: Phase 4 Sample: 100	Effects of Empagliflozin on exercise capacity and left ventricular diastolic function in patients with heart failure with preserved ejection fraction and Type-2 diabetes mellitus	Symptoms 4 signs of heart failure (as defined in 2016 European society of cardiology guidelines) LVEF $\geq 50\%$ LV diastolic dysfunction grade II/III	Permanent atrial flutter or atrial fibrillation	Change from baseline in: 6MWD LVMI left atrial volume index (LAVI) average E/e' ratio NT-proBNP minnesota living with heart failure questionnaire (MLHFQ) score
NCT03332212 Sample: NR	EMPA-VISION: A randomised, double-blind, placebo-controlled, mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac physiology and metabolism in patients with heart failure	LVEF $\geq 50\%$ as measured by ECHO structural heart disease NT-proBNP > 125 pg/mL in patient without AF or NT-pro-BNP > 600 pg/mL in patient with AF	Prior LVEF M 40%.	Change from baseline in myocardial phosphocreatine-to-ATP ratio
CTRI/2017/09/009734 Phase: NS Sample: NR	Empagliflozin trial in patients with chronic heart failure	Chronic symptomatic heart failure (NYHA class II-IV) LVEF > 40% Elevated NT-proBNP > 300 pg/mL for patients without AF, OR > 900 pg/ml for patients with AF	NR	The composite endpoint: CV death or hospitalization for heart failure; All-cause mortality; Change from baseline in clinical summary score of the KCCQ; All-cause hospitalizations
JPRN-jRCTs071180091 Phase: NS Sample: NR	Effect of empagliflozin for HFpEF with Type2 DM A clinical study for cardioprotective effect of empagliflozin in T2DM patients with heart failure and exploring associated factors (EMPOWERMENT)	Symptomatic heart failure (NYHA class II-III) LVEF > 50% BNP ≥ 35 pg/dL	NR	Change from baseline in: uptake efficiency (Peak VO2) BNP LVEF and RVEF(by MRI)

Other SGLT2 inhibitors

Limited evidence from small unpublished Japanese RCTs suggested that luseogliflozin (63 patients), and tofogliflozin (62 patients) improved diastolic dysfunction from baseline in adults with diabetes and HFpEF^[71]. However, luseogliflozin, when compared with voglibose, did not improve diastolic dysfunction or brain natriuretic peptide (BNP) levels in type 2 diabetes patients with HFpEF (defined as LVEF > 45% and BNP =35 pg/mL²)^[72].

We identified 60 registered studies of ipragliflozin, sotagliflozin, luseogliflozin, or tofogliflozin that did not report enrolling patients with HFpEF.

DISCUSSION

Our review found insufficient evidence that SGLT2 inhibitors can improve cardiovascular mortality, morbidity or hospitalizations in patients with HFpEF. We found no studies that reported adverse effects from SGLT2 inhibitors specifically in adults with HFpEF^[73]. Limited evidence of some improvement in intermediate outcomes of diastolic dysfunction lack clinical significance with valid prediction of better patient-centered outcomes and healthcare utilization required in future studies^[74,75]. The absence of RCTs that met pooling criteria precluded planned meta-analyses. Previously published indirect net-work meta-analyses focused on intermediate outcomes of diastolic dysfunction regardless of baseline HFpEF and did not find consistent superiority of SGLT2 inhibitors when compared with placebo or other anti-diabetic medications^[74,75]. Previously published direct meta-analysis concluded that SGLT2 inhibitors reduced the risk of cardiovascular death or heart-failure hospitalization regardless of baseline heart failure diagnosis^[15]. However, this meta-analysis did not look at patient outcomes depending on baseline LVEF and specifically in patients with HFpEF^[15].

Various definitions of HFpEF preclude valid comparisons of patient outcomes among RCTs of the same SGLT2 inhibitor and across RCTs of different SGLT2 inhibitors [Supplementary Table 2]^[28,33,34,37,76-80]. Ongoing studies use various inclusion and exclusion criterias with a potential threat to external validity of completed in future studies^[81]. Consistent consensus definition of HFpEF in guidelines, RCTs, and real life clinical practice and coding is essential for valid assessment of the best treatment options in adults with HFpEF^[35,82-85]. Patient outcomes can differ depending on HFpEF diagnostic criteria and should be assessed by HFpEF phenotypes^[38,79,80]. Subgroup analyses by HFpEF diagnostic criteria and phenotypes should be conducted with prespecified evidence-based definitions, stratified randomization and adequate sample size^[86,87]. Known interactions between HFpEF phenotypes and treatment effects should guide future studies aimed at efficacious treatments^[11,83]. Registered protocols of ongoing RCTs are inconsistent in addressing recommendations by guidelines hard clinical outcomes including all-cause and cardiovascular mortality, morbidity, hospitalizations, or quality of life in people with HFpEF^[88,89]. Such inconsistency indicates that the most important clinical questions regarding the benefits from SGLT2 inhibitors on patient centered outcomes may not be answered in the upcoming years.

Available heart failure guidelines recommend SGLT2 inhibitors to reduce cardiovascular mortality and hospitalizations in patients with diabetes [Supplementary Table 3]^[5,26-28,89,90]. Some guidelines specify recommendations of SGLT2 inhibitors in heart failure with reduced ejection fraction^[5,29]. Very few guidelines including the Canadian Cardiovascular Society and Canadian Heart Failure Society guidelines and the American Diabetes Association Standard of Care statement acknowledge uncertainty regarding potential benefits of SGLT2 inhibitors for patients with midrange or preserved LVEF^[5,29]. Older guidelines do not make recommendations for or against SGLT2 inhibitors aimed at the prevention of heart failure hospitalizations or mortality^[33,34,88,91].

We found no large observational studies of SGLT2 inhibitors in HFpEF. We can speculate that inconsistencies in diagnostic and treatment recommendations for patients with HFpEF preclude optimal treatment choices

in these patients^[92,93]. Diabetes care should be provided by multidisciplinary teams of endocrinologists, cardiologists and nephrologists and include assessment of HFpEF and consequent decisions of the best treatment choices^[5,6,94,95].

Inconsistency in clinical research and practice policies, market approval, and coverage decisions across countries preclude universal patient access to the optimal treatment options^[96-98]. Harmonization of health technology assessments methodology and data sharing across the countries would improve the quality of care in patients with heart failure and specifically HFpEF^[99,100]. The International Network of Agencies for Health Technology Assessment calls for transparency in evidence collection, data sharing, and consistent evidence appraisal to improve patient outcomes across the globe^[101].

Our work has implications for future research. The emerging epidemic of diabetes, arterial hypertension and HFpEF requires international efforts in improving the quality of evidence and the quality of healthcare^[10,26,40]. Professional associations and health technology assessment groups need to collaborate in the development of consensus definitions of HFpEF, in prospective design of high quality powered RCTs in adults with various phenotypes and underlying causes of HFpEF. Individual patient data meta-analyses of completed RCTs and registries of medical records can shed light on optimal treatment choices in adults with HFpEF^[102-105].

In conclusion, existing evidence is insufficient to support definitive clinical recommendations for use of SGLT2- Inhibitors in adults with HFpEF. Future research should employ consistent definitions of HFpEF and examine the effects from SGLT2- Inhibitors in patients with various HFpEF phenotypes and underlying causes.

DECLARATIONS

Authors' contributions

Designed review protocol, research questions and performed data analysis and interpretation: Shamliyan TA

Conceptualized study objectives and goals and contributed to data analysis and interpretation: Aronow WS

Contributed to study design and execution, data analysis and interpretation: Avanesova AA

Made substantial contributions to the writing of the manuscript: Shamliyan TA, Avanesova AA, Aronow WS

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

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