American Journal of Cardiovascular Drugs (2021) 21:701–710
https://doi.org/10.1007/s40256-021-00503-8

ADIS DRUG EVALUATION

Dapagliflozin: A Review in Symptomatic Heart Failure with Reduced Ejection Fraction

Hannah A. Blair[1]

Accepted: 15 September 2021 / Published online: 15 October 2021

Abstract

Dapagliflozin [Farxiga® (USA); Forxiga® (EU)], a sodium–glucose cotransporter 2 (SGLT2) inhibitor, was recently approved in the USA and the EU for the treatment of adults with symptomatic heart failure with reduced ejection fraction (HFrEF). The cardiovascular (CV) benefits of dapagliflozin were first observed in the DECLARE-TIMI 58 trial, in which dapagliflozin 10 mg/day significantly reduced the risk of CV death or hospitalization for HF in patients with type 2 diabetes mellitus (T2DM) who had or were at risk for atherosclerotic CV disease. In the subsequent DAPA-HF trial, dapagliflozin 10 mg/day in addition to standard of care was associated with a significantly lower risk of worsening HF or CV death than placebo in patients with HFrEF, regardless of the presence or absence of T2DM. The benefits of dapagliflozin also remained consistent regardless of background HF therapies. Dapagliflozin was generally well tolerated, with an overall safety profile consistent with its known safety profile in other indications. In conclusion, dapagliflozin is an effective and generally well-tolerated treatment that represents a valuable new addition to the options available for symptomatic HFrEF.

Plain Language Summary

Heart failure (HF) is a major cause of death and disability. HFrEF occurs when the left ventricular ejection fraction is ≤40%. Conventional treatments for HFrEF include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor-neprilysin inhibitors, β-blockers, mineralocorticoid receptor antagonists, hydralazine/isosorbide dinitrate, and ivabradine. Dapagliflozin [Farxiga® (USA); Forxiga® (EU)] is an SGLT2 inhibitor originally developed for the treatment of T2DM. It was the first SGLT2 inhibitor to be approved for the treatment of adults with symptomatic HFrEF. When added to standard therapy, dapagliflozin significantly reduced the risk of worsening HF or CV death in patients with HFrEF, regardless of whether or not they had T2DM. Moreover, the beneficial effects of dapagliflozin were seen regardless of patients' usual HF medications. Dapagliflozin was generally well tolerated and is a valuable option for the treatment of symptomatic HFrEF.

Digital Features for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.16624918

The manuscript was reviewed by: ***M. M. Y. Lee***, Institute of Cardiovascular and Medical Sciences, University of Glasgow, UK; ***B. Pitt***, Cardiovascular Center, School of Medicine, University of Michigan, Ann Arbor, MI, USA; ***J.-Y. Sun***, Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China.

✉ Hannah A. Blair
demail@springer.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

Dapagliflozin: clinical considerations in symptomatic HFrEF

First SGLT2 inhibitor to be approved for HFrEF
Significantly reduces the risk of worsening HF or CV death
Benefits were seen regardless of the presence or absence of T2DM and regardless of background HF therapies
Generally well tolerated

1 Introduction

Heart failure (HF), a complex clinical syndrome characterized by dyspnea, fatigue, exercise intolerance, and fluid retention, is associated with significant morbidity and mortality [1, 2]. HF can be broadly classified according to left ventricular (LV) ejection fraction (EF), and is therefore commonly referred to as HF with reduced EF (HFrEF; LVEF ≤ 40%), HF with mid-range or mildly reduced EF (LVEF 41–49%), or HF with preserved EF (LVEF ≥ 50%) [3, 4]. HFrEF accounts for approximately 50% of all cases of HF worldwide [2].

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), β-blockers, mineralocorticoid receptor antagonists (MRAs), hydralazine/isosorbide dinitrate, and ivabradine have long been the backbone of therapy for HFrEF due to their beneficial effects on symptoms, rates of hospitalization, and mortality in randomized controlled trials [2, 5]. More recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce the risk of hospitalization for HF (HHF) in patients with type 2 diabetes mellitus (T2DM) and a high risk of cardiovascular (CV) disease [6, 7].

Dapagliflozin [Farxiga® (USA); Forxiga® (EU)], an SGLT2 inhibitor, has been approved in several countries, including the USA [8] and those of the EU [9], for the treatment of adults with symptomatic HFrEF. The pharmacological properties of dapagliflozin have been reviewed in detail previously [10–12] and are summarized in Table 1.

Table 1 Overview of key pharmacologic properties of dapagliflozin [8, 9]

Pharmacodynamic properties	
Highly potent (Ki 0.55 nM) and reversible inhibitor of SGLT2; > 1400-fold more selective for SGLT2 than for SGLT1 (the prime intestinal glucose transporter)	
Reduces renal glucose reabsorption, thereby increasing urinary glucose excretion and lowering plasma glucose levels	
Concomitantly reduces sodium reabsorption and increases delivery of sodium to the distal tubule, which is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure	
SGLT2-induced diuresis and natriuresis reduces blood volume and interstitial fluid volume and lowers preload and afterload on the heart (consistent with BP reduction); reduces left ventricular end-diastolic volume and pressure [69]	
Increases hematocrit and reduces bodyweight	
No clinically meaningful effect on QTc interval at supratherapeutic doses (up to 500 mg)	
Pharmacokinetic properties	
Dose-proportional exposure over dose range of 0.1–500 mg; no change in pharmacokinetics after repeated daily administration for up to 24 weeks	
Rapidly absorbed following oral administration; C_{max} is reached within 2 h (fasted state); absolute oral bioavailability is 78% following a single 10 mg dose; ≈ 91% protein bound; mean steady-state volume of distribution is 118 L	
Extensively metabolized by UGT1A9 in the liver and kidney to its major inactive metabolite (dapagliflozin 3-*O*-glucuronide); CYP-mediated metabolism is a minor clearance pathway	
Mainly eliminated via urinary excretion; 75% of radiolabeled dose recovered in urine (< 2% as unchanged parent drug) and 21% in feces (≈ 15% as unchanged parent drug); mean plasma terminal half-life is 12.9 h following a single 10 mg dose	
Special populations[a]	No clinically relevant differences in DAP pharmacokinetics based on age, race (white, black, Asian), or bodyweight; mean steady-state AUC is estimated to be ≈ 22% higher in females than males
	Mean C_{max} and AUC are up to 40 and 67% higher in pts with severe hepatic impairment than healthy matched controls
	At steady state, mean systemic exposures of DAP are higher in pts with mild, moderate, or severe abnormal kidney function than pts with normal kidney function
Drug interactions[a]	Does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4; does not induce CYP1A2, CYP2B6, or CYP3A4; weak substrate of P-gp; does not meaningfully inhibit P-gp, OAT1, OAT3, or OCT2
	DAP did not meaningfully alter the pharmacokinetics of, and its pharmacokinetics were unaltered by, bumetanide, glimepiride, hydrochlorothiazide, metformin, pioglitazone, simvastatin, sitagliptin, or valsartan
	DAP did not alter the pharmacokinetics of digoxin or warfarin (including its anticoagulant effects)
	Rifampicin decreased DAP exposure by 22%, and mefenamic acid (UGT1A9 inhibitor) increased DAP exposure by 55%, but with no clinically meaningful effect on 24-h urinary glucose
	DAP may potentiate the diuretic effect of thiazide and loop diuretics (→ increased risk of dehydration and hypotension)

AUC area under the plasma concentration-time curve, C_{max} maximum plasma concentration, *DAP* dapagliflozin, *Ki* inhibitory constant, *P-gp* P-glycoprotein, *pts* patients, *SGLT* sodium-glucose cotransporter, → leading to

[a]Consult local prescribing information for detailed information

This review focuses on the use of dapagliflozin in patients with symptomatic HFrEF. Dapagliflozin is also approved for the treatment of T2DM [10, 11], type 1 diabetes mellitus (T1DM) [12], and chronic kidney disease (CKD); however, discussion of these indications is beyond the scope of this review.

2 Therapeutic Efficacy of Dapagliflozin

The efficacy of dapagliflozin for the treatment of symptomatic HFrEF was primarily investigated in the pivotal, randomized, double-blind, multinational, phase III DAPA-HF trial [13], which is the main focus of discussion in this section. These data are supported by the earlier phase III DECLARE-TIMI 58 trial [14], as well as the DEFINE-HF [15], DETERMINE-Reduced [16], and DAPA-CKD [17], trials, which are briefly discussed in Sect. 2.2.

2.1 DAPA-HF

The DAPA-HF trial included patients aged ≥ 18 years with New York Heart Association (NYHA) class II–IV symptoms, LVEF of ≤ 40%, and a plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of ≥ 600 pg/mL (or ≥ 400 pg/mL if they had been hospitalized for HF within the previous 12 months); patients with atrial fibrillation or atrial flutter at baseline had to have a plasma NT-proBNP level of ≥ 900 pg/mL, regardless of their history of HHF [13]. Patients were required to receive standard HF device therapy (implantable cardioverter-defibrillator, cardiac resynchronization therapy, or both) and standard drug therapy (including an ACE inhibitor, or an ARB, or sacubitril/valsartan plus a β-blocker). MRA use was encouraged. Glucose-lowering medications were permitted in patients with T2DM. Patients with T1DM and patients with an estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73 m^2 were excluded from the trial [13].

Following a 14-day screening period, eligible patients were randomized to receive oral dapagliflozin 10 mg or placebo once daily [13]. Randomization was stratified by T2DM diagnosis (i.e., an established diagnosis or a glycated hemoglobin level of ≥ 6.5%); 42% of patients had a history of T2DM at screening and 3% of patients received a new diagnosis of T2DM. At baseline, the mean age of patients was 66 years, 68% of patients had NYHA class II

Table 2 Efficacy of dapagliflozin in patients with symptomatic heart failure with reduced ejection fraction in the phase III DAPA-HF trial [13]

Endpoints	DAP (n = 2373)	PL (n = 2371)	HR/RR/TE (95% CI)
Primary composite endpoint (% of pts)			
Worsening HF[a] or CV death	16.3	21.2	HR 0.74 (0.65–0.85)*
Primary composite endpoint components (% of pts)			
Hospitalization or urgent visit for HF	10.0	13.7	HR 0.70 (0.59–0.83)
HHF	9.7	13.4	HR 0.70 (0.59–0.83)
Urgent HF visit	0.4	1.0	HR 0.43 (0.20–0.90)
CV death	9.6	11.5	HR 0.82 (0.69–0.98)
Secondary endpoints			
HHF or CV death (% of pts)	16.1	20.9	HR 0.75 (0.65–0.85)*
Total no. of HHFs and CV deaths	567	742	RR 0.75 (0.65–0.88)*
Change from BL in KCCQ-TSS at 8 months[b]	+6.1	+3.3	TE[c] 1.18 (1.11–1.26)*
Worsening kidney function[d] (% of pts)	1.2	1.6	HR 0.71 (0.44–1.16)
All-cause death (% of pts)	11.6	13.9	HR 0.83 (0.71–0.97)

The primary composite endpoint and secondary endpoints were assessed using a prespecified hierarchical testing strategy; p-values are not applicable for outcomes not included in the hierarchical testing strategy

BL baseline, *CV* cardiovascular, *DAP* dapagliflozin, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *HF* heart failure, *HHF(s)* hospitalization(s) for HF, *HR* hazard ratio, *KCCQ-TSS* Kansas City Cardiomyopathy Questionnaire total symptom score, *PL* placebo, *pts* patients, *RR* rate ratio, *TE* treatment effect

*$p < 0.001$

[a]Hospitalization or an urgent visit resulting in intravenous therapy for HF

[b]Scores range from 0 to 100, with higher scores indicating fewer HF-associated symptoms and physical limitations

[c]The TE is shown as a win ratio, in which a value > 1 indicates superiority

[d]Composite outcome of ≥ 50% reduction in eGFR sustained for ≥ 28 days, ESRD, or death from renal causes; ESRD defined as eGFR < 15 mL/min/1.73 m^2 sustained for ≥ 28 days, long-term dialysis treatment (sustained for ≥ 28 days), or kidney transplantation

HF, mean LVEF was ≈31%, and median NT-proBNP level was ≈1400 pg/mL. The primary endpoint was a composite of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or death from CV causes [13].

2.1.1 Worsening Heart Failure or Cardiovascular Death

Dapagliflozin, in addition to standard of care (SOC), reduced the risk of worsening HF or CV death in patients with HFrEF [13]. Over a median of 18.2 months, the risk of worsening HF or death from CV causes was significantly reduced by 26% with dapagliflozin versus placebo (Table 2). Event rates for all components of the primary composite endpoint favored dapagliflozin over placebo (Table 2). The number of patients needed to have been treated with dapagliflozin in order to prevent one primary endpoint event was 21 [13]. A secondary analysis demonstrated an early benefit of dapagliflozin on the primary composite endpoint, with statistical significance achieved by 28 days after randomization [hazard ratio (HR) 0.51; 95% CI 0.28–0.94; $p = 0.03$] [18]. Similar results were seen for all components of the primary composite endpoint [18].

In general, the effect of dapagliflozin on the primary composite endpoint was consistent across numerous prespecified patient subgroups, including age (≤65 vs >65 years), body mass index (BMI; <30 vs ≥30 kg/m^2), LVEF (≤ vs > median), and NT-proBNP level (≤ vs > median) [13]. In prespecified analyses, dapagliflozin significantly reduced the risk of worsening HF or CV death regardless of gender [19], presence of T2DM [20], MRA use [21], etiology (ischemic vs non-ischemic HF) [22], and eGFR (<60 vs ≥60 mL/min/1.73 m^2) [23]. In an exploratory analysis, dapagliflozin increased event-free survival from a primary composite event by 2.1 years for a patient aged 65 years [24]. Post hoc analyses confirmed that dapagliflozin reduced the risk of worsening HF and CV death across the broad spectrums of age (<55, 55–64, 65–74, and ≥75 years) [25], BMI (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥40.0 kg/m^2) [26], LVEF (<26, 26–30, 31–35, and >35%) [27], and NT-proBNP level (<857, 857–1437, 1438–2649, and ≥2650 pg/mL) [28] studied in DAPA-HF. Additional post hoc analyses demonstrated that the benefit of dapagliflozin on the primary composite endpoint was independent of race (black vs white) [29], mortality risk score [30], duration of HF [31], prior HHF [18], anemia status [32], presence of chronic obstructive pulmonary disease [33], Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (TSS) [34], systolic BP [35], background glucose-lowering therapy [36], and background HF therapy [37–39], including sacubitril/valsartan [37] and diuretics [38].

2.1.2 Other Endpoints

In terms of secondary endpoints, dapagliflozin significantly reduced the risk of HHF or CV death, and the total number of hospitalizations for HF and CV deaths, compared with placebo (Table 2) [13]. In prespecified analyses of DAPA-HF, dapagliflozin significantly reduced the risk of total (first and recurrent) HHF and CV death events (rate ratio 0.75; 95% CI 0.65–0.88; $p = 0.0002$) [40] and outpatient episodes of HF worsening (HR 0.73; 95% CI 0.65–0.82; $p < 0.0001$) [41] compared with placebo. There was no significant between-group difference in the incidence of the prespecified renal composite endpoint (Table 2); however, the rate of eGFR decline was attenuated with dapagliflozin [23]. The risk of death from any cause is shown in Table 2. The change from baseline in NT-proBNP level at 8 months was –196 pg/mL with dapagliflozin versus +101 pg/mL with placebo ($p < 0.001$) [13].

The KCCQ-TSS increased to a significantly greater extent with dapagliflozin versus placebo (Table 2) [13]. The proportion of patients with an increase of ≥5 points (i.e., the minimally important difference) in KCCQ-TSS was significantly ($p < 0.001$) higher with dapagliflozin than placebo [58.3 vs 50.9%; odds ratio (OR) 1.15; 95% CI 1.08–1.23], while significantly ($p < 0.001$) fewer dapagliflozin than placebo recipients had clinically significant deterioration in total KCCQ-TSS (25.3 vs 32.9%; OR 0.84; 95% CI 0.78–0.90) [13]. Dapagliflozin also improved the degree of physical and social activity limitation in patients with HFrEF [42]. At 8 months, KCCQ scores in all physical and social limitation domains except sexual relationships were significantly ($p < 0.05$) improved from baseline with dapagliflozin versus placebo. The greatest improvements were seen in doing gardening or housework or carrying groceries, hobbies and recreational activities, and walking 100 yards on level ground [42].

In (exploratory [43]) analyses of DAPA-HF, dapagliflozin significantly reduced the risk of ventricular arrhythmia, resuscitated cardiac arrest, or sudden death by 21% compared with placebo [44] and reduced the incidence of new-onset diabetes by 32% in patients who did not have T2DM at baseline [43].

2.2 Supportive Trials

2.2.1 DECLARE-TIMI 58

The effects of dapagliflozin on CV outcomes (including HF outcomes) in patients with T2DM were first evaluated in the randomized, double-blind, multinational, phase III DECLARE-TIMI 58 trial [14]. Briefly, the trial enrolled 17,160 patients aged ≥40 years with T2DM and a glycated hemoglobin level of ≥6.5% but <12.0% who had or were at

risk for atherosclerotic CV disease. Of these, 1724 patients (10%) had a history of HF at baseline. Patients were randomized to receive dapagliflozin 10 mg or placebo once daily, and were followed for a median of 4.2 years. The initial trial design included a primary safety endpoint of major adverse cardiac events (MACE; defined as CV death, myocardial infarction, or ischemic stroke), and was subsequently amended to include two primary efficacy endpoints: MACE and a composite of CV death or HHF [14].

Dapagliflozin significantly reduced the risk of CV death or HHF in patients with T2DM who had or were at risk for atherosclerotic CV disease [14]. Dapagliflozin was non-inferior to placebo for the primary safety (and efficacy) endpoint of MACE ($p < 0.001$). The rate of CV death or HHF was 4.9% with dapagliflozin versus 5.8% with placebo (HR 0.83; 95% CI 0.73–0.95; $p = 0.005$); this was due to a significantly lower rate of HHF with dapagliflozin versus placebo (2.5 vs 3.3%; HR 0.73; 95% CI 0.61–0.88). In the subgroup of patients with a history of HF, dapagliflozin significantly reduced the risk of CV death or HHF (HR 0.79; 95% CI 0.63–0.99) [14]. In a prespecified subgroup analysis, dapagliflozin significantly reduced the risk of HHF in patients with (HR 0.64; 95% CI 0.43–0.95) and without (HR 0.76; 95% CI 0.62–0.92) HFrEF at baseline [45].

2.2.2 DEFINE-HF

The effects of dapagliflozin on biomarkers, symptoms, and functional status in patients with HFrEF were assessed in the randomized, multicentre, double-blind DEFINE-HF trial [15]. This study enrolled patients with an established diagnosis of HF for ≥ 16 weeks, LVEF of ≤ 40%, NYHA class II–III symptoms, and an elevated NT-proBNP or BNP level. Patients were randomized to receive oral dapagliflozin 10 mg ($n = 131$) or placebo ($n = 132$) once daily for 12 weeks, in addition to guideline-directed SOC therapy. The primary endpoints were the average of 6- and 12-week mean NT-proBNP levels, and a composite of the proportion of patients with a meaningful improvement in health status [≥ 5-point increase in average of 6- and 12-week KCCQ overall summary score (KCCQ-OS)] or NT-proBNP level (≥ 20% reduction in average of 6- and 12-week NT-proBNP levels) [15].

Dapagliflozin, in addition to SOC therapy, did not affect NT-proBNP levels in patients with HFrEF, but increased the proportion of patients with clinically meaningful improvements in HF-related health status or natriuretic peptides [15]. The average 6- and 12-week adjusted mean NT-proBNP level was not significantly different between dapagliflozin (1133 pg/dL) and placebo (1191 pg/dL). However, significantly more dapagliflozin than placebo recipients achieved a clinically meaningful improvement of ≥ 5 points in KCCQ-OS or ≥ 20% reduction in NT-proBNP level (61.5 vs 50.4%; adjusted OR 1.8; 95% CI 1.03–3.06; nominal $p = 0.039$). This was attributed to numerically higher proportions of dapagliflozin versus placebo recipients with a clinically meaningful ≥ 5-point improvement in KCCQ-OS (43 vs 33%) and a ≥ 20% reduction in NT-proBNP level (44 vs 29%). Results were consistent across all prespecified subgroups, including T2DM status [15].

2.2.3 DETERMINE-Reduced

The effects of dapagliflozin on symptoms and functional capacity in patients with HFrEF were investigated in the randomized, multicentre, double-blind, phase III DETERMINE-Reduced trial [16]. The trial enrolled 313 patients with LVEF of ≤ 40%, an NT-proBNP level of ≥ 400 pg/mL (or ≥ 300 pg/mL if they had HF during the previous 12 months or ≥ 800 pg/mL if they had atrial fibrillation), an eGFR of ≥ 25 mL/min/1.73 m^2, and a 6-min walk distance (6MWD) of ≥ 100 m and ≤ 452 m. Patients were randomized to receive oral dapagliflozin 10 mg ($n = 156$) or placebo ($n = 157$) once daily for 16 weeks. The primary endpoints were the change from baseline in KCCQ-TSS, the change from baseline in KCCQ physical limitation score (KCCQ-PLS), and the change from baseline in 6MWD at week 16 [16].

Dapagliflozin improved HF symptoms but had no effect on physical limitation or exercise capacity in patients with HFrEF [16]. At week 16, KCCQ-TSS increased to a significantly greater extent with dapagliflozin versus placebo (median +2.08 vs 0.00; $p = 0.022$). However, the median change from baseline in KCCQ-PLS (+4.17 vs 0.00) and 6MWD (+20.0 vs +13.5 m) was not significantly different between dapagliflozin and placebo [16].

2.2.4 DAPA-CKD

The beneficial effects of dapagliflozin on HF outcomes were confirmed in the randomized, double-blind, multinational, phase III DAPA-CKD trial [17]. Briefly, the trial enrolled 4304 adult CKD patients with or without T2DM. All patients had an eGFR of 25–75 mL/min/1.73 m^2 and a urinary albumin-to-creatinine ratio of 200–5000 mg/g. Overall, 468 patients (11%) had HF at baseline. Patients were randomized to receive dapagliflozin 10 mg or placebo once daily, and were followed for a median of 2.4 years. The primary endpoint was a composite of a sustained decline in eGFR of ≥ 50%, end-stage kidney disease, or death from renal or CV causes. A composite of HHF or CV death was a secondary endpoint [17].

Dapagliflozin significantly reduced the risk of HHF or CV death in patients with CKD [17]. The primary endpoint occurred in 9.2% of dapagliflozin and 14.5% of placebo

recipients ($p < 0.001$). The rate of HHF or CV death was significantly ($p = 0.009$) lower with dapagliflozin versus placebo (4.6 vs 6.4%; HR 0.71; 95% CI 0.55–0.92) [17]. In a prespecified subgroup analysis, dapagliflozin reduced the risk of HHF or CV death in patients with (HR 0.68; 95% CI 0.44–1.05) and without (HR 0.70; 95% CI 0.51–0.97) a history of HF at baseline [46].

3 Tolerability of Dapagliflozin

Dapagliflozin was generally well tolerated, and its overall safety profile in patients with HF was consistent with its known safety profile in other indications [8, 9]. In DAPA-HF, adverse events (AEs) of special interest (AESIs) included volume depletion (7.5% with dapagliflozin vs 6.8% with placebo), renal AEs (6.5 vs 7.2%), fracture (2.1 vs 2.1%), and amputation (0.5 vs 0.5%) [13]. Few patients (4.7% in the dapagliflozin group and 4.9% in the placebo group) discontinued treatment because of AEs [13]. In DEFINE-HF, AESIs included volume depletion (9.2% with dapagliflozin vs 5.3% with placebo) and acute kidney injury (0.8 vs 0.8%) [15]. AEs led to treatment discontinuation in 8.4% of dapagliflozin and 9.1% of placebo recipients [15].

Due to its mechanism of action (induction of diuresis) [8], dapagliflozin can cause volume depletion, which may present as hypotension [8, 9]. The risk may be higher in elderly patients, patients receiving antihypertensives (including loop diuretics), and patients with abnormal kidney function [8, 9]. In DAPA-HF, serious AEs related to volume depletion occurred in 1.2% of dapagliflozin and 1.7% of placebo recipients [13]. Rates of volume depletion ($p = 0.004$) and renal AEs ($p = 0.024$) were significantly lower with dapagliflozin versus placebo in patients not taking diuretics at baseline, while the incidence of volume depletion was slightly higher with dapagliflozin than placebo in patients taking higher-dose diuretics at baseline [38]. In elderly patients, patients with abnormal kidney function, and in patients receiving loop diuretics, volume status and kidney function should be monitored before starting dapagliflozin and during treatment [8]. If patients develop volume depletion, dapagliflozin should be temporarily interrupted until the depletion is corrected [9].

When coadministered with insulin or an insulin secretagogue, dapagliflozin may increase the risk of hypoglycemia [8]. In DAPA-HF, major hypoglycemic events were reported in 0.2% of dapagliflozin and 0.2% of placebo recipients [13]. In DEFINE-HF, the incidence of severe hypoglycemia was 0.8% with dapagliflozin and 0.8% with placebo [15]. All hypoglycemic events occurred in patients with T2DM [13, 15].

SGLT2 inhibitors, including dapagliflozin, have been associated with cases of diabetic ketoacidosis (DKA), including life-threatening and fatal cases [8, 9]. However, in DAPA-HF, the incidence of DKA was 0.1% with dapagliflozin and 0% with placebo; all cases of DKA occurred in patients with T2DM [13]. There were no reports of DKA in DEFINE-HF [15]. Before initiating dapagliflozin, patients with T2DM should be assessed for DKA risk factors [8, 9]. DKA should be considered if patients develop non-specific symptoms of DKA, regardless of glucose level. If DKA is suspected or diagnosed, dapagliflozin should be discontinued immediately [8, 9].

Dapagliflozin may increase the risk of urinary tract infections (UTIs; including urosepsis and pyelonephritis) and genital infections [8, 9]. There have also been reports of Fournier's gangrene (necrotizing fasciitis of the perineum, a rare but serious and potentially life-threatening infection) in patients receiving SGLT2 inhibitors, including dapagliflozin [8, 9]. In DAPA-HF, serious UTIs were reported in 0.6% of dapagliflozin and 0.7% of placebo recipients, and the UTI-related discontinuation rate was 0.2% in both groups [9]. Genital infections led to treatment discontinuation in 0.3% of dapagliflozin and 0% of placebo recipients [9]. Fournier's gangrene occurred in 0% of dapagliflozin and <0.1% of placebo recipients [13]. Patients should seek medical attention if they develop symptoms of Fournier's gangrene; if it is suspected, dapagliflozin should be discontinued and treatment of Fournier's gangrene should be started promptly [8, 9].

4 Dosage and Administration of Dapagliflozin

Dapagliflozin is approved for the treatment of symptomatic HFrEF in several countries, including the USA [8] and those of the EU [9]. In the USA, dapagliflozin is indicated to reduce the risk of CV death and HHF in adults with NYHA class II–IV HFrEF [8]. In the EU, dapagliflozin is indicated in adults for the treatment of symptomatic chronic HFrEF [9]. The recommended dosage of dapagliflozin is 10 mg once daily administered orally, with or without food [8, 9]. No dosage adjustment is required in patients with mild or moderate hepatic impairment [8, 9]. However, in the EU, the recommended starting dosage of dapagliflozin in patients with severe hepatic impairment is 5 mg once daily [9]. No dosage adjustment is required based on kidney function [8, 9]. In the USA, dapagliflozin is contraindicated in patients on dialysis [8].

Local prescribing information should be consulted for further details regarding contraindications, warnings and precautions, drug interactions, and use in special patient populations.

5 Place of Dapagliflozin in the Management of Symptomatic HFrEF

Traditionally, pharmacologic therapy for HF has focused on targeting the renin-angiotensin-aldosterone system (via ACE inhibitors, ARBs, and MRAs) and the sympathetic nervous system (via β-blockers) [47]. A recent update to the American College of Cardiology expert consensus decision pathway for optimization of HF treatment (based on earlier guidelines [48]) highlights significant new advances in the treatment of HFrEF and provides interim guidance [5]. Evidence-based guideline-directed medical therapy (GDMT) for HFrEF now includes the SGLT2 inhibitors dapagliflozin and empagliflozin along with established therapies [5]. In a recent consensus document of the Heart Failure Association, ACE inhibitors, ARBs, ARNIs, β-blockers, MRAs, and SGLT2 inhibitors are recommended as 'core treatment' for all patients with HF (tailored according to clinical patient profiles) [49]. Newly updated European Society of Cardiology guidelines now include dapagliflozin and empagliflozin as a (class I, level of evidence A) recommendation for patients with HFrEF to reduce the risk of HHF and death, alongside previously recommended classes (ACE inhibitors/ARNIs, β-blockers, and MRAs) [4]. The UK National Institute for Health and Care Excellence (NICE) also recommends dapagliflozin as an option for treating symptomatic chronic HFrEF in adults, only if it is used as an add-on to optimized SOC [50].

Evidence for the benefits of dapagliflozin on HF was first demonstrated in the DECLARE-TIMI 58 trial, in which dapagliflozin significantly reduced the risk of CV death or HHF in patients with T2DM (Sect. 2.2.1). DECLARE-TIMI 58 paved the way for additional phase III trials, including DAPA-HF. In this trial, dapagliflozin was associated with a significantly lower risk of worsening HF or CV death than placebo in patients with HFrEF, regardless of the presence or absence of T2DM (Sect. 2.1.1). Of note, patients in DAPA-HF were at much higher risk for HHF or CV death than patients in DECLARE-TIMI 58 and other previous SGLT2 inhibitor trials [13, 51]. The effect of dapagliflozin on the primary composite endpoint was consistent across many patient subgroups, including patients who were already receiving background HF therapies such as sacubitril/valsartan (Sect. 2.1.1).

NT-proBNP is a measure correlated with cardiac dysfunction [52]. In the DEFINE-HF trial, which was designed, in part, to assess the effects of dapagliflozin on biomarkers, dapagliflozin did not significantly reduce NT-proBNP levels at 6 or 12 weeks compared with placebo (Sect. 2.2.2). However, a higher proportion of dapagliflozin than placebo recipients experienced a clinically meaningful improvement in NT-proBNP levels (Sect. 2.2.2). Longer-term, dapagliflozin significantly reduced NT-proBNP levels at 8 months in an exploratory analysis of DAPA-HF (Sect. 2.1.2).

The CV benefits of dapagliflozin in patients with HF have been confirmed in systematic reviews and meta-analyses, in which dapagliflozin significantly reduced the risk of HHF [53–55] and CV death [54, 55] compared with placebo. Dapagliflozin also significantly reduced the risk of HHF or CV death compared with placebo in patients with CKD in the DAPA-CKD trial, regardless of HF history at baseline (Sect. 2.2.4).

To date, no randomized controlled trials have directly compared dapagliflozin with other pharmacological agents in patients with HFrEF. Indirect comparisons have demonstrated no apparent differences in efficacy (in terms of HHF and/or CV death) between dapagliflozin and other SGLT2 inhibitors [56–58], between dapagliflozin and sacubitril/valsartan [59], or between SGLT2 inhibitors and sacubitril/valsartan or vericiguat [60] in patients with HFrEF. However, given the limitations of indirect comparisons, these results should be treated with caution. Clinical trials comparing dapagliflozin with other agents (particularly SGLT2 inhibitors) in patients with HFrEF would be of interest. Randomized, multicentre trials are currently underway to evaluate the effects of in-hospital initiation of dapagliflozin on CV death or worsening HF in patients with HFrEF (DAPA ACT HF-TIMI 68), the effects of dapagliflozin on short-term functional capacity in patients with HFrEF (DAPA-VO2), the efficacy and safety of dapagliflozin in patients hospitalized with acute HF (DICTATE-HF), and the effects of dapagliflozin on the incidence of HF or CV death in patients with myocardial infarction (DAPA-MI) [61].

Consistent with its known safety profile in other indications, dapagliflozin was generally well tolerated in patients with HF (Sect. 3). Rates of AESIs such as DKA, major hypoglycemia, and serious UTIs were generally low (> 1%) in patients receiving dapagliflozin. Of note, all cases of DKA and major hypoglycemia occurred in patients with T2DM (Sect. 3).

HF is a leading cause of hospitalization and is associated with substantial healthcare costs [62]. In the NICE guidance, dapagliflozin plus optimized SOC (based on ACE inhibitors or ARBs) is reported to be less costly and at least equally effective as optimized sacubitril/valsartan with β-blockers and, if tolerated, MRAs [50]. According to the committee, dapagliflozin is cost effective as an add-on to optimized SOC and represents an acceptable use of health system resources [50]. Modeled pharmacoeconomic studies in the UK, Germany and Spain [62], Australia [63], Thailand [64], the Philippines [65], and the USA [66] suggest that dapagliflozin added to SOC/GDMT is cost effective for the treatment of HFrEF over a lifetime horizon. Results of another Markov model from the perspective of

the UK National Health Service suggest that dapagliflozin plus an ACE inhibitor is cost effective compared with sacubitril/valsartan plus SOC in patients with HFrEF [67]. A budget impact analysis demonstrated that dapagliflozin was cost saving when prescribed as an alternative to sacubitril/valsartan across a range of displacement values (30–50%) [68].

In conclusion, dapagliflozin 10 mg/day in addition to SOC reduces the risk of worsening HF or CV death in patients with HFrEF, regardless of the presence or absence of T2DM. Dapagliflozin is an effective and generally well-tolerated treatment that represents a valuable new addition to the options available for symptomatic HFrEF.

Data Selection Dapagliflozin: 687 records identified	
Duplicates removed	235
Excluded during initial screening (e.g., press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	329
Excluded during writing (e.g., reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	54
Cited efficacy/tolerability articles	36
Cited articles not efficacy/tolerability	33
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were dapagliflozin, Farxiga, type 2 diabetes, heart failure. Records were limited to those in English language. Searches last updated 13 September 2021.	

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40256-021-00503-8.

Acknowledgments During the peer review process, the manufacturer of dapagliflozin was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and Conflict of interest Hannah Blair is a salaried employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to the review and are responsible for the article content.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

References

1. Genuardi MV, Mather PJ. The dawn of the four-drug era? SGLT2 inhibition in heart failure with reduced ejection fraction. Ther Adv Cardiovasc Dis. 2021;15:1–12.
2. Murphy SP, Ibrahim NE, Januzzi JL Jr. Heart failure with reduced ejection fraction: a review. JAMA. 2020;324(5):488–504.
3. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and writing committee of the universal definition of heart failure: endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. Eur J Heart Fail. 2021;23(3):352–80.
4. McDonagh TA, Metra M, Adamo M, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021. https://doi.org/10.1093/eurheartj/ehab368.
5. Maddox TM, Januzzi JL Jr, Allen LA, 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(6):772–810.
6. Ferrari F, Martins VM, Scheffel RS, et al. The role of sodium-glucose cotransporter-2 inhibitors in patients with heart failure, regardless of diabetes status: focus on cardiovascular disease. Ann Pharmacother. 2021;55(10):1267–75.
7. Khan MS, Vaduganathan M. What makes sodium-glucose co-transporter-2 inhibitors stand out in heart failure? Curr Diab Rep. 2020;20:63.
8. AstraZeneca. FARXIGA® (dapagliflozin) tablets, for oral use: US prescribing information. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202293s024lbl.pdf. Accessed 13 Sep 2021.
9. European Medicines Agency. Forxiga (dapagliflozin): EU summary of product characteristics. 2021. https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf. Accessed 13 Sep 2021.
10. Dhillon S. Dapagliflozin: a review in type 2 diabetes. Drugs. 2019;79(10):1135–46.
11. Plosker GL. Dapagliflozin: a review of its use in patients with type 2 diabetes. Drugs. 2014;74(18):2191–209.
12. Paik J, Blair HA. Dapagliflozin: a review in type 1 diabetes. Drugs. 2019;79(17):1877–84.
13. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.

14. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57.
15. 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(18):1463–76.
16. McMurray JJV, de Boer RA, Hammarstedt A, et al. Dapagliflozin effect on exercise capacity using a 6-minute walk test in patients with heart failure (DETERMINE) trials [presentation]. In: European Society of Cardiology Annual Congress. 2021.
17. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.
18. Berg DD, Jhund PS, Docherty KF, et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. JAMA Cardiol. 2021;6(5):499–507.
19. Butt JH, Docherty KF, Petrie MC, et al. Efficacy and safety of dapagliflozin in men and women with heart failure with reduced ejection fraction: a prespecified analysis of the dapagliflozin and prevention of adverse outcomes in heart failure trial. JAMA Cardiol. 2021;6(6):678–89.
20. Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. JAMA. 2020;323(14):1353–68.
21. Shen L, Kristensen SL, Bengtsson O, et al. Dapagliflozin in HFrEF patients treated with mineralocorticoid receptor antagonists: an analysis of DAPA-HF. JACC Heart Fail. 2021;9(4):254–64.
22. Butt JH, Nicolau JC, Verma S, et al. Efficacy and safety of dapagliflozin according to aetiology in heart failure with reduced ejection fraction: insights from the DAPA-HF trial. Eur J Heart Fail. 2021;23(4):601–13.
23. Jhund PS, Solomon SD, Docherty KF, et al. Efficacy of dapagliflozin on renal function and outcomes in patients with heart failure with reduced ejection fraction: results of DAPA-HF. Circulation. 2020;143(4):298–309.
24. Docherty KF, Jhund PS, Claggett B, et al. Extrapolating long-term event-free and overall survival with dapagliflozin in patients with heart failure and reduced ejection fraction: an exploratory analysis of a phase 3 randomized clinical trial. JAMA Cardiol. 2021. https://doi.org/10.1001/jamacardio.2021.2632.
25. Martinez FA, Serenelli M, Nicolau JC, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. Circulation. 2020;141(2):100–11.
26. Adamson C, Jhund PS, Docherty KF, et al. Efficacy of dapagliflozin in heart failure with reduced ejection fraction according to body mass index. Eur J Heart Fail. 2021. https://doi.org/10.1002/ejhf.2308.
27. Dewan P, Solomon SD, Jhund PS, et al. Efficacy and safety of sodium-glucose co-transporter 2 inhibition according to left ventricular ejection fraction in DAPA-HF. Eur J Heart Fail. 2020;22(7):1247–58.
28. Kober L, Docherty K, Inzucchi SE, et al. Dapagliflozin improves outcomes irrespective of NT-proBNP concentration in patients with HFrEF: an analysis of the DAPA-HF trial [abstract no. 1027–07]. J Am Coll Cardiol. 2020;75(11):675.
29. Docherty KF, Inzucchi SE, Kober L, et al. Efficacy and safety of dapagliflozin in black, compared to white, patients with heart failure with reduced ejection fraction: results from DAPA-HF [abstract]. In: Heart Failure 2021 & Word Congress on Acute Heart Failure. 2021.
30. Docherty KF, Jhund PS, Bengtsson O, et al. The effect of dapagliflozin across the spectrum of baseline risk: a post-hoc analysis of DAPA-HF [abstract no. ehaa946.0931]. Eur Heart J. 2020;41(Suppl. 2):931.
31. Yeoh SE, Dewan P, Jhund PS, et al. Patient characteristics, clinical outcomes, and effect of dapagliflozin in relation to duration of heart failure: is it ever too late to start a new therapy? Circ Heart Fail. 2020;13(12):699–709.
32. Docherty KF, Curtain JP, Anand IS, et al. Effect of dapagliflozin on anaemia in DAPA-HF. Eur J Heart Fail. 2021;23(4):617–28.
33. Dewan P, Docherty KF, Bengtsson O, et al. Effects of dapagliflozin in heart failure with reduced ejection fraction, and COPD: an analysis of DAPA-HF. Eur J Heart Fail. 2020;23(4):632–43.
34. Kosiborod MN, Jhund PS, Docherty KF, et al. Effects of dapagliflozin on symptoms, function, and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. Circulation. 2020;141(2):90–9.
35. Serenelli M, Bohm M, Inzucchi SE, et al. Effect of dapagliflozin according to baseline systolic blood pressure in the dapagliflozin and prevention of adverse outcomes in heart failure trial (DAPA-HF). Eur Heart J. 2020;41(36):3402–18.
36. Docherty KF, Jhund PS, Bengtsson O, et al. Effect of dapagliflozin in DAPA-HF according to background glucose-lowering therapy. Diabetes Care. 2020;43(11):2878–81.
37. Solomon SD, Jhund PS, Claggett BL, et al. Effect of dapagliflozin in patients with HFrEF treated with sacubitril/valsartan: the DAPA-HF trial. JACC Heart Fail. 2020;8(10):811–8.
38. Jackson AM, Dewan P, Anand IS, et al. Dapagliflozin and diuretic use in patients with heart failure and reduced ejection fraction in DAPA-HF. Circulation. 2020;142:1040–54.
39. Docherty KF, Jhund PS, Inzucchi SE, et al. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. Eur Heart J. 2020;41(25):2379–92.
40. Jhund PS, Ponikowski P, Docherty KF, et al. Dapagliflozin and recurrent heart failure hospitalizations in heart failure with reduced ejection fraction: an analysis of DAPA-HF. Circulation. 2021;143(20):1962–72.
41. Docherty KF, Jhund PS, Anand I, et al. Effect of dapagliflozin on outpatient worsening of patients with heart failure and reduced ejection fraction: a prespecified analysis of DAPA-HF. Circulation. 2020;142:1623–32.
42. Docherty K, Kosiborod MN, Inzucchi SE, et al. Effects of dapagliflozin on physical and social activity limitations in patients with heart failure and reduced ejection fraction: an analysis of DAPA-HF [abstract no. 16353]. Circulation. 2020;142(Suppl. 3)
43. Inzucchi SE, Docherty KF, Kober L, et al. Dapagliflozin and the incidence of type 2 diabetes in patients with heart failure and reduced ejection fraction: an exploratory analysis from DAPA-HF. Diabetes Care. 2020;44(2):586–94.
44. Curtain JP, Docherty KF, Jhund PS, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest or sudden death in DAPA-HF [presentation]. In: European Society of Cardiology Annual Congress. 2021.
45. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139(22):2528–36.
46. McMurray JJV, Wheeler DC, Stefansson BV, et al. Effects of dapagliflozin in patients with kidney disease, with and without heart failure. JACC Heart Fail. 2021. https://doi.org/10.1016/j.jchf.2021.06.017.
47. von Lueder TG, Kotecha D, Atar D, et al. Neurohormonal blockade in heart failure. Card Fail Rev. 2016;3(1):19–24.
48. Yancy CW, Jessup M, Bozkurt B, 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. 2017;70(6):776–803.
49. Rosano GMC, Moura B, Metra M, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2021;23(6):872–81.
50. National Institute of Health and Care Excellence. Dapagliflozin for treating chronic heart failure with reduced ejection fraction. 2021. http://www.nice.org.uk. Accessed 13 Sep 2021.
51. McMurray JJV, Solomon SD, Docherty KF, et al. The dapagliflozin and prevention of adverse outcomes in heart failure trial (DAPA-HF) in context. Eur Heart J. 2021;42(13):1199–202.
52. Cao Z, Jia Y, Zhu B. BNP and NT-proBNP as diagnostic biomarkers for cardiac dysfunction in both clinical and forensic medicine. Int J Mol Sci. 2019;20(8):1820.
53. Akhtar KH, Hafeez H, Farooqi MS, et al. Cardiovascular outcomes of dapagliflozin (sodium-glucose cotransporter-2 inhibitor): a systematic review and meta-analysis [abstract no. IV-42]. Catheter Cardiovasc Interv. 2020;95(Suppl. 2):S199–200.
54. Cai RP, Xu YL, Su Q. Dapagliflozin in patients with chronic heart failure: a systematic review and meta-analysis. Cardiol Res Pract. 2021. https://doi.org/10.1155/2021/6657380.
55. Zheng XD, Qu Q, Jiang XY, et al. Effects of dapagliflozin on cardiovascular events, death, and safety outcomes in patients with heart failure: a meta-analysis. Am J Cardiovasc Drugs. 2020;21(3):321–30.
56. Teo YH, Yoong CSY, Syn NL, et al. Comparing the clinical outcomes across different sodium/glucose cotransporter 2 (SGLT2) inhibitors in heart failure patients: a systematic review and network meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2021. https://doi.org/10.1007/s00228-021-03147-4.
57. 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(10254):819–29.
58. Qiu M, Ding LL, Zhou HR. Comparative efficacy of five SGLT2i on cardiorenal events: a network meta-analysis based on ten CVOTs. Am J Cardiovasc Drugs. 2021. https://doi.org/10.1007/s40256-021-00484-8.
59. Qin L, Young R, Darlington O, et al. Matching adjusted indirect comparison between DAPA-HF and PARADIGM-HF for the treatment of heart failure with reduced ejection fraction [abstract no. PCV17]. Value Health. 2020;23(Suppl. 2):S489.
60. Aimo A, Pateras K, Stamatelopoulos K, et al. Relative efficacy of sacubitril-valsartan, vericiguat, and SGLT2 inhibitors in heart failure with reduced ejection fraction: a systematic review and network meta-analysis. Cardiovasc Drugs Ther. 2020. https://doi.org/10.1007/s10557-020-07099-2.
61. US National Institutes of Health. 2021. http://www.clinicaltrials.gov. Accessed 13 Sep 2021.
62. McEwan P, Darlington O, McMurray JJV, 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;22(11):2147–56.
63. Savira F, Wang BH, Kompa AR, et al. Cost-effectiveness of dapagliflozin in chronic heart failure: an analysis from the Australian healthcare perspective. Eur J Prev Cardiol. 2020;28(9):975–82.
64. Krittayaphong R, Permsuwan U. Cost-utility analysis of add-on dapagliflozin treatment in heart failure with reduced ejection fraction. Int J Cardiol. 2021;322:183–90.
65. Mendoza VL, Tumanan-Mendoza BA, Punzalan FER. Cost-utility analysis of add-on dapagliflozin in heart failure with reduced ejection fraction in the Philippines. ESC Heart Fail. 2021. https://doi.org/10.1002/ehf2.13583.
66. Isaza N, Calvachi P, Raber I, et al. Cost-effectiveness of dapagliflozin for the treatment of heart failure with reduced ejection fraction. JAMA Netw Open. 2021;4(7):e2114501.
67. McEwan P, Darlington O, Bergenheim K, et al. Cost-effectiveness of dapagliflozin versus sacubitril/valsartan for the treatment of heart failure with reduced ejection fraction [abstract no. PCV45]. Value Health. 2020;23(Suppl. 2):S494.
68. Qin L, Darlington O, Miller R, et al. Budget impact evaluation of the DAPA-HF trial: is dapagliflozin cost-saving for the treatment of heart failure with reduced ejection fraction? [abstract no. 301 plus poster]. In: European Society of Cardiology Heart Failure. 2021.
69. Yu H, Tang W, Greasley PJ, et al. Predicted cardiac hemodynamic consequences of the renal actions of SGLT2i in the DAPA-HF study population: a mathematical modeling analysis. J Clin Pharmacol. 2020;61(5):636–48.