CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

DAPAGLIFLOZIN (FORXIGA)

(AstraZeneca Canada Inc.)

Indication: Heart failure with reduced ejection fraction

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Abbreviations

6MWD	6-minute walk distance
ACEI	angiotensin-converting enzyme inhibitor
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
CHFC	Cardiac Health Foundation of Canada
CI	confidence interval
CV	cardiovascular
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
EQ VAS	EuroQol Visual Analogue Scale
ESRD	end-stage renal disease
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HFSG	Heart Failure Support Group of Manitoba
HR	hazard ratio
ICC	intraclass correlation coefficient
ITC	indirect treatment comparison
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-cs	Kansas City Cardiomyopathy Questionnaire clinical summary score
KCCQ-os	Kansas City Cardiomyopathy Questionnaire overall score
LVEF	left ventricular ejection fraction
MAIC	matching-adjusted indirect comparison
MID	minimal important difference
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OR	odds ratio
PY	person-year
RCT	randomized controlled trial
SD	standard deviation
SF-12	Short Form (12) Health Survey
SGLT2	sodium-glucose cotransporter-2

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Dapagliflozin (Forxiga) 5 mg and 10 mg oral tablets
Indication	In adults, as an adjunct to standard of care therapy, for the treatment of heart failure with reduced ejection fraction to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit
Reimbursement request	As per indication
Health Canada approval status	Approved
Health Canada review pathway	Priority review
NOC date	June 29, 2020
Sponsor	AstraZeneca Canada Inc.

NOC = Notice of Compliance.

Introduction

Heart failure (HF) is a condition that results from the inability of the heart to meet the body's metabolic demands for oxygen because of structural or functional impairment of ventricular filling or ejection of blood.[1] The primary symptoms of HF are dyspnea and fatigue and may also include fluid retention. There are an estimated 669,000 Canadians 40 years or older with HF, with an age-standardized prevalence of 3.5%.[2] Approximately half of those with HF have a reduced left ventricular ejection fraction (LVEF) less than or equal to 40%.[1] The current paradigm of treating individuals with HF with reduced ejection fraction (HFrEF) is to focus on lifestyle modifications, drug therapy, and device implantation to reduce the burden of morbidity and mortality. First-line medication treatments include beta-blockers and an angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), plus a mineralocorticoid receptor antagonist. If individuals are still symptomatic, then sacubitril-valsartan can replace the ACEI or ARB, or ivabradine can be considered. Additional pharmacotherapies include diuretics, hydralazine, nitrates, or digoxin. Implantable cardiac devices may be indicated for some patients. Despite the availability of several treatments, mortality rates in Canadians with HF are 6 times higher than for those without an HF diagnosis.[2]

Dapagliflozin belongs to the sodium-glucose cotransporter-2 (SGLT2) inhibitor class of drugs, although its mechanism of action in HF is not known. Dapagliflozin is approved by Health Canada for use in adults, as an adjunct to standard of care therapy, for the treatment of HFrEF to reduce the risk of cardiovascular (CV) death, hospitalization for HF, and urgent HF visit.[3] Dapagliflozin is available as a 5 mg or 10 mg oral tablet. The recommended dosage for patients with HFrEF is 10 mg once daily, in conjunction with other HF therapies.[3] Dapagliflozin and dapagliflozin-metformin fixed-dose combination tablets were reviewed by CADTH in 2015 and 2016 for reimbursement for patients with type 2 diabetes to improve glycemic control.[4-6]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of dapagliflozin 5 mg and 10 mg tablets for the treatment of HFrEF in adults.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Three responses to CADTH's call for patient input were received for the review of dapagliflozin. The patient groups were the HeartLife Foundation, the Cardiac Health Foundation of Canada (CHFC), and the Heart Failure Support Group of Manitoba (HFSG). Data for this submission were gathered through an in-person round-table workshop (17 patients and caregivers); interviews conducted with 4 participants; an online survey, which had 7 respondents; and 2 meetings composed of patients and their caregivers, which included a total of 55 members.

People with HF experience a wide range of physical, social, and emotional challenges that have a dramatic effect on their lives and the lives of their family caregivers. Patients report feeling "winded while doing any activity" and being "tired all the time," and they "struggle to breathe." Many patients experience disturbed sleep, cognitive impacts, depression, anxiety, and social isolation due to their condition. Heart failure is a condition that requires daily monitoring, adherence, and vigilance on the part of the patient to control the delicate balance of symptoms.

Patients hope that treatments for HF will improve their quality of life (i.e., enable them to breathe easier, walk longer, continue to work, and participate in other activities), prevent hospitalizations, reduce mortality, have fewer adverse effects or at least more tolerable adverse effects, and reduce their symptoms.

Clinician Input

There is an unmet need for additional treatments that prolong life, improve quality of life, help patients maintain independence, reduce caregiver burden, and avoid hospitalizations for patients with HF. According to the experts consulted for this review, patients in the community who meet the inclusion criteria of the DAPA-HF study would be suitable for treatment with dapagliflozin. The experts stated that dapagliflozin would not be considered first-line therapy but would be an add-on treatment to foundational therapy of ACEI, ARB, or sacubitril-valsartan, plus beta-blocker and mineralocorticoid receptor antagonist, in symptomatic patients with HFrEF (LVEF ≤ 40%) who had a suboptimal response to treatment. Response to therapy would be assessed based on frequency of hospitalizations, functional capacity, and patients' symptoms; the occurrence of adverse effects would be the main factor in decisions to stop dapagliflozin treatment.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One pivotal trial (DAPA-HF) and 1 non-pivotal trial (DEFINE-HF) met the inclusion criteria for the systematic review.

The double-blind, randomized controlled DAPA-HF study (N = 4,744) evaluated the efficacy of dapagliflozin versus placebo as an add-on to standard of care therapy in adults with HFrEF (LVEF ≤ 40%; New York Heart Association [NYHA] function classes II to IV). The primary outcome was the time to first occurrence of CV death, hospitalization for HF, or an urgent HF visit, which were adjudicated by an independent blinded committee. Other outcomes included time to worsening of renal function (composite outcome), all-cause mortality, change from baseline in HF symptoms (based on the Kansas City Cardiomyopathy Questionnaire [KCCQ] total symptom score) and health-related quality of life (EuroQol 5-Dimensions 5-Levels questionnaire [EQ-5D-5L]). The mean age of patients enrolled was 66.3 years (standard deviation [SD] = 10.9) and the majority were male (77%) and White (70%). Overall, 68% had NYHA class II symptoms and 32% had NYHA class III HF. The median follow-up duration of this event-driven trial was 18.2 months.

The aim of the DEFINE-HF study was to evaluate the effect of dapagliflozin on natriuretic peptides and health status in optimally treated patients with HFrEF, with and without type 2 diabetes. This 12-week, double-blind, randomized controlled trial (RCT) enrolled patients with an established diagnosis of HF with LVEF less than or equal to 40% (N = 263). Patients were randomized to dapagliflozin 10 mg daily or placebo as an add-on to standard of care HF therapy. Outcomes of interest to this review were time to first HF hospitalization or urgent HF visit and the change in KCCQ overall score (KCCQ-os). The mean age per treatment group was 62.2 years (SD = 11.0) and 60.4 years (SD = 12.0), and 74% were male. Overall, 55% of patients were White and 38% were Black, with NYHA class II (66%) or class III (34%) HF.

Efficacy Results

During the DAPA-HF study, 16.3% of patients in the dapagliflozin group and 21.2% of patients in the placebo group reported a primary outcome event of CV death, HF hospitalization, or urgent HF visit (Table 2). The time to occurrence of primary events was increased for patients in the dapagliflozin group versus those in the placebo group, based on a hazard ratio (HR) of 0.74; 95% confidence interval (CI), 0.65 to 0.85; P < 0.0001. Similar treatment effects were noted for the analysis of time to first occurrence of CV death or HF hospitalization (HR 0.75; 95% CI, 0.65 to 0.85; P < 0.0001). For each component of the primary outcome, the time to first event was increased for dapagliflozin versus placebo; however, these outcomes were not formally tested for statistical significance. According to the clinical experts consulted for this review, the between-group differences in CV death and HF hospitalizations were clinically important, particularly considering that patients were already receiving guideline-recommended treatment for HF.

The total number of CV deaths or HF hospitalizations was lower in the dapagliflozin group than in the placebo group (average 16.3 events per 100 person-years [PYs] versus 21.6 events per 100 PYs, respectively) with a rate ratio of 0.75 (95% CI, 0.65 to 0.88; P = 0.0002).

In the dapagliflozin group, 276 patients died (11.6%) from any cause, compared with 329 patients in the placebo group (13.9%), with an event rate of 7.9 deaths per 100 PYs versus 9.5 deaths per 100 PYs, respectively (Table 2). The time-to-event analysis reported an HR of 0.83 (95% CI, 0.71 to 0.97), but due to failure of a prior outcome in the statistical hierarchy, statistical testing of this outcome was not conducted. Thus, conclusions cannot be drawn in regard to death for any cause.

The time to first occurrence of greater than or equal to 50% sustained decline in estimated glomerular filtration rate (eGFR), end-stage renal disease (ESRD), or renal death was a secondary outcome in the DAPA-HF study (Table 2). In the dapagliflozin group, 28 patients experienced a renal event, compared with 39 patients in the placebo group, with an HR of 0.71 (95% CI, 0.44 to 1.16) for dapagliflozin versus placebo, which was not statistically significant (P = 0.17).

In the DAPA-HF study, the frequency of non-fatal or fatal myocardial infarctions and strokes was similar in the dapagliflozin and placebo groups, with an event rate of 1.2 to 1.3 persons per 100 PYs. Among patients with no atrial fibrillation or atrial flutter at baseline, [redacted] developed atrial fibrillation in the dapagliflozin group, compared with [redacted] of patients in the placebo group.

No statistically significant difference between groups was detected in health-related quality of life outcomes based on exploratory EQ-5D-5L data. The study reported a least squares mean difference of [redacted] in the change from baseline to 8 months in the EQ-5D-5L index score ([redacted]). The DAPA-HF study found statistically significant differences favouring dapagliflozin for the change from baseline in the KCCQ total symptom score (rank analysis of covariance [ANCOVA], P < 0.0001); however, the clinical relevance of these results was difficult to assess. Responder analyses were conducted based on thresholds that exceeded the minimal important difference (MID) of the KCCQ total symptom score, but these were outside the statistical testing hierarchy, with data missing for 13% of patients. Although there were more patients with at least a 5-, 10-, or 15-point increase in the KCCQ total symptom score in the dapagliflozin group (54% to 57%) than in the placebo group (47% to 50%), interpretation of these results should consider the high placebo response rate and the potential inflated risk of type I error. The DAPA-HF study detected no difference between groups in the NYHA functional class, although the clinical experts stated that this subjective classification system has low sensitivity in detecting change. No conclusions can be drawn from the KCCQ-os or clinical summary score (KCCQ-cs) data, which were outside the statistical testing hierarchy.

A second study comparing dapagliflozin to placebo in patients with HFrEF was identified in the literature search (DEFINE-HF), but this study does not provide any additional meaningful evidence for dapagliflozin. Few differences were detected between dapagliflozin and placebo in this 12-week study.

Harms Results

In the DAPA-HF study, 36% and 40% of patients in dapagliflozin and placebo groups, respectively, experienced a serious adverse event. Volume depletion was reported in 7.2% and 6.5% of patients, including serious adverse events, which were reported by 1% and 1.6% of patients, in the dapagliflozin and placebo groups, respectively (Table 3).

Renal adverse events occurred in 6.0% of patients in the dapagliflozin group and 6.7% of patients in the placebo group. These were serious adverse events for 1.4% and 2.4% of patients in the dapagliflozin and placebo groups, respectively. Three patients in the dapagliflozin group experienced diabetic ketoacidosis (adjudicated event), all of which were serious adverse events: 1 patient died.

Five percent of patients in each group of the DAPA-HF study stopped treatment due to adverse events. Four patients per group experienced a major hypoglycemic event; all had diabetes at baseline. The frequency of amputation and fracture was the same in both

treatment groups: 0.5% and 2.1% for amputation and fracture, respectively. No cases of Fournier gangrene were identified in the DAPA-HF study.

In the DEFINE-HF study, 23% and 18% of patients in the dapagliflozin and placebo groups, respectively, reported a serious adverse event over the 12-week treatment period, with 8% and 9% of patients stopping the study drug due to adverse events. One patient in the dapagliflozin group died due to worsening HF, and 1 sudden cardiac death was reported in the placebo group. No lower limb amputations or diabetic ketoacidosis events were reported. One patient in each group (0.8%) experienced a severe hypoglycemic event and an acute kidney injury adverse event. Volume depletion adverse events were reported by 9% and 5% of patients in the dapagliflozin and placebo groups, respectively.

Table 2: Summary of Key Efficacy Results From The Pivotal Study

	DAPA-HF (FAS)					
	Dapagliflozin N = 2,373		Placebo N = 2,371		Treatment effects, dapagliflozin versus placebo	
	n (%)	Event rate[a]	n (%)	Event rate[a]	HR (95% CI)	P value
Time to CV death, hospitalization for HF, or urgent HF visit	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)[b]	< 0.0001
Time to CV death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)[b]	0.0294[c]
Time to hospitalization for HF	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)[b]	< 0.0001[c]
Time to urgent HF visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)[b]	0.0213[c]
Time to CV death or hospitalization for HF	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)[b]	< 0.0001
Time to death from any cause	276 (11.6)	7.9	329 (13.9)	9.5	0.83 (0.71 to 0.97)[d]	0.0217[e]
Composite of ≥ 50% sustained decline in eGFR, ESRD, or renal death	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44 to 1.16)[f]	0.17

CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FAS = full analysis set; HF = heart failure; HR = hazard ratio.

[a] Event rate reported as the number of patients with an event per 100 person-years of follow-up.

[b] Cox proportional hazards model (score test) stratified by type 2 diabetes status at baseline, with factors for treatment group and history of HF hospitalization for the FAS population. Hazard ratio less than 1 favours dapagliflozin. The 95% CI was not adjusted for multiple comparisons.

[c] Individual components of the primary composite outcome were not formally tested for statistical significance.

[d] Cox proportional hazards model (score test) stratified by type 2 diabetes status at baseline with factors for treatment group for the FAS population. Hazard ratio less than 1 favours dapagliflozin. The 95% CI was not adjusted for multiple comparisons.

[e] Not tested for statistical significance due to failure of a prior outcome in the statistical testing hierarchy.

[f] Cox proportional hazards model (score test) stratified by type 2 diabetes status at baseline, with factors for treatment group and eGFR at baseline for the FAS population. Hazard ratio less than 1 favours dapagliflozin.

Source: Clinical Study Report for DAPA-HF.[7]

Table 3: Summary of Harms From The Pivotal Study

	DAPA-HF (safety set)[a]	
	Dapagliflozin N = 2,368	Placebo N = 2,368
Patients with ≥ 1 SAE, n (%)	846 (35.7)	951 (40.2)
Patients who stopped treatment due to adverse events, n (%)	111 (4.7)	116 (4.9)
Deaths, n (%)	227 (9.6)	250 (10.6)
Notable harms, n (%)		
Volume depletion[b]	170 (7.2)	153 (6.5)
Renal adverse event[b]	141 (6.0)	158 (6.7)
Major hypoglycemic event[c]	4 (0.2)	4 (0.2)
Diabetic ketoacidosis[d]	3 (0.1)	0
Amputation[e]	13 (0.5)	12 (0.5)
Fracture[b,e]	49 (2.1)	50 (2.1)

SAE = serious adverse event.

[a] All adverse events were reported based on the on-treatment period (from the first dose of the study drug until 30 days after the last dose), except for fractures, which were reported for the on- and off-treatment period (from the first dose of the study drug to the end of follow-up).

[b] Based on a predefined list of terms.

[c] Major hypoglycemic events were confirmed by the investigator and defined as follows: symptoms of severe impairment in consciousness or behaviour; need of external assistance; intervention to treat hypoglycemia; prompt recovery of acute symptoms following the intervention.

[d] Adjudicated as definite or probable diabetic ketoacidosis events.

[e] Surgical or spontaneous (non-surgical) amputation, excluding amputation due to trauma.

Source: Clinical Study Report for DAPA-HF.[7]

Critical Appraisal

The DAPA-HF trial used accepted methods to randomize and conceal treatment allocation (i.e., interactive voice or web response system; computer-generated block randomization). The baseline patient characteristics and background therapies appear to be balanced between groups, and follow-up for the primary outcome was complete for more than 99% of patients randomized. The trial, however, was not designed to test for superiority of dapagliflozin for health-related quality of life, which was of primary importance to patients. The EuroQol 5-Dimensions questionnaire (EQ-5D) data reported had limitations due to missing data, which were not accounted for in the analysis, and this outcome was not part of the statistical testing hierarchy. The study evaluated differences in HF symptoms using a validated instrument (KCCQ); however, the use of a non-parametric statistical model made it difficult to assess the clinical relevance of the differences reported. Assessment of functional status was based on the change in NYHA class, which may have low sensitivity in detecting changes in patients' ability to participate in daily activities, according to the clinical experts consulted. The DAPA-HF study did not collect data on all adverse effects; thus, it is unclear if the overall pattern of adverse effects in patients with HF is similar to those observed in the previously published dapagliflozin trials in patients with diabetes.

Although a second study comparing dapagliflozin to placebo in patients with HFrEF was identified in the literature search (DEFINE-HF), that study does not provide any additional meaningful evidence for dapagliflozin. The limitations of that study include the sample size (263 patients), duration (12 weeks), unclear allocation concealment, lack of control of type I error, and incomplete reporting of results.

The clinical experts consulted indicated that the population enrolled in the DAPA-HF study reflected those who may be seen in general practice, but the generalizability to patients with more severe HFrEF is unclear. The study excluded patients with more advanced disease, including those with recent HF hospitalization or CV events and those with poor or worsening renal function. Most patients were in NYHA class II (68%), and less than 1% had NYHA class IV HF. The clinical experts also stated that the trial population may not reflect the ethnic diversity in Canada. The trial population was enriched by selecting those with N-terminal pro B-type natriuretic peptide (NT-proBNP) levels greater than or equal to 600 pg/mL. However, the clinical experts consulted stated that natriuretic peptide testing is not widely available in Canada; thus, this patient selection criteria would be difficult to implement in clinical practice.

Indirect Comparisons

The sponsor supplied a matching-adjusted indirect comparison (MAIC) that evaluated the efficacy and safety of dapagliflozin compared to sacubitril-valsartan as an add-on to standard therapies in adults with HFrEF. The analysis used individual patient data from the DAPA-HF study to create a cohort of patients who were weighted to match the characteristics of the control group of the PARADIGM-HF trial. The analysis had several limitations that threatened the internal validity of the results. Most notable were differences in the study design and populations enrolled in the 2 trials (such as the enrolment of an enriched population in the PARADIGM-HF study) and the derivation of patient weights independently for the active and control groups of the DAPA-HF study. The methods used to conduct the MAIC were not consistent with technical guidance[8] and are of uncertain validity. As a result, no conclusions can be drawn from the indirect comparison.

Conclusions

In adults with symptomatic HFrEF who received dapagliflozin as an add-on therapy to guideline-recommended drug therapy, the time to occurrence of CV death, HF hospitalization, or urgent HF visits was increased, relative to those who received placebo in addition to guideline-recommended drug therapy.

The impact of dapagliflozin on patient-valued outcomes of health-related quality of life, functional ability, and HF-related symptoms is uncertain. Although statistically significant differences were detected favouring dapagliflozin rather than placebo in the change from baseline in HF symptoms (measured using the KCCQ total symptom score), the clinical relevance of the differences is unclear.

No new safety signals were identified in patients with HFrEF; however, the pivotal DAPA-HF study did not collect data for all non-serious adverse events.

The evidence consisted of a single placebo-controlled trial, with a median duration of 18 months. Thus, longer-term safety and efficacy are uncertain in patients with HFrEF. No meaningful safety or efficacy data for dapagliflozin were provided by the second 12-week RCT included in the systematic review. There was no direct evidence comparing dapagliflozin to other second-line therapies for HF. The sponsor supplied an MAIC that compared dapagliflozin to sacubitril-valsartan; however, the analysis had major methodological flaws, and thus no conclusions could be drawn from the results.

Introduction

Disease Background

Heart failure is a condition that results from the inability of the heart to meet the body's metabolic demands for oxygen because of structural or functional impairment of ventricular filling or ejection of blood.[1] The underlying etiologies include disorders of the pericardium, myocardium, endocardium, heart valves, or great vessels or certain metabolic abnormalities.[1] The primary symptoms of HF are dyspnea and fatigue and may also include fluid retention. Patients report that HF can have a profound impact on their physical, social, and emotional well-being, which dramatically affects their lives and the lives of their family caregivers. Their condition requires daily monitoring, adherence, and vigilance by patients to control the delicate balance of symptoms.

There are an estimated 669,000 Canadians older than 40 years with HF, with an age-standardized prevalence of 3.5%.[2] Between 2001 and 2013, the HF incidence rate in Canada has declined, as has the age-standardized all-cause mortality rate among people living with HF.[2] However, Canadians 40 years or older with HF are 6 times more likely to die than those without an HF diagnosis.[2] The economic burden due to HF is substantial, with costs associated with health care services, medications, and lost productivity. Hospitalizations due to HF are frequent, with 83% of patients hospitalized at least once, and 43% hospitalized 4 or more times after HF diagnosis.[1] Approximately half of those with HF have a reduced LVEF (≤ 40%); it is in this population that the evidence base regarding treatment is better established.[1]

Standards of Therapy

The following text was based on input from clinicians consulted by CADTH for the purpose of this review.

The current paradigm of treating individuals with HFrEF is to focus on lifestyle modifications, drug therapy, and device implantation to reduce the burden of morbidity and mortality. Additionally, management of underlying comorbidities (e.g., diabetes, thyroid disease, anemia) should continue as per guidelines.

The lifestyle modification primarily focuses on adherence to salt and water restriction and exercise rehabilitation. The medication treatments include the use of beta-blockers, ACEIs, or ARBs, plus a mineralocorticoid receptor antagonist as the foundational therapy. If individuals are still symptomatic, then sacubitril-valsartan can replace ACEIs or ARBs, or ivabradine can be considered (if the heart rate is greater than 77 beats per minute and patients are not in permanent atrial fibrillation). Additional pharmacotherapies include hydralazine, nitrates, or digoxin. Diuretics are frequently prescribed to manage fluid status. Cardiac resynchronization device implantation may be indicated for individuals with left bundle branch block, and if patients have persistently reduced LVEF, an implantable cardioverter-defibrillator can be considered. Currently, SGLT2 inhibitors are recommended by Canadian guidelines, despite being off label in patients with HFrEF without type 2 diabetes.[9]

The main goals of treatment are to prolong life, improve quality of life, help patients maintain independence, avoid hospitalizations, and reduce caregiver burden, while minimizing the risk of adverse effects from treatment.

Drug

Dapagliflozin belongs to the SGLT2 inhibitor class of drugs, although its mechanism of action in HF is not known. Dapagliflozin is approved by Health Canada for use in adults, as an adjunct to standard of care therapy, for the treatment of HFrEF to reduce the risk of CV death, hospitalization for HF, and urgent HF visit.[3] The sponsor requested reimbursement as per the indication.[10]

Dapagliflozin was previously approved in Canada as an adjunct to diet and exercise (as monotherapy or combination therapy) to improve glycemic control in adult patients with type 2 diabetes mellitus.[3] It is also approved as an adjunct to diet, exercise, and standard of care therapy to reduce the risk of hospitalization for HF in adults with type 2 diabetes mellitus and CV risk factors or established CV disease. Dapagliflozin and dapagliflozin-metformin fixed-dose combination tablets were reviewed by CADTH in 2015 and 2016 for reimbursement in patients with type 2 diabetes to improve glycemic control.[4-6]

Dapagliflozin is available as a 5 mg or 10 mg oral tablet. The recommended dosage for patients with HFrEF is 10 mg once daily, in conjunction with other HF therapies.[3]

Table 4: Key Characteristics of Dapagliflozin

Characteristic	Description
Mechanism of action	SGLT2 inhibitor
Indication[a]	In adults, as an adjunct to standard of care therapy, for the treatment of HFrEF to reduce the risk of CV death, hospitalization for heart failure, and urgent heart failure visit
Route of administration	Oral
Recommended dosage	10 mg daily
Serious adverse effects or safety issues	Contraindications: patients with an eGFR less than 30 mL/min/1.73m^2; patients with ESRD or patients on dialysis; patients with type 1 diabetes Warnings: Use with caution in patients at risk of volume depletion, hypotension, and/or electrolyte imbalances; in patients with a history of DKA; or for the treatment of DKA Genital mycotic infections, urinary tract infections, and necrotizing fasciitis of the perineum (Fournier gangrene) Elevated hemoglobin and hematocrit Monitoring of renal function recommended Risk of hypoglycemia when used in combination with other with medications known to cause hypoglycemia

CV = cardiovascular; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease, HFrEF = heart failure with reduced ejection fraction; SGLT2 = sodium-glucose cotransporter-2.

[a] Health Canada approved indication.

Source: Forxiga product monograph.[3]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

About the Patient Groups and Information Gathered

Three responses to CADTH's call for patient input were received for the review of dapagliflozin. The patient groups were the HeartLife Foundation, the CHFC, and the HFSG.

The HeartLife Foundation is a national patient-led, volunteer-run charity aimed at engaging patients, families, and caregivers to provide education, support, and access to the latest treatments and research. The foundation collaborates with partners in health care, government, and industry with the ultimate goal of improving patient care in Canada. The HeartLife Foundation fulfills this mandate through administering service programs, support groups, workshops, public awareness campaigns, and government relation activities. The CHFC is a national charitable organization dedicated to cardiac rehabilitation, advocacy for disease prevention, and public education. The CHFC runs a national Walk of Life campaign, which raises funds for national initiatives such as cardiac rehabilitation programs, access to equipment and medical research, scholarships, and invited lectures. The HFSG brings together patients and their families and caregivers to provide support and education through invited guest speakers.

A disclosure of any conflicts of interest for all 3 organizations is available on the CADTH website. The HeartLife Foundation gathered information for its submission through an in-person round-table workshop held in May 2019, which had 17 patients and caregivers (aged 34 to 67) from 8 provinces, and through interviews conducted with 4 participants aged 33 to 56 years, including a patient with HF, a family caregiver, and 2 patients who had had heart transplants. Furthermore, the HeartLife Foundation worked in collaboration with the CHFC to develop a survey that was distributed through both organizations' Facebook and Twitter platforms and through the CHFC's website in March and April 2020; this survey had 7 respondents. The HFSG gathered information for its submission from 2 meetings composed of patients and their caregivers, which had 30 members (November 2019) and 25 members (February 2020).

Disease Experience

It is estimated that between 600,000 and 1 million people are currently living with HF in Canada and that between 50,000 and 92,900 Canadians are newly diagnosed with HF each year. The HeartLife Foundation stated that patients can be born with the disease, develop it throughout their adult lives, or be diagnosed in late adulthood.

People with HF experience a wide range of physical, social, and emotional challenges that have a dramatic effect on their lives and the lives of their family caregivers. HF is a condition that requires daily monitoring, adherence, and vigilance on the part of the patient to control the delicate balance of symptoms. These symptoms include shortness of breath, extreme fatigue, low blood pressure, dizziness, edema, and bloating. Many patients also have palpitations and arrhythmia as a result of the underlying cause of their HF. HF has no cure and, if left untreated, will become progressively worse over time. HF is commonly associated with a variety of comorbidities, anxiety, depression, and a decline in cognitive ability, and it can have a negative impact on mental health.

Patients report feeling “winded while doing any activity” and being “tired all the time,” and they “struggle to breathe.” Many patients experience disturbed sleep due to difficulty breathing at night, and in the later stages, breathing in a horizontal position can feel like choking or drowning. The fatigue and the need for frequent rest periods affect their ability to work and do household chores. In the later stages, daily activities are difficult and exhausting, leading most patients to spend most of their time resting at home, living increasingly isolated lives. Cognitive impairments become more severe as a result of the lack of blood flow to the brain, resulting in difficulty focusing, reading, and carrying on conversations.

Caregivers of HF patients often report fatigue, interrupted sleep, and psychological tolls such as anxiety and depression. Moreover, family members and caregivers undergo a financial toll due to the cost of treatment and loss of wages when accompanying patients to appointments and hospitalizations. Stressors can be persistent and recurrent due to the nature of the disease and may present a physical and psychological trauma to caregivers when they are faced with watching their loved one progress to the end stages of their disease: “Heart failure was to become a family disease… we still were cognisant of the meals we cooked, the places we went, and the activities we participated in. Something as simple as walking a trail could be the most difficult thing in the world for a patient living with heart failure.”

Experience With Treatment

The patients surveyed reported taking multiple medications to manage their HF symptoms. Many patients were on triple therapy (ACEI or ARB, beta-blockers, and mineralocorticoid receptor antagonist). Other medications included ivabradine (Lancora), sacubitril-valsartan (Entresto), anticoagulants (apixaban and warfarin), amiodarone, furosemide (Lasix), and digoxin.

None of the treatments available are a cure for HF; in addition, many patients remain intolerant to beta-blockers and ACEI. Thus, there is a need to add new medications to treatment regimens. Among patients surveyed, most respondents indicated they experienced adverse effects with medications. Some patients had undergone cardiac rehabilitation therapy, although access to rehabilitation programs can be limited. In the later stage of HF, the only remaining alternatives for treatment are high-risk surgical interventions, including left ventricular assist devices and heart transplantation.

Based on the findings of the HeartLife Foundation’s round-table workshop, the top 3 challenges to patients and caregivers were equal access to care (e.g., medication, rehabilitation, digital records), multidisciplinary care, and mental health support. Furthermore, based on input from the HFSG, patients felt they had challenges related to lack of reimbursement by provincial plans, perceived adverse effects of the medications, lack of knowledge about potential benefits of the treatment, and multi-pharmacy (i.e., “I am already taking too many medications”).

Within the submissions, there was 1 patient who had taken dapagliflozin previously and 2 others on a different SGLT2 inhibitor. No details were provided on how these treatments impacted the patients’ condition.

Improved Outcomes

All 3 patient groups highlighted that patients hope that treatments for HF will improve their quality of life (i.e., enable them to breathe easier, walk longer, and sleep better), prevent hospitalizations, reduce mortality, have fewer adverse effects or at least more tolerable adverse effects, and reduce their symptoms. Furthermore, patients want self-management techniques, such as ways to breathe easier.

The HeartLife Foundation stated that to its patient population, quality of life is as important as quantity of life. Along with decreased hospitalizations, patients would like to be able to spend time with loved ones, work on a regular basis, pursue outdoor activities, and travel.

The CHFC stressed the importance of the availability of cardiac rehabilitation programs and mental health support for patients with HF. The HeartLife Foundation stressed that although HF has no cure, if left untreated it can become progressively worse over time and that patients and caregivers want to be given the opportunity to have a good quality of life.

Clinician Input

All CADTH review teams include at least 1 clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). In addition, as part of the dapagliflozin review, a panel of clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). A summary of this panel discussion is presented in the sections that follow.

Unmet Needs

Despite the availability of treatments to manage symptoms and prevent clinical decline, HFrEF is associated with substantial morbidity and mortality. Patients may experience frequent hospitalizations, reduced quality of life, and functional impacts that may limit their ability to work and participate in social events and day-to-day activities. There are no known treatments to cure HF, and once HFrEF develops, the individuals will always be patients with HF. There is a need for additional treatments that prolong life, improve quality of life, help patients maintain independence, avoid hospitalizations, and reduce caregiver burden.

The clinical experts stated that access to existing treatments may be an issue due to limited or restrictive reimbursement criteria for some drugs. Application of treatment guidelines may be poor in ambulatory populations, as many patients do not have access to specialized HF clinics. Patient adherence to treatments may be suboptimal; thus once-a-day formulations may be preferred to reduce pill burden. In addition, there is a need for treatments without hemodynamic impacts, as many patients with HFrEF have low blood pressure.

Place in Therapy

Dapagliflozin belongs to a different drug class than the currently available HF therapies; thus, its currently unknown mechanism of action appears to be complementary to standard of care treatments. Dapagliflozin would be considered an add-on treatment to foundational therapy of ACEI, ARB, or sacubitril-valsartan, plus beta-blocker and mineralocorticoid receptor antagonist, in symptomatic patients with HFrEF (LVEF ≤ 40%). It would not be considered first-line therapy, but may be added to background therapy, in patients with suboptimal response to treatment.

Patient Population

The clinical experts indicated that patients in the community who meet the inclusion criteria of the DAPA-HF study would be suitable for treatment with dapagliflozin. This includes patients with HFrEF who were symptomatic (predominantly NYHA class II and III) — with an eGFR greater than or equal to 30 mL/min/1.73m^2 and no recent major CV events or HF hospitalizations — and who were managed with ACEI or ARB, beta-blocker, or mineralocorticoid receptor antagonist therapy. The experts did not identify any subgroups of patients who were more or less likely to respond to treatment. Although the trial had inclusion criteria based on NT-proBNP levels, the clinical experts stated that natriuretic peptide testing is not widely available across Canada and that patients with natriuretic peptide levels above and below the clinical trial threshold would be expected to benefit from therapy.

The diagnosis of HFrEF can be made with an echocardiogram, which is a standardized and reproducible imaging test.

Dapagliflozin would not be suitable for patients with eGFR less than 30 mL/min/1.73m^2. The experts stated that patients should be tried on ACEI, ARB, or sacubitril-valsartan, plus beta-blocker, before considering dapagliflozin therapy. Pre-symptomatic patients (NYHA class I) without diabetes should not be treated with dapagliflozin, given the absence of data in this patient group. Dapagliflozin may be considered in pre-symptomatic HF patients with type 2 diabetes, regardless of LVEF, as a CV and renal risk-modifying drug.

Assessing Response to Treatment

In practice, response to therapy is assessed based on frequency of hospitalizations, functional capacity, and patients' symptoms. Functional capacity is routinely assessed using the NYHA classification, but other instruments, such as the KCCQ, are infrequently used in clinical practice. Routine management includes monitoring of fluid status, electrolytes, vital signs, and potential adverse effects.

Ideally, patients with HFrEF should be assessed every 3 to 4 months for evaluation of clinical status and medical optimization. However, monitoring frequency may be limited by the clinical environment, as many patients do not have access to a setting that enables them to see a physician routinely.

Discontinuing Treatment

The occurrence of adverse effects is the main factor in decisions to stop treatment with dapagliflozin. The clinical experts identified the development of diabetic ketoacidosis, lower extremity ulcerations or worsening peripheral arterial disease, acute volume depletion, refractory hypoglycemia, hypotension, and worsening kidney function as important adverse

effects that may require discontinuation of dapagliflozin. In addition, patients should be monitored for urinary tract infections or genital mycotic infections, and treatment should be put on hold during an acute illness.

Prescribing Conditions

The clinical experts stated that prescribing of dapagliflozin should not be limited to specialists, as the majority of patients with HF in Canada are managed by non-cardiologists in community settings.

For some patients, such as those with unstable type 2 diabetes, a co-management model would be appropriate to help ensure glycemic as well as HF-related treatment goals were met and to minimize the risk of adverse effects such as hypoglycemia or diabetic ketoacidosis.

Clinical Evidence

The clinical evidence included in the review of dapagliflozin is presented in 3 sections. Section 1, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. Section 2 includes indirect evidence from the sponsor (if submitted) and indirect evidence selected from the literature that met the selection criteria specified in the review. Section 3 includes sponsor-submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of dapagliflozin 5 mg and 10 mg tablets for the treatment of HFrEF in adults.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 5.

Table 5: Inclusion Criteria for the Systematic Review

Patient population	Adults with heart failure with reduced ejection fraction Subgroups: • history of type 2 diabetes • background treatments for heart failure • renal function • left ventricular ejection fraction • NYHA class • history of atrial fibrillation
Intervention	Dapagliflozin 10 mg daily as add-on therapy to standard treatments
Comparators	Standard heart failure therapies (with or without placebo), such as: • ACEI (or ARB) plus beta-blocker (may also include mineralocorticoid receptor antagonist [eplerenone, spironolactone]) • sacubitril-valsartan plus beta-blocker ± mineralocorticoid receptor antagonist • ivabradine plus ACEI (or ARB) plus beta-blocker ± mineralocorticoid receptor antagonist
Outcomes	**Efficacy outcomes:** • mortality (all cause and cardiovascular related) • hospitalization (all cause and cardiovascular related)[a] • renal events (e.g., progression to ESRD) • cardiovascular events (e.g., myocardial infarction, stroke, worsening heart failure) • new onset atrial fibrillation or another arrhythmia • health-related quality of life[a] • symptoms of heart failure (e.g., dyspnea, fatigue)[a] • functional status[a]

	Harm outcomes: AEs, SAEs, WDAEs, notable harms (hypoglycemia, volume depletion, ketoacidosis, genitourinary AEs, renal AEs, amputations, fractures)
Study design	Published and unpublished phase III and IV RCTs

ACEI = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin receptor blocker; ESRD = end-stage renal disease; NYHA = New York Heart Association; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[11]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were dapagliflozin and heart failure. Clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and WHO's International Clinical Trials Registry Platform search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on May 11, 2020. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on September 16, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[12] health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, clinical trials registries, and databases (free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 1 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Findings From the Literature

Two studies were identified from the literature for inclusion in the systematic review (Figure 1).

The included studies are summarized in Table 6. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

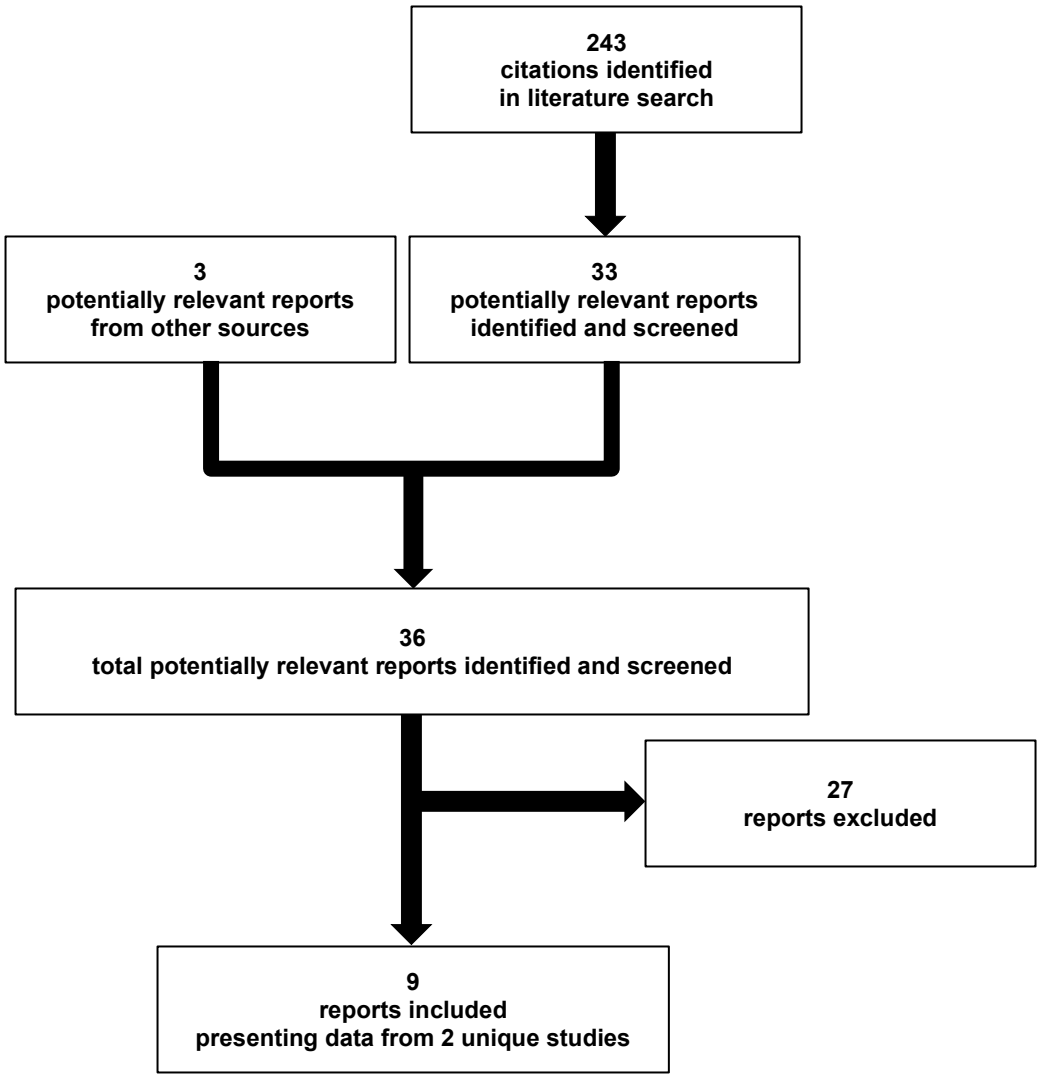


Table 6: Details of Included Studies

		DAPA-HF	DEFINE-HF
Designs and Populations	**Study design**	DB RCT	DB RCT
	Locations	US, Canada, Asia, Europe, South America	US
	Randomized (N)	4,744	263
	Inclusion criteria	• Aged ≥ 18 years with documented diagnosis of HFrEF (NYHA classes II to IV) present for at least 2 months and optimally treated with drug or device therapy including ACEI, ARB, or sacubitril-valsartan, plus beta-blocker, plus mineralocorticoid receptor antagonist (if appropriate) • LVEF ≤ 40% within last 12 months • NT-proBNP ≥ 600 pg/mL (or if hospitalized within past year, ≥ 400 pg/mL, or if concomitant AF or flutter, ≥ 900 pg/mL) • eGFR ≥ 30 mL/min/1.73 m^2	• Aged ≥ 18 years with documented diagnosis of HFrEF (NYHA classes II or III) present for at least 16 weeks that is optimally treated • LVEF ≤ 40% documented by an imaging modality within last 24 months • BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL (or if concomitant AF, then BNP ≥ 125 pg/mL or NT-proBNP ≥ 600 pg/mL)
	Exclusion criteria	• Symptomatic hypotension or systolic BP < 95 mm Hg • Current decompensated HF or hospitalization for decompensated HF with past 4 weeks • MI, unstable angina, stroke, or transient ischemic attack within 12 weeks • PCI, CABG, valvular repair or replacement, or implantation of CRT within past 12 weeks or plan to undergo these procedures • Prior cardiac transplant • HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy, or uncorrected primary valvular disease • Symptomatic bradycardia or second- or third-degree heart block without pacemaker • Unstable or rapidly progressing renal disease at randomization • Type 1 diabetes; received SGLT2 inhibitor in past 8 weeks	• Decompensated HF (hospitalization for HF in past 30 days or NYHA class IV HF at screening) • eGFR < 30 mL/min/1.73 m^2 • MI, unstable angina, PCI, or cardiac surgery within past 30 days • CRT within past 90 days • Planned PCI, CABG, valvular repair or replacement, cardiac transplant, or CRT within the 90 days after screening • Volume depleted at start of study • Received SGLT2 inhibitors within past 12 weeks • Systolic blood pressure < 90 mm Hg • Type 1 diabetes or prior bladder cancer • HF due to restricted cardiomyopathy, active myocarditis, constrictive pericarditis, severe stenotic valve disease, or hypertrophic obstructive cardiomyopathy
Drugs	**Intervention**	Dapagliflozin 10 mg oral tablet per day plus standard of care treatments for HF	Dapagliflozin 10 mg oral tablet per day plus standard of care treatments for HF
	Comparator(s)	Placebo plus standard of care treatments for HF	Placebo plus standard of care treatments for HF
Duration	**Phase**		
	DB	Event-driven trial (844 primary outcome events)	12 weeks
	Follow-up	6 weeks	1 week
Outcome	**Primary end point**	Time to first occurrence of CV death, hospitalization for HF, or urgent HF visit	Co-primary: • average of 6-week and 12-week mean NT-proBNP level • proportion of patients with meaningful change in health status (> 5-point increase in average

		DAPA-HF	DEFINE-HF
			of KCCQ overall score or ≥ 20% decrease in average NT-proBNP level)
	Secondary and exploratory end points	Secondary: • time to first occurrence of CV death or HF hospitalization • total number of HF hospitalizations and CV death • change from baseline at 8 months in KCCQ total symptom score • time to first occurrence of renal-related composite outcomes • time to death Exploratory: • change in NYHA class • new onset AF or type 2 diabetes • time to MI or stroke • change from baseline in EQ-5D-5L • change in hemoglobin A1C and other lab values • SAE and other notable harms	Secondary: • proportion with ≥ 5-point increase in KCCQ • proportion with ≥ 20% decrease in NT-proBNP levels • change in KCCQ score over 12 weeks • change in 6MWD over 12 weeks • change in BNP levels, weight, systolic BP, and hemoglobin A1C over 12 weeks Exploratory: • hospitalization for HF or urgent HF visit • change in NYHA class over 12 weeks • change in diuretic dose or fluid status • harms
NOTES	**Publications**	McMurray et al. (2019a)[13] Supplementary reports[14-18]	Nassif et al. (2019)[19]

6MWD = 6-minute walk distance; ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; BP = blood pressure; CABG = coronary artery bypass graft; CRT = cardiac resynchronization therapy; CV = cardiovascular; DB = double-blind; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2.

Note: One additional report was included (Common Drug Review submission[10]).

Source: Clinical Study Report for DAPA-HF;[7] Nassif et al. (2019).[19]

Description of Studies

One pivotal trial (DAPA-HF) and 1 non-pivotal trial (DEFINE-HF) met the inclusion criteria for the systematic review and have been summarized in this report (Table 6). The objective of the DAPA-HF study was to determine the superiority of dapagliflozin versus placebo in reducing the time to first occurrence of CV death, hospitalization for HF, or urgent HF visit. This double-blind, parallel design RCT enrolled 4,744 adults with documented diagnosis of symptomatic HF (NYHA function classes II to IV) and LVEF less than or equal to 40%. Patients were randomized 1:1 to dapagliflozin 10 mg daily or placebo, as add-on therapy to standard HF medications, via an interactive voice or web response system. The computer-generated block randomization was stratified according to type 2 diabetes status, defined as either a diagnosis of type 2 diabetes or hemoglobin A1C greater than or equal to 6.5% at enrolment. The event-driven trial was to stop once 844 adjudicated primary end points had occurred. The study enrolled patients from North America, Europe, Asia, and South America, including 26 Canadian study sites (233 Canadians).

The aim of the DEFINE-HF study was to evaluate the effect of dapagliflozin on natriuretic peptides and health status in optimally treated patients with HFrEF, with and without type 2 diabetes. This study was a randomized, double-blind, parallel design, placebo-controlled

trial that enrolled patients with an established diagnosis of HF with LVEF less than or equal to 40% and in NYHA class II or III (N = 263). Patients were randomized to dapagliflozin 10 mg daily or placebo as an add-on to standard of care HF therapy. The 12-week multi-centre trial was conducted at 26 sites in the US.

Populations

Inclusion and Exclusion Criteria

Both trials enrolled adults 18 years or older with a documented diagnosis of HFrEF (LVEF ≤ 40%; NYHA classes II to IV) who met protocol-defined criteria for natriuretic peptide levels and renal function (see Table 6). Patients with decompensated HF were excluded, as were those with recent myocardial infarction, unstable angina, or stroke or who had undergone CV procedures in the past 3 months. The trials excluded patients with type 1 diabetes and those who had recently received SGLT2 inhibitors. The DAPA-HF trial also excluded patients with prior cardiac transplant, symptomatic bradycardia, and second- or third-degree heart block without a pacemaker.

Baseline Characteristics

DAPA-HF Study

In the DAPA-HF study, the baseline characteristics of patients appeared balanced between treatment groups. The mean age of patients enrolled was 66.3 years (SD = 10.9), and the majority were male (77%), with HF due to ischemic causes (56%) (Table 7). Overall, 70% of patients were White, 24% were Asian, and 5% were Black. Patients had NYHA class II symptoms (68%), or class III (32%), with approximately 1% rated as class IV at baseline. The mean eGFR was 65.8 mL/min/1.73m^2 (SD = 19.4); 24% had atrial fibrillation or atrial flutter, and 45% were classified as having type 2 diabetes at baseline. Almost half the patients had had a prior hospitalization for HF (48%).

Most patients (94%) in the DAPA-HF study were receiving an ACEI, ARB, or neprilysin inhibitor–ARB at baseline, with 90% receiving a renin angiotensin inhibitor plus beta-blocker and 65% receiving a renin angiotensin inhibitor plus beta-blocker and mineralocorticoid receptor antagonist (Table 8). In the DAPA-HF trial, 38% (n = 1,517) of patients who were taking an ACEI or ARB, and 52% (n = 2,349) who were taking a beta-blocker, received greater than or equal to 50% of the guideline-recommended doses.[18] Overall, 93% of patients were treated with diuretics, 16% with vasodilators, 19% with digoxin, and 5% with ivabradine. With regard to device therapy, 20% of patients had an implantable cardioverter-defibrillator, 8% had a cardiac resynchronization therapy pacemaker or defibrillator, and 7% had a conventional pacemaker.

DEFINE-HF Study

In the DEFINE-HF study, the baseline mean age per treatment group was 62.2 years (SD = 11.0) and 60.4 years (SD = 12.0) in the dapagliflozin and placebo groups, respectively. Overall, 74% of patients were male, 55% were White, and 38% were Black, with NYHA class II (66%) or class III (34%) HF. The mean LVEF was 27.2% (SD = 8.0) and 25.7% (SD = 8.2), and 77% and 82% had a prior hospitalization for HF in the dapagliflozin and placebo groups, respectively. The median NT-proBNP levels were 1,136 pg/mL in both groups, and 63% had type 2 diabetes at baseline. The majority of patients (53%) had a history of ischemic heart disease, and 40% had atrial fibrillation or flutter at baseline. No major differences were noted between groups in the baseline characteristics of patients enrolled.

At baseline, patients were treated with the following drugs and devices in the dapagliflozin and placebo groups, respectively: ACEI or ARB (58% and 61%), neprilysin inhibitor–ARB (36% and 29%), beta-blocker (99% and 94%), mineralocorticoid receptor antagonist (58% and 64%), loop diuretics (87% and 84%), and internal cardiac defibrillator (67% and 57%).

Table 7: Summary of Baseline Characteristics: DAPA-HF Study

	DAPA-HF (FAS)	
	Dapagliflozin N = 2,373	Placebo N = 2,371
Mean age, years (SD)	66.2 (11.0)	66.5 (10.8)
Age > 75 years, n (%)	516 (22)	487 (21)
Male, n (%)	1,809 (76)	1,826 (77)
Median BMI, kg/m^2 (range)	27.0 (14 to 77)	27.0 (14 to 60)
Race, n (%)		
White	1,662 (70)	1,671 (71)
Black	122 (5)	104 (4)
Asian	552 (23)	564 (24)
Other	37 (2)	32 (1)
NYHA class, n (%)		
II	1,606 (68)	1,597 (67)
III	747 (32)	751 (32)
IV	20 (1)	23 (1)
Mean LVEF, % (SD)	31.2 (6.7)	30.9 (6.9)
Main etiology of HF, n (%)		
Ischemic	1,316 (56)	1,358 (57)
Non-ischemic	857 (36)	830 (35)
Unknown	200 (8)	183 (8)
AF or atrial flutter at enrolment, n (%)	569 (24)	559 (24)
Time from HF diagnosis to enrolment, n (%)		
≤ 1 year	531 (22)	567 (24)
> 1 to 2 years	320 (14)	366 (15)
> 2 to 5 years	578 (24)	527 (22)
> 5 years	944 (40)	911 (38)
Prior HF hospitalization, n (%)	1,124 (47)	1,127 (48)
Median NT-proBNP, pg/mL (IQR)	1,428 (857 to 2,655)	1,446 (857 to 2,641)
Mean eGFR, mL/min/1.73 m^2 (SD)	66.0 (19.6)	65.5 (19.3)
Mean systolic blood pressure, mm Hg (SD)	122.0 (16.3)	121.6 (16.3)
Classified as type 2 diabetes at baseline, n (%)	1,075 (45)	1,064 (45)
History of type 2 diabetes, n (%)	993 (42)	990 (42)
Hemoglobin A1C ≥ 6.5% at baseline, n (%)	82 (3)	74 (3)

AF = atrial fibrillation; BMI = body mass index; eGFR = estimated glomerular filtration rate; FAS = full analysis set; HF = heart failure; IQR = interquartile range; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation.

Source: Clinical Study Report for DAPA-HF.[7]

Table 8: Summary of Heart Failure Treatments at Baseline: DAPA-HF Study

	DAPA-HF (FAS)	
	Dapagliflozin N = 2,373	Placebo N = 2,371
Drug therapy at baseline, n (%)		
ACEI or ARB or neprilysin inhibitor–ARB	2,235 (94)	2,207 (93)
ACEI or ARB or neprilysin inhibitor–ARB plus beta-blocker	2,151 (91)	2,125 (90)
ACEI or ARB or neprilysin inhibitor–ARB plus beta-blocker and mineralocorticoid receptor antagonist	1,558 (66)	1,533 (65)
ACEI	1,332 (56)	1,329 (56)
ARB	675 (28)	632 (27)
ACEI or ARB	1,999 (84)	1,953 (82)
Neprilysin inhibitor–ARB	250 (11)	258 (11)
Beta-blocker	2,278 (96)	2,280 (96)
Mineralocorticoid receptor antagonist	1,696 (72)	1,674 (71)
Ivabradine	119 (5)	109 (5)
Diuretics	2,216 (93)	2,217 (94)
Loop diuretics	1,907 (80)	1,918 (81)
Digitalis glycosides	445 (19)	442 (19)
Vasodilators	404 (17)	362 (15)
Device therapy at baseline, n (%)		
Pacemaker (conventional)	158 (7)	151 (6)
CRT-D or CRT-P	190 (8)	164 (7)
Implantable cardioverter-defibrillator	467 (20)	486 (21)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; FAS = full analysis set.

Source: Clinical Study Report for DAPA-HF.[7]

Interventions

In the DAPA-HF study, patients were randomized to dapagliflozin or matching placebo tablets, which were identical in size, colour, smell, and taste. The dosage of dapagliflozin was 10 mg daily, unless the patient was experiencing hypotension, volume depletion, or worsening of kidney function that could not be managed by altering other medications, in which case the dapagliflozin dosage could be reduced to 5 mg daily.

All patients were required to receive standard of care therapies for HF, including either an ACEI, an ARB, or sacubitril-valsartan in combination with a beta-blocker, and, if appropriate, a mineralocorticoid receptor antagonist at baseline and during the study period. Doses of medications were to follow regional guidelines unless drugs were contraindicated or not tolerated, with therapy optimized and stable for at least 4 weeks prior to enrolment. Wherever possible, doses were to remain stable during the study period. In addition, patients may have been receiving diuretics with doses titrated to achieve optimal volume status for each patient. Table 9 includes a summary of the HF drugs patients had received at 8 months in the DAPA-HF study. The proportion of patients receiving these drugs were similar in the dapagliflozin and placebo groups and were generally consistent across various time points during the study.

For patients with diabetes, management was to follow the American Diabetes Association and European Association for the Study of Diabetes Joint Position Statement guidelines. Prohibited medications included SGLT2 inhibitors.

In the DEFINE-HF study, patients were randomized to dapagliflozin 10 mg daily or matching placebo, as an add-on therapy to guideline-directed standard of care treatments for HF. In patients with type 2 diabetes and baseline glycated hemoglobin levels less than or equal to 7%, a dose reduction of 20% was suggested for insulin or insulin secretagogues to minimize the risk of hypoglycemia.

Table 9: Summary of Heart Failure Treatments During DAPA-HF Study

	DAPA-HF (FAS)	
	Dapagliflozin N = 2,373	Placebo N = 2,371
Drug therapy at 8 months, n (%)	**N = 2,265**	**N = 2,252**
ACEI	1,257 (56)	1,245 (55)
ARB	678 (30)	647 (29)
Neprilysin inhibitor–ARB	361 (16)	408 (18)
Beta-blocker	2,183 (96)	2,165 (96)
Mineralocorticoid receptor antagonist	1,662 (73)	1,670 (74)
Diuretic	2,123 (94)	2,139 (95)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; FAS = full analysis set.

Source: Clinical Study Report for DAPA-HF.[7]

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 11 and Table 13.

A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

DAPA-HF Study

The primary outcome in the DAPA-HF study was the time to first occurrence of CV death, hospitalization for HF, or urgent HF visit. All potential events for the primary and secondary outcomes were adjudicated by an independent blinded clinical event committee based on event definitions and procedures that were defined a priori in the clinical event adjudication charter. The criteria for HF hospitalization or urgent HF visit are summarized in Table 10. Potential events were identified by questioning the patients, through standard medical practice, and from laboratory data. Events forwarded for adjudication included all deaths, any HF-related events, potential renal events (dialysis, kidney transplant, doubling of serum creatinine), cardiac ischemic events (myocardial infarction or unstable angina), cerebrovascular events (stroke or transient ischemic attack), and diabetic ketoacidosis (a safety outcome). Other events, including decline in eGFR or new diagnosis of atrial fibrillation or type 2 diabetes were recorded but not adjudicated.

Table 10: Criteria for HF Hospitalization or Urgent HF Visit: DAPA-HF Study

HF hospitalization	Urgent HF visit
1. Admitted to hospital for at least 24 hours with a primary diagnosis of HF	1. Urgent unscheduled office or emergency department visit for a primary diagnosis of HF but not meeting the criteria for hospitalization
2. Patient exhibits new or worsening symptoms of HF, including dyspnea, decreased exercise tolerance, or fatigue	2. All signs or symptoms for HF hospitalization items 2 and 3 must be met
3. Patient has objective evidence of new or worsening HF that include 2 of the following physical exam findings, or 1 physical exam finding and 1 lab finding: • Physical: peripheral edema; increased abdominal distention or ascites; pulmonary rales, crackles, or crepitations; increased jugular venous pressure or hepatojugular reflux; S_3 gallop; clinically significant or rapid weight gain related to fluid retention • Lab: Increase in BNP > 500 pg/mL or NT-proBNP levels > 2,000 pg/mL or a significant increase above baseline; radiological evidence of pulmonary congestion; invasive or non-invasive diagnostic evidence showing elevated left- or right-sided ventricular filling pressure or low cardiac output	
4. Patient receives initiation or intensification of treatment for HF including 1 of the following: • augmentation in oral diuretic • IV diuretic or vasoactive agent • mechanical or surgical intervention (i.e., circulatory support or mechanical fluid removal)	3. Patient receives initiation or intensification of treatment for HF including: • IV diuretic or vasoactive agent • mechanical or surgical intervention (i.e., circulatory support or mechanical fluid removal)

BNP = B-type natriuretic peptide; HF = heart failure; NT-proBNP = N-terminal pro B-type natriuretic peptide.

Source: Clinical Study Report for DAPA-HF.[7]

Table 11 lists the secondary and exploratory outcomes for the DAPA-HF study that were identified as outcomes of interest in the CADTH systematic review protocol.

Table 11: Efficacy Outcomes of Interest Identified in the CADTH Review Protocol: DAPA-HF Study

Outcome measure	DAPA-HF
Time to first occurrence of CV death, hospitalization for HF, or urgent HF visit	Primary
Time to first occurrence of CV death or hospitalization for HF	Secondary
Total number of (first or recurrent) HF hospitalizations or CV death	Secondary
Change from baseline to 8 months in the total symptom score of the KCCQ	Secondary
Time to first occurrence of: 1. ≥ 50% sustained decline in eGFR[a] 2. End-stage renal disease (i.e., sustained eGFR[a] <15 mL/min/1.73m^2, chronic dialysis treatment,[b] or renal transplant) 3. Renal death	Secondary
Time to death from any cause[c]	Secondary
Time to first occurrence of CV death, hospitalization for HF, urgent HF visit, or documented worsening of HF signs or symptoms leading to initiation of a new treatment for HF sustained for at least 4 weeks or augmentation of existing oral therapy for HF (e.g., increase in dose of diuretic) sustained for at least 4 weeks	Exploratory
Change from baseline in NYHA class	Exploratory

Outcome measure	DAPA-HF
Proportion of patients without history of AF at baseline with a new diagnosis of AF during the study	Exploratory
Time to first fatal or non-fatal myocardial infarction	Exploratory
Time to first fatal or non-fatal stroke	Exploratory
Proportion of patients with clinically meaningful improvement or deterioration in HF-related symptoms based on ≥ 5-point, 10-point, or 15-point increase, or ≥ 5-point or 10-point decrease, in KCCQ total symptom scores from baseline to 8 months	Exploratory
Change from baseline in EQ-5D-5L	Exploratory
Change from baseline in KCCQ overall summary score and clinical summary score	Other

AF = atrial fibrillation; CV = cardiovascular; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.

[a] Estimates of eGFR were based on 2 consecutive central laboratory creatinine levels at least 28 days apart and were calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. Estimated glomerular filtration rate event definitions were pre-specified in the clinical event charter but were not adjudicated by the committee.

[b] Chronic dialysis is defined as treatment ongoing for at least 28 days or when end-stage renal disease is deemed irreversible and the dialysis treatment was stopped before day 28.

[c] Includes deaths that occurred after the withdrawal of consent, where vital status was available from public sources. These events were not adjudicated.

Source: Clinical Study Report for DAPA-HF.[7]

The KCCQ is a 23-item, patient-reported health status instrument that includes domains for HF-related symptoms, physical limitations, social limitations, symptom stability, self-efficacy, and health-related quality of life. The symptom domain assesses the symptom burden and frequency of fatigue, shortness of breath, paroxysmal nocturnal dyspnea, and edema or swelling, each measured on a Likert scale. Symptom burden and frequency are combined into the total symptom score. The instrument also includes an overall summary score, which includes total symptom, physical function, social limitations, and quality of life scores, and a clinical summary score, which includes the total symptom and physical function domains. The domain and composite scores are transformed to a range of 0 to 100, with higher scores representing better outcomes. There is evidence to support the validity, reliability, and responsiveness of the KCCQ (see Appendix 4). A MID of 4.7 to 5.0 points has been reported for the total symptom score.[20,21] Responder analyses were conducted based on a greater than or equal to 5-point increase or decrease in the KCCQ total symptom score from baseline to 8 months. The sponsor stated that a 5-point change may be considered the lower limit for clinically meaningful change and conducted planned blinded anchor-based analyses of the DAPA-HF data to identify thresholds with more clinical relevance. This analysis was anchored on the patient global impression of severity, and a greater than or equal to 15-point increase was considered a moderate or large improvement, while a decrease of greater than or equal to 10 points was considered a large deterioration. In the responder analyses, patients who died were imputed as not improved or as deteriorated. Those with a baseline score near the top or the bottom of the scale, so that it was not possible to show the threshold of change (e.g., a 5-point improvement or deterioration), were analyzed as improved (if they maintained the high score) or deteriorated (if they maintained the low score). The change from baseline in the KCCQ total symptom score was added to the statistical analysis plan (in place of the KCCQ-cs) in a protocol amendment dated October 2017, after the start of patient recruitment.

Health-related quality of life was measured using the EQ-5D-5L instrument. The EQ-5D-5L descriptive system includes 5 dimensions — mobility, self-care, usual activities, pain or discomfort, and anxiety or depression — that are each rated on 5 levels of perceived problems (level 1: no problems; 2: slight problems; 3: moderate problems; 4: severe problems; 5: extreme problems) measured on that day. The value set for the EQ-5D-5L

from the UK was used to convert the descriptive system to the health status index score (range: –0.594 to 1), which was anchored at 0 (health state value equal to dead) and 1 (full health). A Canadian-specific MID of 0.037 has been reported.[22,23] No MID was identified in patients with HF.

The EQ-5D instrument also includes a 20 cm visual analogue scale (EuroQol Visual Analogue Scale [EQ VAS]) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ VAS that best represents their health on that day.

The NYHA functional classification is described in Table 12.

Table 12: New York Heart Association Functional Classification

Class	Patient symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, or dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Source: Clinical Study Report for DAPA-HF.[7]

In the DAPA-HF study, comprehensive data were not collected on all adverse events. Instead, safety data were collected for serious adverse events, adverse events that led to drug discontinuation, and adverse events of special interest. The adverse events of special interest included volume depletion, renal adverse effects, fractures, major hypoglycemic events, diabetic ketoacidosis, and adverse events leading to amputation or a risk of lower limb amputation. All potential episodes of diabetic ketoacidosis were adjudicated. Events suggestive of volume depletion, renal adverse effects (i.e., acute renal failure), and fractures were based on a predefined list of *Medical Dictionary for Regulatory Activities* preferred terms. Major hypoglycemic events were confirmed by the investigator and included any events where the patient experienced symptoms of severe impairment in consciousness or behaviour; the patient needed external assistance; intervention was needed to treat the hypoglycemia; and there was prompt recovery of acute symptoms following the intervention. Documented plasma glucose levels were not required.

The primary reporting of adverse event data was based on the on-treatment period, which included all events with an onset on or after the first dose of the study drug up until 30 days after the last dose of the study drug. Data on fractures and amputations were reported based on the "on and off" treatment period, which included all events on or after the first dose of the study drug until the end of follow-up.

DEFINE-HF Study

For the DEFINE-HF study, the co-primary biomarker and the health status outcomes were not outcomes of interest according to the CADTH review protocol.

Table 13 lists the secondary or exploratory outcomes that were consistent with the CADTH protocol. A blinded clinical event committee adjudicated all deaths, hospitalizations for HF, urgent HF visits, and myocardial infarction or stroke events. KCCQ and 6-minute walk distance (6MWD) outcomes were assessed at study site visits on weeks 6 and 12.

The 6MWD is a supervised test in which the patient walks on level ground covering the greatest distance possible in 6 minutes. Studies have shown it has consistently good test-retest reliability, as determined by the intraclass correlation coefficient (ICC) (ICC > 0.75 is considered adequate;[24] and ICC > 0.9 is considered excellent[25]).[26-29] The literature has reported an MID of 30 to 37 m for patients with HF.[27,28]

Table 13: Efficacy Outcomes of Interest Identified in the CADTH Review Protocol: DEFINE-HF Study

Outcome measure	DEFINE-HF
Proportion with ≥ 5-point increase in KCCQ overall score	Secondary
Change in KCCQ overall score over 12 weeks	Secondary
Change in 6MWD over 12 weeks	Secondary
Time to first hospitalization for HF or urgent HF visit	Exploratory
Change in NYHA class over 12 weeks	Exploratory
All-cause death, CV death, non-fatal myocardial infarction, stroke	Safety variable

6MWD = 6-minute walk distance; CV = cardiovascular; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.

Source: Nassif et al. (2019).[19]

Statistical Analysis

DAPA-HF Study

The primary composite outcome of time to first occurrence of CV death, HF hospitalization, or urgent HF visit was analyzed using a Cox proportional hazards model that included treatment group and history of HF hospitalization as factors and was stratified by type 2 diabetes status at randomization. Only adjudicated events were included in the analysis, counting events up until the primary analysis censoring date, regardless of whether the patient had discontinued the study drug prematurely. Any deaths where the cause could not be determined by the adjudication committee were included as CV deaths in the primary efficacy analysis. Patients without an event were censored at the earliest date of withdrawal of consent or non-CV death (if applicable), and otherwise at the earliest of the last clinical assessment or study end date. Each component of the composite outcome was also analyzed separately, using the same methods, but was not formally tested for significance. For patients who withdrew consent, an attempt was made to determine their vital status using public sources; however, data for other events (such as hospitalization) may be incomplete.

With 844 primary events, the DAPA-HF study had 90% power for the primary outcome, assuming a true HR of 0.80 between dapagliflozin and placebo and a 1-sided alpha of 0.025. The HR of 0.8 was based on the HF outcomes in the EMPA-REG study (Fitchett et al. 2016).[30] The sponsor estimated that 4,500 patients needed to be enrolled to achieve the required number of events, assuming the placebo event rate was 11%, an 18-month recruitment period, and an average follow-up period of 24 months. The placebo event rate was based on a review of the literature, including the PARADIGM-HF study (McMurray

2014).[31] The Clinical Study Report states that since losses to follow-up were predicted to be low, attrition was not taken into consideration in the power calculations.

There was 1 planned interim analysis for the primary composite outcome, which was conducted when 75% of the events had occurred. The study used the Haybittle-Peto boundary function (a 1-sided alpha of 0.001) to control the type I error, leaving a 1-sided alpha of 2.496% for the final primary outcome analysis. Following the interim analysis, the study was recommended to continue as planned.

Two sensitivity analyses were conducted for the primary outcome. In 1 analysis, patients who died from an unknown cause were censored. A tipping point analysis was planned to test the sensitivity of the results to missing data. The sponsor stated that due to the low frequency of missing data and the size of the observed treatment effect, the planned analysis was changed post hoc to a worst-case analysis. Any patients with missing data in the dapagliflozin group were analyzed as having the primary event.

Of the subgroups listed in the CADTH review protocol, the following subgroup analyses were pre-specified in the DAPA-HF study: type 2 diabetes at baseline, LVEF at enrolment, NYHA class at enrolment, baseline eGFR (< 60 or ≥ 60 mL/min/1.73m^2), atrial fibrillation or flutter at enrolment, or use of a mineralocorticoid receptor antagonist at baseline. Time-to-event outcomes were analyzed using Cox proportional hazards models as per the primary outcome analysis, with the addition of treatment by subgroup interaction terms. The analyses were not adjusted for multiple comparisons, and the sponsor specified that they were to be interpreted descriptively. Additional post hoc subgroup analyses were also conducted according to background HF therapy.[18]

The study used a hierarchical test sequence to control the type I error rate for the secondary outcomes, which were analyzed in the order shown in Table 14. Testing was to continue sequentially through the hierarchy only if the null hypothesis of the preceding end point was rejected at a 1-sided significance level of 0.02496. No multiplicity adjustment was applied to the 95% CI for all outcomes, and the sponsor stated the CIs were to be interpreted descriptively.

Secondary and exploratory time-to-event outcomes were analyzed using similar Cox proportional hazards models as the primary outcome, and binomial outcomes were analyzed using logistic regression. The study did not report any testing of the proportional hazards assumption for the time-to-event outcomes. The total number of HF hospitalizations or CV deaths was analyzed using a semi-parametric proportional rates model. The change from baseline to 8 months in the KCCQ total symptom score was analyzed using a rank ANCOVA model to account for non-normal distribution of scores and for early deaths. Scores were assigned ranks, with any patient who died prior to 8 months assigned the worst ranks within each stratum. Missing KCCQ data were imputed using multiple imputation methods, assuming data were missing at random. The proportion of patients who met response criteria for the KCCQ total symptom score were analyzed using a logistic regression model stratified by type 2 diabetes status and including the symptom score at baseline. In the responder analyses, patients who died were imputed as nonresponders: there was no imputation for patients with missing data for reasons other than death. The change from baseline in EQ-5D-5L was analyzed using a repeated measures model, with treatment group, visit, treatment by visit interaction term, and baseline measurement as covariates, with no imputation for missing data. All other secondary or exploratory analyses were stratified by patients' type 2 diabetes at baseline,

with additional covariates for prior hospitalization for HF or baseline values included for some end points (see Table 14 for details).

Table 14: Statistical Analysis of Efficacy End Points: DAPA-HF Study

End point	Statistical model	Adjustment factors	Sensitivity analyses
Primary			
Time to first occurrence of CV death, hospitalization for HF, or urgent HF visit	Cox proportional hazards model (score test)	• Stratified by type 2 diabetes status at randomization • Prior HF hospitalization	• Patients with undetermined cause of death were censored • Post hoc worst-case analysis: censored patients in the dapagliflozin group were assumed to have an event
Secondary			
Time to first occurrence of CV death or hospitalization for HF	Cox proportional hazards model (score test)	• Stratified by type 2 diabetes status at randomization • Prior HF hospitalization	
Total number of HF hospitalizations or CV death	Semi-parametric proportional rates model (Lin-Wei-Yang-Yang method)	• Stratified by type 2 diabetes status at randomization • Prior HF hospitalization	
Change from baseline to 8 months in KCCQ total symptom score	Rank ANCOVA method Transformed to a composite end point with fractional ranks using the mean method of ties Deaths prior to 8 months assigned worst ranks within each stratum Multiple imputation methods for missing data, assuming missing at random	• Stratified by type 2 diabetes status at randomization • Adjusted for ranked baseline total score	• Cochran-Mantel-Haenszel test stratified by type 2 diabetes status • Win ratio test
Time to first occurrence of renal composite outcomes (≥ 50% sustained decline in eGFR, ESRD, renal death)	Cox proportional hazards model (score test)	• Stratified by type 2 diabetes status at randomization • Baseline eGFR	
Time to death from any cause	Cox proportional hazards model (score test)	• Stratified by type 2 diabetes status at randomization	
Exploratory			
Time to first occurrence of CV death, hospitalization for HF, urgent HF visit, or worsening of HF	Cox proportional hazards model (score test)	• Stratified by type 2 diabetes status at randomization • Prior HF hospitalization	
KCCQ total symptom score responder analysis (i.e., proportion of patients with ≥ 5-, 10-, or 15- point	Logistic regression model	• Type 2 diabetes status at randomization • Baseline total symptom score	

End point	Statistical model	Adjustment factors	Sensitivity analyses
increase and proportion with ≥ 5- or 10-point decrease from baseline to 8 months)[a]			
Proportion of patients with no worsening in NYHA class	Logistic regression model	• Type 2 diabetes status at randomization • Baseline NYHA class	
Proportion of patients with new onset AF	Logistic regression model	• Stratified by type 2 diabetes status at baseline	
Time to first fatal or non-fatal myocardial infarction or stroke	Cox proportional hazards model (score test)	• Stratified by type 2 diabetes status at baseline	
Change from baseline in EQ-5D-5L	Repeated measures methods[b]	• Treatment group, visit, treatment-visit interaction term, baseline measurement	

AF = atrial fibrillation; ANCOVA = analysis of covariance; CV = cardiovascular; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; ESRD = end-stage renal disease; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.

[a] Patients with values near the ceiling or floor at baseline (e.g., ≥ 95 or ≤ 5 points) were defined as having a 5-point improvement if their total score remained greater than or equal to 95 points at 8 months or were defined as having a 5-point deterioration if their score remained less than or equal to 5 points at 8 months. Patients who died prior to 8 months were imputed as a nonresponders; there was no other imputation for missing data.

[b] No imputation for missing data.

Source: Clinical Study Report for DAPA-HF.[7]

DEFINE-HF Study

Binary outcomes were analyzed using a logistic regression model, and continuous outcomes were analyzed using a generalized linear mixed model. Time-to-event outcomes were analyzed using a Cox proportional hazards model. Models were adjusted for the baseline outcome values (for binary and continuous outcomes), history of type 2 diabetes, baseline eGFR, and age (all outcomes). There was no control of the type I error rate for secondary and exploratory outcomes.

The DEFINE-HF study had 80% power, with alpha 0.05 for the co-primary biomarker and health status outcomes if 125 patients were enrolled per treatment group (assuming a 13% withdrawal rate). The study was not powered for secondary or exploratory outcomes of interest to this review.

Analysis Populations

The efficacy analyses of the DAPA-HF study were based on the full analysis set, which included all patients randomized to treatment, according to the treatment they were assigned to receive. Safety analyses were based on the safety set, which included all randomized patients who received at least 1 dose of the study drug and were analyzed according to the treatment actually received.

In the DEFINE-HF study, efficacy analyses were based on the modified intention-to-treat population, which included all randomized patients who received at least 1 dose of the study drug and who had at least 1 evaluable post-baseline measurement for each analysis. The safety population included all randomized patients who received at least 1 dose of the study drug.

Results

Patient Disposition

In the DAPA-HF study, 8,134 patients were screened, of which 4,744 (58%) were randomized. The most common reason patients were not randomized was that they did not meet the NT-proBNP inclusion criteria (2,570 of 3,390 patients; 76%), followed by failure to meet LVEF criterion(N = 208, 6%). Few patients discontinued the study after randomization. Nine patients withdrew consent (5 in the dapagliflozin group and 4 in the placebo group), though these patients' vital status was known at the end of the study. Complete follow-up data for the primary outcome were available for 2,359 (99.4%) and 2,351 (99.2%) patients in the dapagliflozin and placebo groups, respectively. Vital status was known for all patients in the dapagliflozin group and unknown for 2 patients in the placebo group.

In the DEFINE-HF study, 510 patients were screened and 263 were randomized (52%). The reasons for screening failure were not reported. Of the 131 patients randomized to dapagliflozin, 1 patient discontinued the study early due to death and 11 patients (8%) discontinued the study drug prematurely. In the placebo group, 132 patients were randomized, 1 patient died, and 12 patients (9%) discontinued the study drug early. The reasons for stopping treatment were adverse events (3% and 5%), patient decision (2% and 4%), and study drug supply issue (4% and 1%) for the dapagliflozin and placebo groups, respectively.

Table 15: Patient Disposition

	DAPA-HF		DEFINE-HF	
	Dapagliflozin	Placebo	Dapagliflozin	Placebo
Screened, N	8,134		510	
Randomized, N (%)	4,744 (58)[a]		263 (52)	
	2,373	2,371	131	132
Discontinued study, n (%)	5 (0.2)	4 (0.2)	1 (0.8)	1 (0.8)
Reason for study discontinuation, N (%)				
Withdrew consent	5 (0.2)	4 (0.2)	NR	NR
Death	NA	NA	1 (0.8)	1 (0.8)
Discontinued study drug, N (%)	249 (10.5)[b]	258 (10.9)[b]	11 (8.4)	12 (9.1)
Study drug supply issue	NR	NR	5 (3.8)	1 (0.8)
Adverse event	NR	NR	4 (3.1)	6 (4.5)
Patient decision	NR	NR	2 (1.5)	5 (3.8)
FAS, N	2,373	2,371	NA	NA
mITT, N	NA	NA	131	132
Safety, N	2,368[c]	2,368[c]	131	132

FAS = full analysis set; mITT = modified intention to treat; NA = not applicable; NR = not reported.

[a] Of the 3,390 patients who were not randomized, 3,279 did not meet eligibility criteria and 111 were excluded for other reasons.

[b] Patients who discontinued the study drug prematurely were followed until the end of the study and were included in analyses unless they had withdrawn consent.

[c] The safety population excluded 5 patients in the dapagliflozin group and 3 patients in the placebo group who did not receive any doses of the study drug.

Source: Clinical Study Report for DAPA-HF;[7] Nassif et al. (2019).[19]

Exposure to Study Treatments

In the DAPA-HF study, the median follow-up duration was 18.2 months (range 0 to 27.8 months) for the overall study population. The median duration of exposure was similar in the dapagliflozin (17.8 months; interquartile range, 13.5 to 21.5 months) and placebo groups (17.6 months; interquartile range, 13.2 to 21.3 months) (Table 16). The cumulative percentage of patients who stopped study drug treatment prematurely is shown in Figure 2. Adherence to the study drug was similar in both treatment groups, with 81% and 80% of patients in the dapagliflozin and placebo groups, respectively, reporting adherence greater than 80% (based on pill counts), and 75% and 74% of patients, respectively, reporting adherence greater than 90%.

No treatment exposure data were reported for the DEFINE-HF study.

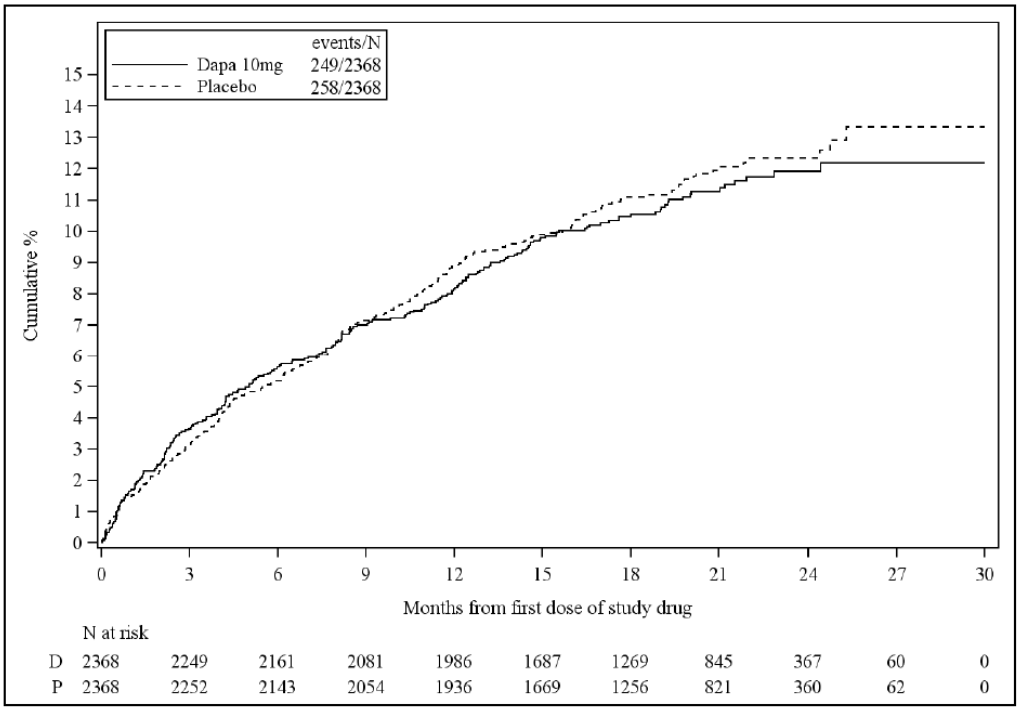
Table 16: Duration of Exposure

	DAPA-HF (safety set)	
	Dapagliflozin N = 2,368	Placebo N = 2,368
Median duration of exposure, months (IQR)	17.8 (13.5 to 21.5)	17.6 (13.2 to 21.3)
Cumulative exposure over time, n (%)		
≥ 1 month	2,316 (98)	2,317 (98)
≥ 6 month	2,152 (91)	2,137 (90)
≥ 12 month	1,955 (83)	1,905 (80)
≥ 18 month	1,168 (49)	1,133 (48)
≥ 24 month	261 (11)	255 (11)

IQR = interquartile range.

Source: Clinical Study Report for DAPA-HF.[7]

Figure 2: Kaplan-Meier Plot of Cumulative Percentage of Patients With Premature Permanent Discontinuation of Study Drug (Safety Set)



D or dapa = dapagliflozin; P = placebo.

Source: Clinical Study Report for DAPA-HF.[7]

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported below. See Appendix 3 for detailed efficacy data.

DAPA-HF Study

Mortality and Hospitalization

During the DAPA-HF study, 16.3% of patients in the dapagliflozin group and 21.2% of patients in the placebo group reported a primary outcome event of CV death, HF hospitalization, or urgent HF visit (Table 17). The event rates for the dapagliflozin and placebo groups, respectively, were 11.6 and 15.6 patients with events per 100 PYs of follow-up. The time to first occurrence of primary events was increased for patients in the dapagliflozin group versus those in the placebo group, with an HR of 0.74; 95% CI, 0.65 to 0.85; P < 0.0001. Figure 3 shows the Kaplan-Meier plot of the primary composite outcome and shows separation between the groups starting within 3 months.

Sensitivity analyses and subgroup data for the primary outcome are shown in Appendix 3, Table 31 and Table 32. Treatment effects were generally consistent across planned subgroups based on type 2 diabetes status at baseline, atrial fibrillation or flutter at baseline, baseline LVEF, eGFR, or use of mineralocorticoid receptor antagonist at baseline, as well as post hoc subgroup analyses based on background therapies at baseline

(Appendix 3, Figure 4). Of the planned subgroups of interest to this CADTH review, possible differences were noted for subgroups based on NYHA class (II versus III and IV) as the treatment by subgroup interaction term was statistically significant (P = 0.0087) (Appendix 3, Table 31). Both groups reported HR point estimates that favoured dapagliflozin over placebo for the composite outcome, but for the class III and IV subgroup, the 95% CI included the null (class II: HR 0.63; 95% CI, 0.52 to 0.75; class III and IV: HR 0.90; 95% CI, 0.74 to 1.09). In the NYHA III and IV subgroup, the HR for HF hospitalizations and urgent HF visits was 0.82 (95% CI, 0.64 to 1.05) and CV mortality was 1.09 (95% CI, 0.85 to 1.41). Whereas in the NYHA class II subgroup, the HR for HF hospitalizations and urgent visits was 0.61 (95% CI, 0.48 to 0.77) and CV mortality was 0.63 (95% CI, 0.49 to 0.81). Results for the patients with type 2 diabetes (HR 0.75; 95% CI, 0.63 to 0.90) and those without diabetes (HR 0.73; 95% CI, 0.60 to 0.88) were consistent (randomization was stratified by type 2 diabetes status at baseline). Both of the sensitivity analyses the sponsor conducted supported the primary analysis, including the conservative worst-case scenario analysis, which also reported results that favoured dapagliflozin over placebo (HR 0.85; 95% CI, 0.74 to 0.96; P = 0.010) (Appendix 3, Table 32).

For the secondary outcome of time to first occurrence of CV death or HF hospitalization, 16.1% of patients in the dapagliflozin group had an event (11.4 per 100 PYs) and 20.9% in the placebo group had an event (15.3 per 100 PYs). The HR for dapagliflozin versus placebo was 0.75 (95% CI, 0.65 to 0.85; P < 0.0001).

Each component of the primary composite outcome was analyzed separately (Table 17).

The most common events reported were CV deaths (dapagliflozin: 6.5 deaths per 100 PYs; placebo: 7.9 deaths per 100 PYs) and HF hospitalization (dapagliflozin: 6.9 persons with event per 100 PYs; placebo: 9.8 persons with event per 100 PYs). The event rate for urgent HF visits was 0.3 and 0.7 persons with events per 100 PYs in the dapagliflozin and placebo groups, respectively. The time to first event was increased for dapagliflozin versus placebo for each component; however, these outcomes were not formally tested for statistical significance.

The time to first occurrence of CV death, HF hospitalization, urgent HF visit, or worsening of HF (defined as signs or symptoms leading to new or augmented HF treatments) was an exploratory outcome with a reported HR of 0.73 (95% CI, 0.65 to 0.82; P < 0.0001; not controlled for type I error).

Table 17: Mortality and HF Hospitalization Outcomes: DAPA-HF Study

	DAPA-HF (FAS)					
	Dapagliflozin N = 2,373		Placebo N = 2,371		Treatment effects dapagliflozin versus placebo	
	n (%)	Event rate[a]	n (%)	Event rate[a]	HR (95% CI)	P value
Time to CV death, hospitalization for HF, or urgent HF visit	386 (16.3)	11.6	502 (21.2)	15.6	0.74 (0.65 to 0.85)[b]	< 0.0001
Time to CV death	227 (9.6)	6.5	273 (11.5)	7.9	0.82 (0.69 to 0.98)[b]	0.0294[c]
Time to hospitalization for HF or urgent HF visit	237 (10.0)	7.1	326 (13.7)	10.1	0.70 (0.59 to 0.83)[b]	< 0.0001[c]
Time to hospitalization for HF	231 (9.7)	6.9	318 (13.4)	9.8	0.70 (0.59 to 0.83)[b]	< 0.0001[c]

	DAPA-HF (FAS)					
	Dapagliflozin N = 2,373		Placebo N = 2,371		Treatment effects dapagliflozin versus placebo	
Time to urgent HF visit	10 (0.4)	0.3	23 (1.0)	0.7	0.43 (0.20 to 0.90)[b]	0.0213[c]
Time to CV death or hospitalization for HF	382 (16.1)	11.4	495 (20.9)	15.3	0.75 (0.65 to 0.85)[b]	< 0.0001
Time to death from any cause	276 (11.6)	7.9	329 (13.9)	9.5	0.83 (0.71 to 0.97)[d]	0.0217[e]
Time to CV death, hospitalization for HF, urgent HF visit, or worsening of HF[f]	527 (22.2)	16.5	684 (28.8)	22.6	0.73 (0.65 to 0.82)[b]	< 0.0001[g]

CI = confidence interval; CV = cardiovascular; FAS = full analysis set; HF = heart failure; HR = hazard ratio.

[a] Event rate reported as the number of patients with event per 100 person-years of follow-up.

[b] Cox proportional hazards model (score test) stratified by type 2 diabetes status at baseline, with factors for treatment group and history of HF hospitalization for the full analysis set population. Hazard ratio less than 1 favours dapagliflozin. The 95% CI was not adjusted for multiple comparisons.

[c] Individual components of the primary composite outcome were not formally tested for statistical significance.

[d] Cox proportional hazards model (score test) stratified by type 2 diabetes status at baseline with factors for treatment group for the FAS population. Hazard ratio less than 1 favours dapagliflozin. The 95% CI was not adjusted for multiple comparisons.

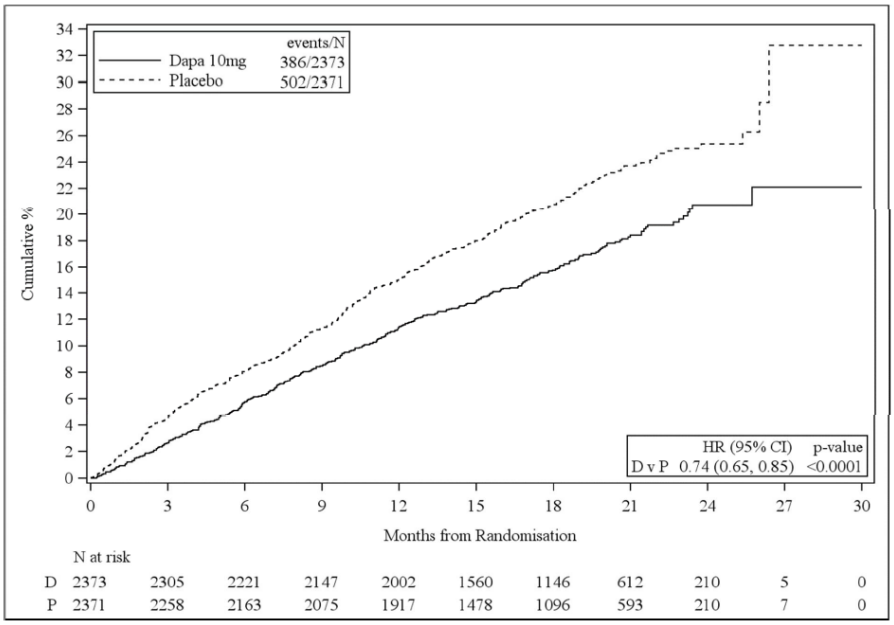
[e] Not tested for statistical significance due to failure of a prior outcome in the statistical testing hierarchy.

[f] Evidence of worsening HF included symptoms or signs leading to initiation of a new treatment or augmentation of existing treatments for HF sustained for at least 4 weeks.

[g] Exploratory outcome. P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Report for DAPA-HF.[7]

Figure 3: Kaplan-Meier Plot of Composite Outcome of CV Death, HF Hospitalization, or Urgent HF Visit



CI = confidence interval; CV = cardiovascular; D or dapa = dapagliflozin; HF = heart failure; HR = hazard ratio; P = placebo.

Source: Clinical Study Report for DAPA-HF.[7]

In the dapagliflozin group, 276 patients died (11.6%) from any cause, compared with 329 patients in the placebo group (13.9%), with an event rate of 7.9 deaths per 100 PYs versus 9.5 deaths per 100 PYs (Table 17).

The time-to-event analysis reported an HR of 0.83 (95% CI, 0.71 to 0.97), but due to failure of a prior outcome in the statistical hierarchy, statistical testing of this outcome was not conducted. Thus, no conclusions can be drawn for this outcome. The adjudicated cause of death is summarized in Table 18.

Table 18: Summary of Adjudicated Deaths: DAPA-HF Study

	DAPA-HF (FAS)	
	Dapagliflozin N = 2,373	Placebo N = 2,371
All deaths, n (%)	276 (11.6)	329 (13.9)
CV death, n (%)	173 (7.3)	207 (8.7)
Non-CV death, n (%)	48 (2.0)	54 (2.3)
Undetermined cause of death, n (%)	54 (2.3)	66 (2.8)
Death after withdrawal of consent (not adjudicated), n (%)	1 (0.0)	2 (0.1)

CV = cardiovascular; FAS = full analysis set.

Source: Clinical Study Report for DAPA-HF.[7]

Data for the total number of CV deaths or HF hospitalizations during the DAPA-HF study are summarized in Table 19. There were 567 CV deaths or HF hospitalizations in the dapagliflozin group, compared with 742 events in the placebo group, with an average of 16.3 events per 100 PYs versus 21.6 events per 100 PYs for the dapagliflozin and placebo groups, respectively. The rate ratio of 0.75 (95% CI, 0.65 to 0.88) favoured dapagliflozin over placebo (P = 0.0002), a key secondary outcome.

During the study, most patients did not have an HF-related hospitalization (dapagliflozin: 90.3%; placebo: 86.6%). In the dapagliflozin group, 158 patients (6.7%) had 1 HF hospitalization and 72 (3.0%) had 2 or more hospitalizations, compared with 222 patients (9.4%) and 96 patients (4.0%) in the placebo group who had 1 HF hospitalization or 2 or more hospitalizations, respectively. The rate ratio for HF hospitalizations favoured dapagliflozin over placebo (rate ratio 0.72; 95% CI, 0.59 to 0.86); however, this outcome was not part of the statistical testing hierarchy, and thus the type I error rate has not been controlled for this outcome.

Table 19: Total Number of CV Deaths or HF Hospitalizations: DAPA-HF Study

	DAPA-HF (FAS)					
	Dapagliflozin N = 2,373		Placebo N = 2,371		Treatment effects dapagliflozin versus placebo	
	Number of events	Event rate[a]	Number of events	Event rate[a]	Rate ratio (95% CI)[b]	P value
CV death or HF hospitalization	567	16.3	742	21.6	0.75 (0.65 to 0.88)	0.0002
Recurrent HF hospitalization	340	9.8	469	13.6	0.72 (0.59 to 0.86)	0.0005[c]

CI = confidence interval; CV = cardiovascular; FAS = full analysis set; HF = heart failure.

[a] Event rate reported as the average number of events per 100 person-years of follow-up.

[b] Rate ratio based on the Lin-Wei-Yang-Yang proportional rates model stratified by type 2 diabetes status at baseline, with factors for treatment group and history of HF hospitalization for FAS population. Rate ratio less than 1 favours dapagliflozin. The 95% CI was not adjusted for multiple comparisons.

[c] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Report for DAPA-HF.[7]

Renal Events

The time to first occurrence of greater than or equal to 50% sustained decline in eGFR, ESRD, or renal death was a secondary outcome in the DAPA-HF study (Table 20).

In the dapagliflozin group, 28 patients experienced a renal event, compared with 39 patients in the placebo group. The HR was 0.71 (95% CI, 0.44 to 1.16) for dapagliflozin versus placebo, which was not statistically significant (P = 0.17).

Table 20: Time to Composite Renal Function Worsening Outcome: DAPA-HF Study

	DAPA-HF (FAS)					
	Dapagliflozin N = 2,373		Placebo N = 2,371		Treatment effects dapagliflozin versus placebo	
	n (%)	Event rate[a]	n (%)	Event rate[a]	HR (95% CI)[b]	P value
Composite of ≥ 50% sustained decline in eGFR, ESRD, or renal death	28 (1.2)	0.8	39 (1.6)	1.2	0.71 (0.44 to 1.16)	0.17
≥ 50% sustained decline in eGFR	14 (0.6)	0.4	23 (1.0)	0.7	0.60 (0.31 to 1.16)	0.13[c]
ESRD	16 (0.7)	0.5	16 (0.7)	0.5	1.00 (0.50 to 1.99)	0.99[c]
Renal death	0	0	1 (< 0.1)	0	NE	

CI = confidence interval; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FAS = full analysis set; HR = hazard ratio; NE = not estimable.

[a] Event rate reported as the number of patients with event per 100 person-years of follow-up.

[b] Cox proportional hazards model (score test) stratified by type 2 diabetes status at baseline with factor for baseline eGFR for FAS population. Hazard ratio less than 1 favours dapagliflozin. The 95% CI was not adjusted for multiple comparisons.

[c] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Report for DAPA-HF.[7]

Cardiovascular Events

In the DAPA-HF study, the frequency of non-fatal or fatal myocardial infarctions and strokes was similar in the dapagliflozin and placebo groups, with an event rate of 1.2 to 1.3 persons with an event per 100 PYs (Table 21).

New Onset Atrial Fibrillation or Another Arrhythmia

Among patients with no atrial fibrillation or atrial flutter at baseline, [redacted] developed atrial fibrillation in the dapagliflozin group, compared with [redacted] of patients in the placebo group (Table 21). Results were similar for the subgroup without atrial fibrillation at baseline.

Table 21: Other Cardiovascular Outcomes: DAPA-HF Study

	DAPA-HF (FAS)					
	Dapagliflozin N = 2,373		Placebo N = 2,371		Treatment effects dapagliflozin versus placebo	
Myocardial infarction or stroke	**n (%)**	**Event rate[a]**	**n (%)**	**Event rate[a]**	**HR (95% CI)[b]**	**P value**
Time to fatal or non-fatal myocardial infarction[b]	46 (1.9)	1.3	41 (1.7)	1.2	1.11 (0.73 to 1.69)	0.63[c]
Time to fatal or non-fatal stroke[b]	42 (1.8)	1.2	46 (1.9)	1.3	0.90 (0.59 to 1.37)	0.63[c]
New diagnosis of AF	**N**	**n (%)**	**N**	**n (%)**	**OR (95% CI)[d]**	**P value**
Patients without AF at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients without AF or atrial flutter at baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AF = atrial fibrillation; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; OR = odds ratio.

[a] Event rate reported as the number of patients with event per 100 person-years of follow-up.

[b] Cox proportional hazards model (score test) stratified by type 2 diabetes status at baseline for FAS population. Hazard ratio less than 1 favours dapagliflozin.

[c] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[d] Logistic regression model with baseline type 2 diabetes as covariate for FAS population. Odds ratio less than 1 favours dapagliflozin.

Source: Clinical Study Report for DAPA-HF.[7]

Health-Related Quality of Life

The change from baseline in the EQ-5D-5L was an exploratory outcome in the DAPA-HF study. At 8 months, index score data were missing for [redacted] of patients, and at 12 months, [redacted] had missing data in the dapagliflozin and placebo groups, respectively. [redacted] between groups at 8 months or 12 months (Table 22).

Descriptive data for the EQ VAS are summarized in Appendix 3, Table 33, and show similar scores in both treatment groups at baseline, 8 months, and 12 months. No between-groups comparison was reported for the change from baseline in EQ VAS.

Table 22: Change From Baseline in EQ-5D-5L Index Score: DAPA-HF Study

EQ-5D-5L index score	DAPA-HF (FAS)	
	Dapagliflozin N = 2,373	Placebo N = 2,371
8 month[a]		
Patients included in the analysis, N (%)	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
8 months, mean (SD)	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]
LS mean difference versus placebo (95% CI)	[redacted]	Reference
P value	[redacted]	
12 month[a]		
Patients included in the analysis, N (%)	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]
12 months, mean (SD)	[redacted]	[redacted]
LS mean change from baseline (SE)	[redacted]	[redacted]
LS mean difference versus placebo (95% CI)	[redacted]	Reference
P value	[redacted]	

CI = confidence interval; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; FAS = full analysis set; LS = least squares; SD = standard deviation; SE = standard error.

[a] Repeated measures model with terms for treatment group, visit, treatment by visit interaction, and baseline measurement for the FAS population, with no imputation for missing data. Least squares mean difference greater than 1 favours dapagliflozin.

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Report for DAPA-HF.[7]

Symptoms of Heart Failure

Symptoms were measured using the KCCQ total symptom score, which incorporates symptom burden and frequency into a single score that is transformed to a range of 0 to 100 (higher scores represent better outcomes). For the analysis of the KCCQ total symptom score, 8-month data were missing from 16% and 17% of patients from the dapagliflozin and placebo groups, respectively, including 5.1% and 5.7% of patients with missing data due to death. The primary analysis based on ranked ANCOVA tests showed a statistically significant difference in the change in total symptom score favouring dapagliflozin ($P < 0.0001$). Mean scores at baseline, 8 months, and change from baseline were reported descriptively, but the mean difference between groups was not estimated (Table 23).

Table 23: Change From Baseline to 8 Months in KCCQ Total Symptom Score: DAPA-HF Study

KCCQ total symptom score	DAPA-HF (FAS)	
	Dapagliflozin N = 2,373	Placebo N = 2,371
Change from baseline to 8 months		
Number of patients included in the analysis, N (%)	1,998 (84)	1,957 (83)
Baseline, mean (SD)	73.2 (22.2)	74.1 (21.3)
8 months, mean (SD)	80.4 (19.7)	78.1 (20.7)
Change from baseline (SD)	6.1 (18.7)	3.3 (19.2)
Mean difference in change from baseline versus placebo (95% CI)	Not estimated	
Win ratio dapagliflozin versus placebo (95% CI)[a,b]	1.18 (1.11 to 1.26)	
P value[c]	< 0.0001	

CI = confidence interval; FAS = full analysis set; KCCQ = Kansas City Cardiomyopathy Questionnaire; SD = standard deviation.

[a] "The win ratio represents the odds of having a more favourable outcome versus a less favourable outcome when assigned to the dapagliflozin 10 mg treatment group as opposed to placebo. This was accomplished by creating all possible pairs of patients across arms and labelling patients on dapagliflozin 10 mg in each pair as 'winner', 'loser' or 'tied', based on their ranks. The crude win ratio is defined as the ratio of the number of "winner" pairs divided by the number of 'loser' pairs and an estimated win ratio greater than 1 favours dapagliflozin."[7]

[b] The 95% CI was not adjusted for multiple comparisons.

[c] P value based on rank analysis of covariance adjusted for baseline KCCQ score and stratified by type 2 diabetes status at baseline for the FAS population. Change from baseline converted to ranks, with patients who died assigned the worst ranks.

Source: Clinical Study Report for DAPA-HF.[7]

Responder analyses were also conducted for the change from baseline in KCCQ total symptom score, although these outcomes were not part of the statistical testing hierarchy (Table 24).

At 8 months, 57% of patients in the dapagliflozin group reported at least a 5-point increase in the KCCQ total symptom score, compared with 50% of patients in the placebo group (odds ratio [OR] 1.15; 95% CI, 1.08 to 1.23). Similar treatment effects were noted for analyses based on at least a 10-point increase and at least a 15-point increase in symptom scores.

At 8 months, 25% and 33% of patients in the dapagliflozin and placebo groups, respectively, reported at least a 5-point decrease in KCCQ total symptom scores, with an OR of 0.84 (95% CI, 0.78 to 0.90). Between-group differences were similar for the proportion of patients reporting at least a 10-point decrease in scores (Table 24).

Other KCCQ data reported included the change from baseline to 8 months in the KCCQ-os and KCCQ-cs (Appendix 3, Table 34). These data also favoured dapagliflozin over placebo; however, these outcomes were not part of the planned statistical analysis, according to the study's final protocol.

Table 24: Responder Analysis for KCCQ Total Symptom Score: DAPA-HF Study

KCCQ total symptom score	DAPA-HF (FAS)			
	Dapagliflozin N = 2,373	Placebo N = 2,371	OR (95% CI)[a]	P value
Responder analyses	**N = 2,086 (88%)**	**N = 2,062 (87%)**		
Patients with increase from baseline to 8 months, n (%)[b]				
≥ 5 points	1,198 (57)	1,030 (50)	1.15 (1.08 to 1.23)	< 0.0001[c]
≥ 10 points	1,124 (54)	968 (47)	1.15 (1.08 to 1.22)	< 0.0001[c]
≥ 15 points	1,120 (54)	984 (48)	1.14 (1.07 to 1.22)	< 0.0001[c]
Patients with decrease from baseline to 8 months, n (%)[d]				
≥ 5 points	524 (25)	682 (33)	0.84 (0.78 to 0.90)	< 0.0001[c]
≥ 10 points	385 (19)	495 (24)	0.85 (0.79 to 0.92)	< 0.0001[c]

CI = confidence interval; FAS = full analysis set; KCCQ = Kansas City Cardiomyopathy Questionnaire; OR = odds ratio.

[a] Logistic regression model with baseline KCCQ score as covariate and stratified by type 2 diabetes status at baseline for the FAS population.

[b] Analysis included patients who reported KCCQ total symptom score at 8 months or who had died before that time point. Patients who died prior to 8 months were counted as not improved.

[c] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[d] Patients who died prior to 8 months were counted as deteriorated.

Source: Clinical Study Report for DAPA-HF.[7]

Functional Status

In the first 8 months of the DAPA-HF study, [redacted] in their NYHA functional class. At 8 months, [redacted] of patients in the dapagliflozin group and [redacted] in the placebo group had [redacted] (exploratory outcome).

Table 25: Change From Baseline in NYHA Functional Class: DAPA-HF Study

	DAPA-HF (FAS)			
	Dapagliflozin N = 2,373	Placebo N = 2,371	Treatment effects dapagliflozin versus placebo	
No worsening in NYHA class	**n (%)**	**n (%)**	**OR (95% CI)[a]**	**P value[b]**
4 months	[redacted]	[redacted]	[redacted]	[redacted]
8 months	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; FAS = full analysis set; NYHA = New York Heart Association; OR = odds ratio.

[a] Logistic regression model with NYHA class and type 2 diabetes status at baseline as covariates for the FAS population. Odds ratio greater than 1 favours dapagliflozin.

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Report for DAPA-HF.[7]

DEFINE-HF Study

Efficacy results for the DEFINE-HF study are summarized in Appendix 3, Table 35. These outcomes were secondary or exploratory end points or part of the safety data collected. The P values reported have not been controlled for type I error. The study failed on its primary outcome, with no between-groups difference detected in the adjusted mean NT-proBNP levels.

During the 12-week DEFINE-HF study, 12 patients (9.1%) in the dapagliflozin group and 13 patients (9.8%) in the placebo group had an HF hospitalization or urgent HF visit (HR 0.84; 95% CI, 0.36 to 1.97; P = 0.68). One patient in the dapagliflozin and 1 patient in the placebo group (0.8%) died due to CV causes. No patients in the dapagliflozin group experienced a non-fatal myocardial infarction or stroke, whereas in the placebo group, 4 patients (3%) reported a myocardial infarction and 1 patient reported a stroke (0.8%).

In the dapagliflozin group, 43% of patients reported at least a 5-point increase in KCCQ-os, compared with 33% of patients in the placebo group (OR 1.73; 95% CI, 0.98 to 3.05; P = 0.06). The study reported a P value of 0.04 for the between-groups difference in the mean KCCQ-os at week 12; however, the point estimate and 95% CI were not reported. No statistically significant difference was found between groups in the mean 6MWD at week 12 (P = 0.79).

Harms

Only those harms identified in the review protocol are reported. See Table 26 for detailed harms data.

DAPA-HF Study

Adverse Events

Data were not collected on all non-serious adverse events in the DAPA-HF trial.

Serious Adverse Events

In the DAPA-HF study, 36% of patients in the dapagliflozin group and 40% of patients in the placebo group experienced a serious adverse event. The most frequently reported serious adverse events in both groups were cardiac failure, pneumonia, and ventricular arrhythmias (Table 26).

Stopped Treatment due to Adverse Events

Five percent of patients in each group stopped treatment due to adverse events (Table 26). Approximately 0.7% of patients stopped treatment due to cardiac failure in both groups. The next most common reasons for stopping treatment were dizziness, hypotension, urinary tract infection, and renal impairment, which were reported in 2 to 5 patients per treatment group (≤ 0.2%)

Mortality

In the dapagliflozin group, 227 patients died (9.6%) compared with 250 patients in the placebo group (10.6%) during the on-treatment period (i.e., up to 30 days after the last dose of the study drug) (Table 26). The most common causes reported in the dapagliflozin and placebo groups were cardiac failure (2.2% and 3.2%), death (2.0% and 2.0%), sudden death (0.8% and 0.4%), and sudden cardiac death (0.8% and 1.1%, respectively).

Notable Harms

Volume depletion was reported in 7.2% and 6.5% of patients, including serious adverse events, which were reported by 1% and 1.6% of patients, in the dapagliflozin and placebo groups, respectively (Table 26).

Renal adverse events occurred in 6.0% and 6.7% of patients in the dapagliflozin and placebo groups, respectively. These were serious adverse events for 1.4% and 2.4% of patients.

Four patients per group experienced a major hypoglycemic event. All 8 patients had diabetes at baseline, and all but 1 were receiving sulfonylureas or insulin at the time of the event.

Three patients in the dapagliflozin group experienced an adverse event adjudicated as definite diabetic ketoacidosis, all of which were serious adverse events: 1 patient died. All 3 patients had diabetes at baseline, 2 were on insulin, and the most common contributing factors were infection, illness, and dehydration.

Of 6 potential cases of Fournier gangrene, no cases were confirmed through the internal blinded medical assessment by the sponsor.

The frequency of amputation and fracture was the same in both treatment groups: 0.5% and 2.1% for amputation and fracture, respectively.

Table 26: Summary of Harms: DAPA-HF Study

	DAPA-HF (safety set)[a]	
	Dapagliflozin N = 2,368	Placebo N = 2,368
Patients with ≥ 1 adverse event		
n (%)	NR	NR
Patients with ≥ 1 SAE		
n (%)	846 (35.7)	951 (40.2)
Most common events[b], n (%)		
Cardiac failure	238 (10.1)	325 (13.7)
Pneumonia	70 (3.0)	73 (3.1)
Cardiac failure congestive	57 (2.4)	65 (2.7)
Cardiac failure acute	36 (1.5)	51 (2.2)
Ventricular tachycardia	32 (1.4)	53 (2.2)
Patients who stopped treatment due to adverse events		
n (%)	111 (4.7)	116 (4.9)
Most common events[b], n (%)		
Cardiac failure	17 (0.7)	15 (0.6)
Dizziness	4 (0.2)	4 (0.2)
Hypotension	4 (0.2)	4 (0.2)
Urinary tract infection	4 (0.2)	2 (0.1)
Renal impairment	2 (0.1)	5 (0.2)
Cardiac failure congestive	1 (0.0)	6 (0.3)
Deaths		
n (%)	227 (9.6)	250 (10.6)
Most common events[b], n (%)		
Cardiac failure	53 (2.2)	76 (3.2)

	DAPA-HF (safety set)[a]	
	Dapagliflozin N = 2,368	Placebo N = 2,368
Death	48 (2.0)	48 (2.0)
Sudden death	19 (0.8)	10 (0.4)
Sudden cardiac death	18 (0.8)	27 (1.1)
Notable harms		
n (%)		
Volume depletion[c]	170 (7.2)	153 (6.5)
Volume depletion SAE	23 (1.0)	38 (1.6)
Renal adverse event[c]	141 (6.0)	158 (6.7)
Renal SAE	34 (1.4)	58 (2.4)
Major hypoglycemic event[d]	4 (0.2)	4 (0.2)
Diabetic ketoacidosis[e]	3 (0.1)	0
Amputation[f]	13 (0.5)	12 (0.5)
Fracture[c,f]	49 (2.1)	50 (2.1)

NR = not reported; SAE = serious adverse event.

[a] All adverse events were reported based on the on-treatment period (from the first dose of the study drug until 30 days after the last dose), except for fractures, which were reported for the on- and off-treatment period (from the first dose of the study drug to the end of follow-up).

[b] Frequency greater than or equal to 2% for SAEs and greater than or equal to 1% for deaths; adverse events leading to drug discontinuation in 4 or more patients in 1 treatment group.

[c] Based on a predefined list of terms.

[d] Major hypoglycemic events were confirmed by the investigator and defined as follows: symptoms of severe impairment in consciousness or behaviour; need of external assistance; intervention to treat hypoglycemia; prompt recovery of acute symptoms following the intervention.

[e] Adjudicated as definite or probable diabetic ketoacidosis events.

[f] Surgical or spontaneous (non-surgical) amputation, excluding amputation due to trauma.

Source: Clinical Study Report for DAPA-HF.[7]

DEFINE-HF Study

In the DEFINE-HF study, 23% and 18% of patients in the dapagliflozin and placebo groups, respectively, reported a serious adverse event over the 12-week treatment period, with 8% and 9% of patients stopping the study drug due to adverse events. One patient in the dapagliflozin group died due to worsening HF, and 1 sudden cardiac death was reported in the placebo group. No lower limb amputations or diabetic ketoacidosis events were reported. One patient in each group (0.8%) experienced a severe hypoglycemic event and an acute kidney injury adverse event. Volume depletion adverse events were reported by 9% and 5% of patients in the dapagliflozin and placebo groups, respectively.

Critical Appraisal

Internal Validity

DAPA-HF Study

The DAPA-HF study used accepted methods to randomize patients and conceal allocation (i.e., interactive voice or web response system, or computer-generated block randomization). The baseline characteristics appear to be balanced between groups. Few patients withdrew from the study, and patients who stopped treatment early (10% and 11% in the dapagliflozin and placebo groups, respectively) continued to be followed and were

included in outcome analysis. A matched placebo tablet that was identical in size, colour, smell, and taste to dapagliflozin was used to maintain blinding. Because the study did not collect complete adverse event data, it is not possible to assess the risk of unblinding due to adverse effects known to be associated with dapagliflozin.

All primary outcome events were adjudicated by an independent blinded committee based on criteria defined a priori in the clinical event committee charter. The clinical experts consulted for this review stated that the criteria for HF hospitalization and urgent HF visits and for the composite renal function outcome were acceptable. Complete follow-up was high (> 99% of patients) for the primary outcome, and vital status was known for all but 2 patients in the placebo group. Deaths with an unknown cause were relatively infrequent, with a similar frequency between groups (dapagliflozin 2.3% and placebo 2.8%). In the primary analysis, deaths with an unknown cause were attributed to CV death, which was consistent with other HF trials. The sensitivity analyses (which censored patients with an unknown cause of death) and a worst-case analysis (which assumed dapagliflozin patients with missing data had a primary event) supported the conclusions of the primary data analysis.

The statistical analysis methods appear to be acceptable, although it is unclear if the proportional hazards assumption was met for the time-to-event outcomes. The type I error rate was controlled for the interim analysis and across the secondary outcomes tested. The trial, however, was not designed to test for superiority of dapagliflozin for health-related quality of life, which was of primary importance to patients. Moreover, EQ-5D data were missing for [redacted]. The study evaluated differences in HF symptoms using a validated instrument (KCCQ); however, the use of a non-parametric statistical model made it difficult to assess the clinical relevance of the differences reported. KCCQ data were missing for 17% of patients at 8 months, although in the rank ANCOVA analysis, imputation methods were applied to account for missing data. Patients with missing data due to death were assigned the worst ranks, and multiple imputation methods were used to account for other missing data (assuming data were missing at random). Responder analyses were based on thresholds that exceeded the MID of the KCCQ total symptom score that had been reported in the literature (4.7 to 5.0 points[20,21]); however, these analyses were not part of the statistical testing hierarchy, and there was no imputation for the 12% to 13% of patients with missing data. Assessment of functional status was based on the change in NYHA class, which may have low sensitivity in detecting changes in patients' ability to participate in daily activities, according to the clinical experts consulted. The study also reported data for the change from baseline in the KCCQ-cs and KCCQ-os, which include the physical function domain. However, these were exploratory outcomes and were outside the statistical testing hierarchy; thus, no conclusions can be drawn from these data.

The DAPA-HF study did not collect data on all adverse effects; thus, it is unclear if the overall pattern of adverse effects is similar in patients with HF, as was observed in the previously published dapagliflozin trials in patients with diabetes. The sample size and follow-up duration were likely insufficient to detect safety signals for rare events or those with a longer lag time.

DEFINE-HF Study

The DEFINE-HF study was a short-term (12-week) study with a limited sample size (263 patients) that was conducted in the US only. The study did not report the methods used to conduct the randomization and conceal allocation to treatment. A matching placebo tablet

was used to maintain blinding. The co-primary outcomes were based on biomarkers, which the FDA states have not been validated as surrogate end points for clinical benefit in patients with HF.[32] Although the study reported secondary and exploratory outcomes of interest to this review, the study was not powered for these outcomes, there was no control for the type I error rate, and reporting of results was incomplete (i.e., no between-group differences were reported for the change from baseline in KCCQ scores or 6MWD).

External Validity

The clinical experts consulted indicated that the population enrolled in the DAPA-HF study reflects those who may be seen in general practice, but the generalizability to patients with more severe HFrEF is unclear. The study excluded patients with more advanced disease, including those with recent HF hospitalization or CV events and those with poor or worsening renal function. Most patients were NYHA class II (68%), and less than 1% had NYHA class IV HF. To meet the inclusion criteria of the trial, all patients were receiving guideline-recommended treatments for HF, and thus they represented patients who are optimally managed. The clinical experts also stated that the trial population may not reflect the ethnic diversity in Canada.

The trial population was enriched by selecting those with NT-proBNP levels greater than or equal to 600 pg/mL. However, the clinical experts consulted stated that natriuretic peptide testing is not widely available in Canada; thus, this patient selection criteria would be difficult to implement in clinical practice.

The DEFINE-HF study enrolled patients from the US only, who were predominantly NYHA class II (66%) and White (55%). As with the DAPA-HF study, the patients enrolled reflect those with moderate HF. Treatment patterns in the US and Canada may differ, as the DEFINE-HF study had a higher proportion of patients with implantable cardioverter-defibrillators than expected within Canada, according to the clinical experts consulted for this review.

Indirect Evidence

Objectives and Methods for the Summary of Indirect Evidence

No direct evidence comparing dapagliflozin to other therapies for HFrEF was identified; thus, a review of indirect evidence was undertaken. CADTH reviewed the sponsor's Common Drug Review submission and conducted a literature search to identify potentially relevant indirect treatment comparisons (ITCs) in patients with HF. The Ovid MEDLINE and Embase databases were searched using a combination of MeSH (Medical Subject Headings) and keywords. The main search concept was dapagliflozin (Forxiga). An indirect comparison filter was applied to limit study type to ITCs. Retrieval was not limited by publication date or by language. Titles, abstracts, and full text articles were screened for inclusion by 1 reviewer based on the population, intervention, comparator, and outcome criteria outlined in Table 5.

One potentially relevant ITC was identified in the literature search. The report by Vaduganathan et al.[33] was excluded as it did not report disaggregated results for dapagliflozin versus other treatment options. One sponsor-submitted ITC was included in this review.[10,34] Data from this ITC were used to inform the pharmacoeconomic model.

Description of Indirect Comparison

The sponsor provided an MAIC that examined the comparative effectiveness and safety of dapagliflozin versus sacubitril-valsartan in patients with HFrEF.

Methods of Indirect Comparison

Objectives

The objective of the MAIC was to compare the investigational treatment arms for the DAPA-HF and PARADIGM-HF trials across 4 potential treatment combinations for 6 trial end points (Table 27).

Table 27: Planned Treatment Comparisons and Outcomes in the MAIC

Treatment comparison	Outcomes
• Dapagliflozin in combination with an ACEI as part of SOC versus sacubitril-valsartan in combination with SOC • Dapagliflozin in combination with an ARB as part of SOC versus sacubitril-valsartan in combination with SOC • Dapagliflozin in combination with an ACEI or an ARB as part of SOC versus sacubitril-valsartan in combination with SOC • Dapagliflozin in combination with sacubitril-valsartan as part of SOC versus sacubitril-valsartan in combination with SOC	• Time to the earliest death due to cardiovascular causes or first hospitalization due to worsening heart failure • Time to death due to cardiovascular causes • Time to first hospitalization due to worsening heart failure • Time to death due to any cause • Incidence during study of adverse events • Incidence during study of serious adverse events

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MAIC = matching-adjusted indirect comparison; SOC = standard of care.

Source: Common Drug Review submission.[10]

Study Selection Methods

No systematic literature review was conducted as part of this MAIC. The authors stated that sacubitril-valsartan was the most relevant comparator to dapagliflozin; thus, the analysis was limited to these drugs and was based on individual patient data from the DAPA-HF study and aggregate data from the PARADIGM-HF study.[31]

The authors did not assess the quality of the 2 trials, and it is unclear if data extraction was validated by a second reviewer.

ITC Analysis Methods

The authors conduced an MAIC, using data from the DAPA-HF (index study) and the PARADIGM-HF (comparator study). Although not explicitly stated, it was implied that MAIC methods were necessary due to heterogeneity between trials in standard of care therapies. No patient characteristics were explicitly identified as heterogeneous between the 2 studies to justify the MAIC approach.

The authors conducted a review of the study design, population, interventions, and background therapies of both studies and identified differences between trials. Patients from the DAPA-HF study were excluded from the MAIC based on background treatments received at baseline.[35] For all analyses, the control group for the DAPA-HF trial included 1,329 of 2,371 patients (56%) who received an ACEI as part of their background therapy. The primary intervention group included patients who received dapagliflozin and an ACEI as background therapy (1,332 out of 2,373; 56%). Also tested were dapagliflozin subgroups that included an ARB (n = 674; 28%) or an ACEI or ARB as background therapy (n = 1,998;

84%). No other criteria were used to exclude index trial patients in order to match them to the inclusion and exclusion criteria of the PARADIGM-HF study.

The authors reported that potential treatment effect modifiers were identified using statistical methods (i.e., generalized linear regression model with forward stepwise process). The authors tested a list of potential covariates, which were selected based on expert input (no details provided) and which also had data available from the comparator trial. Using a Cox proportional hazards model (for time-to-event outcomes) or a binomial logistic model (for safety outcomes), a forward stepwise process was used to identify interaction terms that correlated with each outcome in the DAPA-HF study. All covariates identified from the analyses of individual outcomes were included in the primary MAIC model and are listed in Table 28. A sensitivity analysis was conducted that included covariates for body mass index and serum creatinine level at baseline in addition to those in Table 28.

Patient weights were derived from a logistic regression model that estimated propensity scores for patients in the DAPA-HF study using the method of moments. The report states that "patient weights were derived independently for each arm subpopulation in DAPA-HF, matching to the aggregate baseline characteristics of the PARADIGM-HF enalapril population."[34] The authors state that this approach was taken to avoid residual differences of treatment effect modifiers in the weighted individual patient data between the investigational and control groups. After adjustment, the effective sample size for the control group in the DAPA-HF study (i.e., placebo plus ACEI as background therapy) was 503 patients (38%) and in the primary active group (dapagliflozin plus ACEI as background therapy) was 568 patients (43%). The effective sample size of the 2 dapagliflozin subgroups was 227 patients (34%) and 872 patients (44%) for those with ARB background therapy or those with ACEI or ARB background therapy, respectively. A weighted Cox model and weighted logistic regression model were used to generate comparative outcome data for dapagliflozin versus sacubitril-valsartan.

Although there was a planned analysis for the subgroup of patients who received dapagliflozin in combination with sacubitril-valsartan as part of standard of care versus sacubitril-valsartan in combination with standard of care, the authors stated this was not feasible due to the limited number of patients who received sacubitril-valsartan background therapy in the DAPA-HF study. The efficacy outcomes analyzed included time to first occurrence of CV death or hospitalization for HF, time to CV death, time to first HF hospitalization, and time to death from any cause. The authors planned to analyze the comparative incidence of adverse events and serious adverse events for safety; however, due to the limited reporting of adverse events in the DAPA-HF study, only an analysis of serious adverse events was possible. The authors did not conduct an analysis of the overall frequency of serious adverse events but instead analyzed individual serious adverse events to inform the pharmacoeconomic model.[35]

Table 28: Potential Effect Modifiers Included in MAIC Primary Analysis

Covariates	
• Age (mean years) • Sex (male, female) • Race (White, Black, Asian, other) • Region (Europe, North America, Latin America, Asia Pacific) • Systolic blood pressure (mean mm Hg) • Heart rate (mean BPM) • Ischemic cardiomyopathy (present, absent) • LVEF (mean %)	• NT-proBNP (pg/mL) (above median, below median) • NYHA class (< III, III, IV) • History of hypertension (present, absent) • History of diabetes (present, absent) • History of atrial fibrillation (present, absent) • History of previous hospitalization for HF (present, absent) • History of previous myocardial infarction (present, absent) • History of previous stroke (present, absent)

BPM = beats per minute; HF = heart failure; LVEF = left ventricular ejection fraction; MAIC = matching-adjusted indirect comparison; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association.

Source: Common Drug Review submission.[10]

Results of Indirect Comparison

Summary of Included Studies

The authors of the MAIC compared the study design, populations, and interventions of the 2 trials to identify potential sources of heterogeneity. The inclusion criteria of the 2 trials were similar, although there were some criteria that resulted in patients being excluded from PARADIGM-HF who would not have been excluded from DAPA-HF. Patients with LVEF greater than 35% but less than or equal to 40% would have been excluded from PARADIGM-HF after the protocol revision on December 15, 2010. In addition, patients with a known history of angioedema or a history of intolerance to ACEI or ARB; aspartate aminotransferase or alanine aminotransferase values exceeding 2 times the upper limit of normal but less than 3 times the upper limit of normal; life expectancy greater than or equal to 2 years but less than 5 years; serum potassium greater than 5.2 mmol/L; or surgical or medical conditions that might significantly alter the absorption, distribution, metabolism, or excretion of the study drugs would have been excluded from PARADIGM-HF but not DAPA-HF. The DAPA-HF study excluded patients with type 1 diabetes, but these patients could have been enrolled in the PARADIGM-HF trial. The authors stated that there was more ethnic diversity in the patients enrolled in the PARADIGM-HF study, which was conducted in 47 countries, than in the DAPA-HF trial, which was conducted in 20 countries.

Several other potential sources of heterogeneity were identified between the DAPA-HF and PARADIGM-HF studies (Table 29). Differences were noted between trials in the treatments received in the control arm. All patients in the control group of the PARADIGM-HF study received enalapril 10 mg twice daily as an add-on to background therapy of beta-blocker (93%) and mineralocorticoid receptor antagonist (56%),[31] whereas the control group of the DAPA-HF study received placebo plus standard of care therapy. The standard of care treatments patients received at baseline in the DAPA-HF study included ACEI (56%), ARB (28%), or sacubitril-valsartan (11%), plus beta-blocker (96%), and, if indicated, a mineralocorticoid receptor antagonist (72%) or ivabradine (5%).[7]

The MAIC authors did not discuss differences in the outcome definitions in each trial or the potential impact of any differences. The primary outcome in the 2 trials varied: The DAPA-HF study including urgent HF visits in the composite measure, whereas the PARADIGM-HF trial reported the time to CV death or first HF hospitalization only. It is unclear if differences existed between trials in the other outcomes analyzed.

Patients in the PARADIGM-HF study underwent a 2-week run-in phase with enalapril and a 4- to 6-week run-in phase with sacubitril-valsartan, and those patients able to tolerate the study drug doses were eligible for randomization.[31] This meant that patients unable to tolerate either enalapril 10 mg twice daily or sacubitril-valsartan 200 mg twice daily were dropped from the study. Approximately 20% of patients who entered the trial withdrew during the run-in phases. There was no run-in phase in the DAPA-HF study to ensure the patients randomized were able to tolerate the study drug.

The follow-up duration of the PARADIGM-HF study was 27 months, compared with 18 months for the DAPA-HF study.

Table 29: Assessment of Homogeneity for MAIC

	Description and handling of potential effect modifiers
Disease severity	There were differences between trials in baseline characteristics (PARADIGM-HF patients were younger, with a higher proportion in NYHA class I or II, fewer patients with diabetes, and more with a history of atrial fibrillation and hospitalization for HF).
Treatment history	The DAPA-HF trial was conducted more recently (2017–2019) and included background therapies that were not available when the PARADIGM-HF study was conducted (2009–2012).
Clinical trial eligibility criteria	Although inclusion criteria were similar in the 2 trials, differences were noted in baseline LVEF; history of angioedema or intolerance to ACEI or ARB; hepatic enzyme levels; serum potassium levels; anticipated life expectancy; presence of a condition that might significantly alter the absorption, distribution, metabolism, or excretion of study drugs; type 1 diabetes; ethnic diversity.
Dosing of comparators	PARADIGM-HF had minimum dosing requirements for ACEI or ARB therapy prior to enrolment and after randomization. It is unclear what doses of ACEI or ARB patients were receiving in DAPA-HF.
Control group response	The primary outcome event frequency was higher in the control group of the PARADIGM-HF study (26.5%) than in that of the DAPA-HF study (21.2%).
Definitions of end points	There was no discussion of differences in outcome definitions between trials. In the DAPA-HF study, the primary composite outcome included urgent HF visits in addition to CV death and HF hospitalization. Urgent HF visits were not included in the primary outcome for the PARADIGM-HF study.
Timing of end point evaluation or trial duration	The trial duration was longer for PARADIGM-HF (median 27 months) than for DAPA-HF (18 months).
Withdrawal frequency	No assessment.
Clinical trial setting	No assessment.
Study design	Both were international double-blind, event-driven trials. The PARADIGM-HF study included run-in periods to ensure the study drugs were tolerable (20% withdrew during run-in phases).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CV = cardiovascular; HF = heart failure; LVEF = left ventricular ejection fraction; MAIC = matching-adjusted indirect comparison; NYHA = New York Heart Association.

Source: Common Drug Review submission;[10] McMurray et al. (2014);[31] Clinical Study Report for DAPA-HF.[7]

Results

Due to the sources of the heterogeneity between the DAPA-HF and PARADIGM-HF studies being unaccounted for, and limitations in the MAIC methods, the results of the analyses have not been summarized in this report.

Critical Appraisal of Indirect Comparison

The authors conducted a focused ITC that estimated the comparative efficacy and safety of dapagliflozin versus sacubitril-valsartan. Although no systematic literature review was conducted, this focused approach was reasonable as both treatments will likely have a similar place in therapy. The rationale for conducting an MAIC, rather than standard indirect comparison methods, was not stated. Of note, although MAIC methods can control for some sources of heterogeneity, there were several differences between the 2 trials that cannot be controlled for. These include the enrolment of an enriched population in the PARADIGM-HF study, differences in the duration of each study (median 27 months versus 18 months), and study time frame (2009 to 2012 versus 2017 to 2019). In addition, the authors compared the inclusion and exclusion criteria of the 2 studies and identified differences; however, there was no discussion of the differences in outcome definitions and no assessment of potential sources of bias within each trial.

Overall, the reporting of the methods used to conduct the MAIC lacked clarity, and based on the descriptions provided, it would not be possible to replicate the analyses. The authors provided a general description of MAIC methods as per the National Institute for Health and Care Excellence Decision Support Unit technical guidance 18;[8] however, the methods applied to the MAIC deviate from this methodology. Key issues identified include the following:

- Patients from the DAPA-HF study were excluded from the MAIC based on the background therapy received; no other criteria were used to match the inclusion and exclusion criteria of the PARADIGM-HF study.
- A data-driven approach was used to identify potential effect modifiers, using individual patient data from the DAPA-HF study.
- Patient weights were derived independently for each treatment group in the DAPA-HF study, thereby breaking randomization.
- Patient weights were matched to the enalapril (control) group of the PARADIGM-HF study, rather than the overall study population.

The authors did not present any literature that supports the methods used; thus, it is unclear if the methods applied are validated. Of the points listed, the most notable was the independent derivation of patient weights for the dapagliflozin and control groups. This approach breaks randomization, which presents a clear risk of bias for the results, since the weighting process could introduce differences across the study arms in measured and unmeasured confounders. The authors state they assumed that randomization was incomplete and attempted to balance the arms based on the measured variables they identified as effect modifiers. No evidence was provided to support their assumption that randomization was incomplete in either study. By breaking randomization, results are at risk of bias unless all effect modifiers and prognostic factors have been accounted for in the weighting process. This assumption is largely considered impossible to meet, and thus there are major concerns regarding the validity of the analyses.

Although the authors identified a number of differences between the inclusion criteria of the 2 trials, patients were excluded solely on the basis of background therapies. Thus, it is unclear if all patients included in the DAPA-HF cohort would have been eligible for the PARADIGM-HF study. In addition, the authors used a data-driven approach to identify effect modifiers using individual patient data from the DAPA-HF trial. The Decision Support Unit guidance states that “effect modifiers must be prespecified and clinically plausible, and

that supporting evidence must be provided from a thorough review of the subject area or from expert opinion."[8] The clinical experts consulted for this review stated that renal function and background therapies, including devices, are important effect modifiers that were not included in the MAIC analyses. The effective sample size was substantially reduced (38% to 44% of the DAPA-HF subpopulation), which suggests the weighted estimates are being influenced by a small portion of the patients in the DAPA-HF study. As a result, precision about the weighted estimates has been reduced, which will reduce power for detecting differences between the treatments.

Summary

The sponsor supplied an MAIC that evaluated the efficacy and safety of dapagliflozin compared to sacubitril-valsartan as an add-on to standard therapies in adults with HFrEF. The analysis used individual patient data from the DAPA-HF study to create a cohort that was weighted to match the characteristics of the control group of the PARADIGM-HF trial. The analysis had several limitations that threatened the internal validity of the results. Most notable were differences in the study design and populations enrolled in the 2 trials (such as the enrolment of an enriched population in the PARADIGM-HF study) and the derivations of patients' weights independently for the active and control groups of the DAPA-HF study. The methods used to conduct the MAIC were not consistent with technical guidance and are of uncertain validity. As a result, no conclusions can be drawn from the ITC.

Other Relevant Evidence

No other relevant evidence was identified.

Discussion

Summary of Available Evidence

One pivotal trial (DAPA-HF) and 1 other trial (DEFINE-HF) met the inclusion criteria for the systematic review. The double-blind, randomized controlled DAPA-HF study (N = 4,744) evaluated the efficacy of dapagliflozin versus placebo as an add-on to standard of care therapy in adults with HFrEF (LVEF ≤ 40%; NYHA functional classes II to IV). The primary outcome was the time to first occurrence of CV death, hospitalization for HF, or an urgent HF visit. Other outcomes included time to worsening of renal function (composite outcome), all-cause mortality, change from baseline in HF symptoms (based on the KCCQ total symptom score), and health-related quality of life (EQ-5D-5L). The mean age of patients enrolled was 66.3 years (SD = 10.9), and the majority were male (77%) and White (70%). Overall, 68% had NYHA class II symptoms, and 32% had NYHA class III HF. The median follow-up duration of this event-driven trial was 18.2 months.

The aim of the DEFINE-HF study was to evaluate the effect of dapagliflozin on natriuretic peptides and health status in optimally treated patients with HFrEF, with and without type 2 diabetes. This 12-week, double-blind RCT enrolled patients with an established diagnosis of HF with LVEF less than or equal to 40% (N = 263). Patients were randomized to dapagliflozin 10 mg daily or placebo as an add-on to standard of care HF therapy. Outcomes of interest to this review were time to first HF hospitalization or urgent HF visit and the change in the KCCQ-os. The mean age per treatment group was 62.2 years (SD = 11.0) and 60.4 years (SD = 12.0), and 74% were male. Overall, 55% of patients were White and 38% were Black, with NYHA class II (66%) or class III (34%) HF.

This report also includes a summary and critical appraisal of the sponsor-submitted indirect comparison. No other relevant evidence was identified.

Interpretation of Results

Efficacy

The DAPA-HF study reported statistically significant differences favouring dapagliflozin over placebo in the time to first occurrence of CV death, HF hospitalization, or urgent HF visit. Each component of the composite outcome also showed differences favouring dapagliflozin, and the total number of HF hospitalizations and CV deaths was lower in the dapagliflozin group (16.3 events per 100 PYs) than in the placebo group (21.6 events per 100 PYs). As shown in the Kaplan-Meier plot of the primary composite outcomes, the groups began to diverge within the first 3 months of therapy, and differences persisted throughout the study. Treatment effects were generally consistent across most planned subgroups, including for patients with and without type 2 diabetes status at baseline. According to the clinical experts consulted for this review, the between-group differences in CV death and HF hospitalizations were clinically important, particularly considering that patients were already receiving guideline-recommended treatment for HF. Although the time to death from any cause also favoured dapagliflozin over placebo, these data should be interpreted as indeterminate due to failure of a prior outcome in the statistical analysis hierarchy.

The frequency of renal events was low during the DAPA-HF study, and no statistically significant difference was detected between groups in the time to first occurrence of greater

than or equal to 50% sustained decline in eGFR, ESRD, or renal death. In addition, the frequency of myocardial infarctions, stroke, or new onset atrial fibrillation was similar in the dapagliflozin and placebo groups during the trial.

Patients stated that improvement in health-related quality of life and functional ability as well as reduced HF-related symptoms were of primary importance. Although the DAPA-HF study reported some measures for these outcomes, these data had limitations. The change in EQ-5D-5L scores was an exploratory outcome (which was not part of the statistical testing hierarchy) and had missing data for [redacted], which was not accounted for in the analysis. The results did not show a statistically significant difference between groups in health-related quality of life. While statistically significant differences favouring dapagliflozin were reported for the change from baseline in the KCCQ total symptom score, the clinical relevance of these data was difficult to assess. The KCCQ change from baseline analysis was based on a non-parametric model; thus, inferences are based on a P value only, and the magnitude of the between-groups difference in mean scores was not reported. KCCQ responder analyses were conducted based on thresholds that exceeded the MID of the KCCQ total symptom score, but these were outside the statistical testing hierarchy, with missing data for 13% of patients and no imputation for missing data. Although there were more patients with at least a 5-, 10-, or 15-point increase in the dapagliflozin group than in the placebo group, interpretation of these results should consider the high placebo response rate (47% to 50%) and the potential inflated risk of type I error. The DAPA-HF study showed no difference between groups in the NYHA functional class, although the clinical experts stated that this subjective classification system has low sensitivity to change. The study also reported data for the change from baseline in the KCCQ-cs and KCCQ-os. These data suggest there may be benefit favouring dapagliflozin over placebo; however, the clinical relevance of the differences is unclear, and no conclusions can be drawn from these exploratory data.

A second study comparing dapagliflozin to placebo in patients with HFrEF was identified in the literature search (DEFINE-HF), but this study did not provide any additional meaningful evidence for dapagliflozin. Few differences were detected between dapagliflozin and placebo in this short-term (12-week), small sample (N = 263) study. Other limitations include unclear allocation concealment, lack of control of the type I error rate, and incomplete reporting of results.

The evidence for dapagliflozin in patients with HFrEF was limited to a single placebo-controlled trial with a median duration of 18 months. There was no direct evidence comparing dapagliflozin to other add-on therapies such as sacubitril-valsartan. The sponsor supplied an indirect comparison, but this analysis had major methodological flaws, and thus no conclusions can be drawn from the results.

The clinical experts consulted indicated that the population enrolled in the DAPA-HF study reflects those who may be seen in general practice, but the generalizability to patients with more severe HFrEF is unclear. The study excluded patients with more advanced disease, including those with recent HF hospitalization or CV events and those with poor or worsening renal function. Most patients were in NYHA class II (68%), and less than 1% had NYHA class IV HF. The clinical experts also stated that the trial population may not reflect the ethnic diversity in Canada. The trial population was enriched by selecting those with NT-proBNP levels greater than or equal to 600 pg/mL. However, the clinical experts consulted stated that natriuretic peptide testing is not widely available in Canada; thus, this patient selection criteria would be difficult to implement in clinical practice.

Harms

The DAPA-HF study did not collect data on all non-serious adverse events; thus, it is not clear if the adverse effect profile of dapagliflozin is the same in patients with and without type 2 diabetes. Data for non-serious urinary tract infections or genital mycotic infections were not collected; thus, it is unclear if these events occur as frequently in patients with HF as observed in previous trials in patients with type 2 diabetes. The proportion of patients with serious adverse events and those who stopped treatment due to adverse events was similar in the dapagliflozin and placebo groups. No new safety signals were identified in the 18-month pivotal trial.

Conclusions

In adults with symptomatic HFrEF who received dapagliflozin as add-on therapy to guideline-recommended drug therapy, the time to occurrence of CV death, HF hospitalization, or urgent HF visits was increased relative to those who received placebo in addition to guideline-recommended drug therapy.

The impact of dapagliflozin on patient-valued outcomes of health-related quality of life, functional ability, and HF-related symptoms is uncertain. Although statistically significant differences were detected favouring dapagliflozin over placebo in the change from baseline in HF symptoms (measured using the KCCQ total symptom score), the clinical relevance of the differences is unclear.

No new safety signals were identified in patients with HFrEF; however, the pivotal DAPA-HF study did not collect data for all non-serious adverse events.

The evidence consisted of a single placebo-controlled trial, with a median duration of 18 months. Thus, longer-term safety and efficacy is uncertain in patients with HFrEF. No meaningful safety or efficacy data for dapagliflozin were provided by the second 12-week RCT included in the systematic review. There was no direct evidence comparing dapagliflozin to other second-line therapies for HF. The sponsor supplied an MAIC that compared dapagliflozin to sacubitril-valsartan; however, the analysis had major methodological flaws, and thus no conclusions could be drawn from the results.

Appendix 1: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) Cochrane Central Register of Controlled Trials (CCTR) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 11, 2020
Alerts:	Weekly search updates until project completion
Study Types:	No search filters were applied
Limits:	Publication date limit: No date limits used Humans Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase); keyword (CDSR and DARE)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.yr	Publication year
.jw	Journal word title
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

MULTI-DATABASE STRATEGY
1. (dapagliflozin* or forxiga* or farxiga* or edistride* or bms-512148 or bms512148 or 1ULL0QJ8UC or 887K2391VH).ti,ab,rn,nm,kf,ot,hw.
2. exp heart failure/
3. (((Heart* or cardio* or cardiac or ventric* or cordis or vascular or angiology or thoracic or artery or arterial or pericardial or ischaem* or ischem* or myocard*) adj3 (failure or decompensat* or stand-still or incompetenc* or insufficienc* or overload*)) or hfref).ti,ab,kf.
4. 2 or 3
5. 1 and 4
6. 5 use medall
7. *dapagliflozin/
8. (dapagliflozin* or forxiga* or farxiga* or edistride* or bms-512148 or bms512148).ti,ab,kw,dq.
9. exp heart failure/
10. ((Heart* or cardio* or cardiac or ventric* or cordis or vascular or angiology or thoracic or artery or arterial or pericardial or ischaem* or ischem* or myocard*) adj3 (failure or decompensat* or stand-still or incompetenc* or insufficienc* or overload*)).ti,ab,kw,dq.
11. 7 or 8
12. 9 or 10
13, 11 and 12
14. 13 use oemezd
15. conference abstract.pt.
16. conference review.pt.
17. 15 or 16
18. 14 not 17
19. 6 or 18
20. remove duplicates from 19

CLINICAL TRIAL REGISTRIES		
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.	
WHO ICTRP	International Clinical Trials Registry Platform, produced by WHO. Targeted search used to capture registered clinical trials. Search updated prior to the completion of stakeholder feedback period.	

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Cochrane Central Register of Controlled Trials	Same MeSH, keywords, and limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for Wiley platform.	

Grey Literature

Search date:	May 5, 2020
Keywords:	Dapagliflozin and heart failure
Limits:	Publication years: No date limits used
Updated:	Search updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- health statistics
- internet search
- open access journals.

Appendix 2: Excluded Studies

Table 30: Excluded Studies

Reference	Reason for exclusion
1. 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;141:100-11. 2. Eickhoff MK, Olsen FJ, Frimodt-Moller M, et al. Effect of dapagliflozin on cardiac function in people with type 2 diabetes and albuminuria - A double blind randomized placebo-controlled crossover trial. J Diabetes Complications 2020:107590. 3. Kato ET, Silverman MG, Mosenzon O, et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. Circulation 2019;139:2528-36. 4. Phrommintikul A, Wongcharoen W, Kumfu S, et al. Effects of dapagliflozin vs vildagliptin on cardiometabolic parameters in diabetic patients with coronary artery disease: a randomised study. Br J Clin Pharmacol 2019;85:1337-47. 5. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019;380:347-57. 6. Akerblom A, Oldgren J, Latva-Rasku A, et al. Effects of DAPAgliflozin on CARDiac substrate uptake, myocardial efficiency, and myocardial contractile work in type 2 diabetes patients-a description of the DAPACARD study. Ups J Med Sci 2019;124:59-64. 7. Bonora BM, Vigili de Kreutzenberg S, Avogaro A, Fadini GP. Effects of the SGLT2 inhibitor dapagliflozin on cardiac function evaluated by impedance cardiography in patients with type 2 diabetes. Secondary analysis of a randomized placebo-controlled trial. Cardiovasc Diabetol 2019;18:106. 8. Brown AJM, Lang C, McCrimmon R, Struthers A. Does dapagliflozin regress left ventricular hypertrophy in patients with type 2 diabetes? A prospective, double-blind, randomised, placebo-controlled study. BMC Cardiovasc Disord 2017;17:229. 9. Buysschaert M. Dapagliflozin and cardiovascular events in type 2 diabetes: The model of the DECLARE-TIMI 58 trial. Louv Med 2019;138:3-7. 10. Cefalu WT, Leiter LA, De Bruin TWA, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin's effects on glycemia and cardiovascular risk factors in high-risk patients with type 2 diabetes: A 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. Diabetes Care 2015;38:1218-27. 11. Del Prato S, Rosenstock J, Garcia-Sanchez R, et al. Safety and tolerability of dapagliflozin, saxagliptin and metformin in combination: Post-hoc analysis of concomitant add-on versus sequential add-on to metformin and of triple versus dual therapy with metformin. Diabetes, Obesity and Metabolism 2018;20:1542-6. 12. Ebell MH. Dapagliflozin in High-Risk Type 2 Diabetes Reduces Hospitalization for Heart Failure But Does Not Reduce Death, Myocardial Infarction, or Stroke. Am Fam Physician 2019;100:184-5. 13. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Previous Myocardial Infarction: Subanalysis From the DECLARE-TIMI 58 Trial. Circulation 2019;139:2516-27. 14. Mathieu C, Ranetti AE, Li D, et al. Randomized, Double-Blind, phase 3 trial of triple therapy with dapagliflozin Add-on to saxagliptin plus metformin in type 2 diabetes. Diabetes Care 2015;38:2009-17. 15. Matthaei S, Catrinoiu D, Celinski A, et al. Randomized, Double-Blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin inpatientswith type 2 Diabetes. Diabetes Care 2015;38:2018-24. 16. Matthaei S, Aggarwal N, Garcia-Hernandez P, et al. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. Diabetes, Obesity and Metabolism 2016;18:1128-33. 17. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA(1c), body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012;35:1473-8.	Population

Reference	Reason for exclusion
18. Tanaka H, Soga F, Tatsumi K, et al. Positive effect of dapagliflozin on left ventricular longitudinal function for type 2 diabetic mellitus patients with chronic heart failure. Cardiovasc Diabetol 2020;19:6. 19. Seo Y, Yamamoto M, Machino-Ohtsuka T, Ishizu T, Aonuma K. Effects and safety of sodium glucose cotransporter 2 inhibitors in diabetes patients with drug-refractory advanced heart failure. Circ J 2018;82:1959-62. 20. Singh JS, Fathi A, Vickneson K, et al. Research into the effect Of SGLT2 inhibition on left ventricular remodelling in patients with heart failure and diabetes mellitus (REFORM) trial rationale and design. Cardiovasc Diabetol 2016;15:97. 21. Soga F, Tanaka H, Tatsumi K, et al. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure UMIN000019789 UMIN. Cardiovasc Diabetol 2018;17 (1) (no pagination). 22. Yoshihara F, Imazu M, Hamasaki T, et al. An Exploratory Study of Dapagliflozin for the Attenuation of Albuminuria in Patients with Heart Failure and Type 2 Diabetes Mellitus (DAPPER). Cardiovasc Drugs Ther 2018;32:183-90. 23. Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 Trial. Am Heart J 2018;200:83-9.	Study design
24. Singh JSS, Mordi IR, Vickneson K, et al. Dapagliflozin Versus Placebo on Left Ventricular Remodeling in Patients With Diabetes and Heart Failure: The REFORM Trial. Diabetes Care 2020;03:03. 25. DETERMINE-reduced - Dapaglifozine effect on exercise capacity using a 6-minute walk test in patients with heart failure with reduced ejection fraction.	Outcomes
26. Baglioni P. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:1880-1. 27. Bhatt DL, Verma S, Braunwald E. The DAPA-HF Trial: A Momentous Victory in the War against Heart Failure. Cell Metab 2019;30:847-9.	Report type (letter, commentary, review article)

Appendix 3: Detailed Outcome Data

Table 31: Planned Subgroup Analyses for Time to CV Death, HF Hospitalization, or Urgent HF Visit: DAPA-HF Study

Time to CV death, hospitalization for HF, or urgent HF visit	DAPA-HF (FAS)						
	Dapagliflozin N = 2,373		Placebo N = 2,371		Treatment effects dapagliflozin versus placebo		
Subgroup	**N**	**n (%)**	**N**	**n (%)**	**HR (95% CI)[a]**	**P value[b]**	**Interaction P value**
NYHA class							**0.0087**
II	1,606	190 (11.8)	1,597	289 (18.1)	0.63 (0.52 to 0.75)	< 0.0001	
III/IV	767	196 (25.6)	774	213 (27.5)	0.90 (0.74 to 1.09)	0.28	
LVEF (%)							**0.33**
≤ median	1,230	222 (18.0)	1,239	307 (24.8)	0.70 (0.59 to 0.84)	< 0.0001	
> median	1,143	164 (14.3)	1,132	195 (17.2)	0.81 (0.65 to 0.99)	0.041	
MRA at baseline							**0.97**
Yes	1,696	281 (16.6)	1,674	361 (21.6)	0.74 (0.63 to 0.87)	0.0001	
No	677	105 (15.5)	697	141 (20.2)	0.74 (0.57 to 0.95)	0.018	
Type 2 diabetes at baseline							**0.80**
Yes	1,075	215 (20.0)	1,064	271 (25.5)	0.75 (0.63 to 0.90)	0.0018	
No	1,298	171 (13.2)	1,307	231 (17.7)	0.73 (0.60 to 0.88)	0.0014	
AF or atrial flutter at baseline							**0.40**
Yes	569	109 (19.2)	559	126 (22.5)	0.82 (0.63 to 1.06)	0.13	
No	1,804	277 (15.4)	1,812	376 (20.8)	0.72 (0.61 to 0.84)	< 0.0001	
Baseline eGFR (mL/min/1.73 m^2)							**0.64**
< 60	962	191 (19.9)	964	254 (26.3)	0.72 (0.59 to 0.86)	0.0005	
≥ 60	1,410	195 (13.8)	1,406	248 (17.6)	0.76 (0.63 to 0.92)	0.0047	

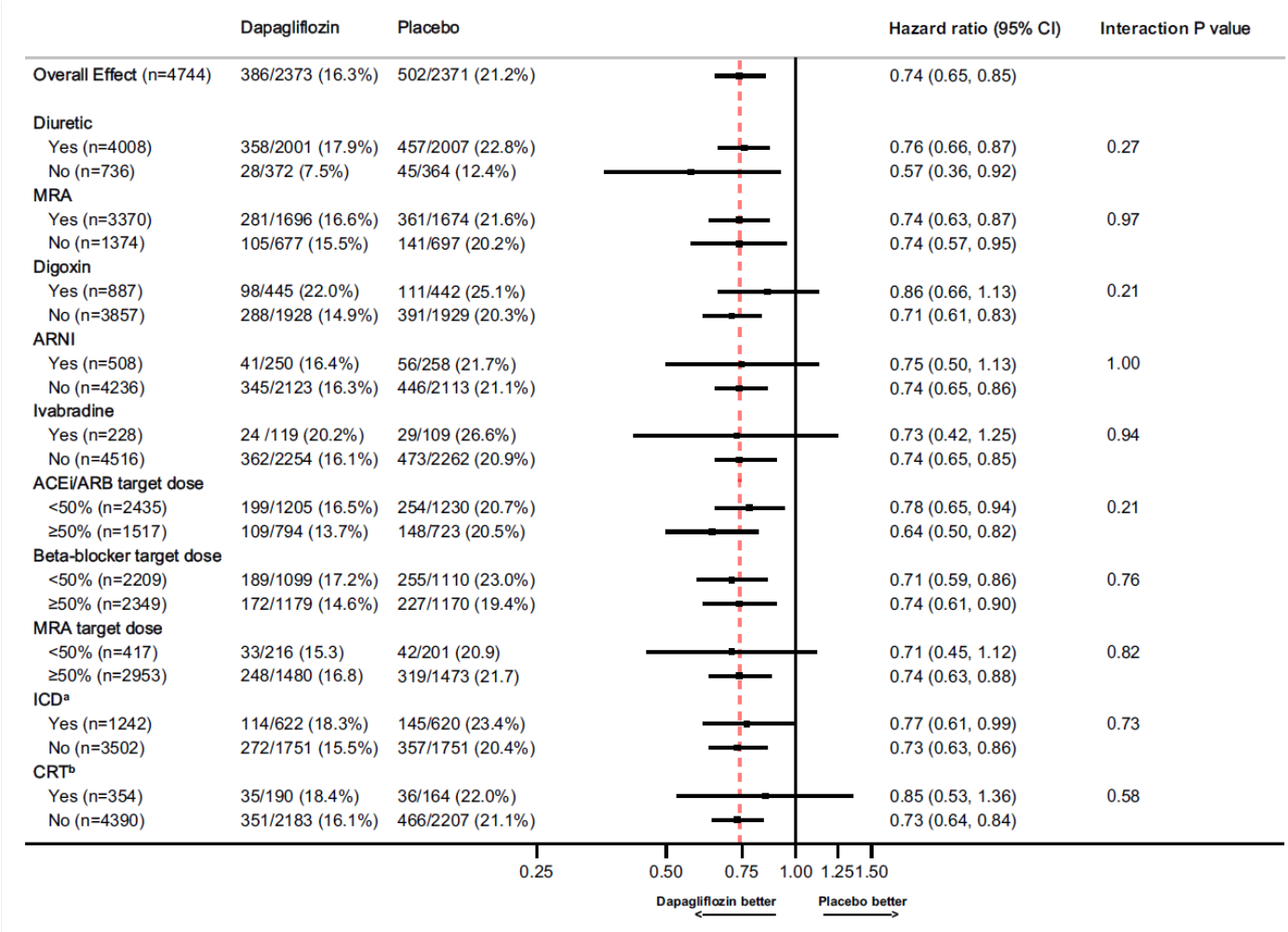
AF = atrial fibrillation; CI = confidence interval; CV = cardiovascular; eGFR = estimated glomerular filtration rate; FAS = full analysis set; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

[a] Cox proportional hazards model (score test) stratified by type 2 diabetes status at baseline, with factors for subgroup, treatment group, treatment by subgroup interaction, and history of HF hospitalization for the FAS population. Hazard ratio less than 1 favours dapagliflozin.

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Report for DAPA-HF.[7]

Figure 4: Post Hoc Subgroup Analyses for Time to CV Death, HF Hospitalization, or Urgent HF Visit: DAPA-HF Study



ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CI = confidence interval; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist.

[a] ICD or cardiac resynchronization therapy with a defibrillator.

[b] Cardiac resynchronization therapy with or without a defibrillator.

Source: Permission obtained from the publisher to use Figure 1 from "Effects of Dapagliflozin in DAPA-HF According to Background Heart Failure Therapy" by Docherty KF, Jhund PS, Inzucchi SE, et al. 2020.[18]

Table 32: Sensitivity Analyses for Time to CV Death, HF Hospitalization, or Urgent HF Visit: DAPA-HF Study

Time to CV death, hospitalization for HF, or urgent HF visit	DAPA-HF (FAS)					
	Dapagliflozin N = 2,373		Placebo N = 2,371		Treatment effects dapagliflozin versus placebo	
Sensitivity analysis	**n (%)**	**Event rate[a]**	**n (%)**	**Event rate[a]**	**HR (95% CI)[b]**	**P value[c]**
Excluding deaths adjudicated as undetermined cause	341 (14.4)	10.2	456 (19.2)	14.1	0.72 (0.63 to 0.83)	< 0.0001
Worst-case scenario analysis[d]	440 (18.5)	13.2	502 (21.2)	15.6	0.85 (0.74 to 0.96)	0.010

CI = confidence interval; CV = cardiovascular; FAS = full analysis set; HF = heart failure; HR = hazard ratio; .

[a] Event rate reported as the number of patients with event per 100 person-years of follow-up.

[b] Cox proportional hazards model (score test) stratified by type 2 diabetes status at baseline, with factors for treatment group and history of HF hospitalization for the FAS population. Hazard ratio less than 1 favours dapagliflozin.

[c] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[d] Patients in the dapagliflozin group who were censored prior to the end of the study were considered to have the primary end point at the time of censoring.

Source: Clinical Study Report for DAPA-HF.[7]

Table 33: Change From Baseline in EQ VAS: DAPA-HF Study

EQ VAS	DAPA-HF (FAS)	
	Dapagliflozin N = 2,373	Placebo N = 2,371
Baseline		
Patients included in the analysis, N (%)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
8 months		
Patients included in the analysis, N (%)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
12 months		
Patients included in the analysis, N (%)	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]

EQ VAS = EuroQol Visual Analogue Scale; FAS = full analysis set; SD = standard deviation.

Source: Clinical Study Report for DAPA-HF.[7]

Table 34: Change From Baseline to 8 Months for KCCQ Summary Scores: DAPA-HF Study

Change from baseline to 8 months	DAPA-HF (FAS)	
	Dapagliflozin N = 2,373	Placebo N = 2,371
Clinical summary score		
Patients included in the analysis, N (%)[a]	1,965 (83)	1,926 (81)
Baseline, mean (SD)	70.7 (21.1)	71.6 (20.5)
8 months, mean (SD)	77.3 (19.2)	75.3 (20.1)
Change from baseline (SD)	5.5 (17.0)	2.9 (17.7)
Win ratio dapagliflozin versus placebo (95% CI)[a]	1.20 (1.12 to 1.28)	Reference
P value[b,c]	< 0.0001	
Overall summary score		
Patients included in the analysis, N (%)[a]	1,965 (83)	1,926 (81)
Baseline, mean (SD)	67.8 (21.1)	68.6 (20.3)
8 months, mean (SD)	75.1 (19.3)	73.1 (20.2)
Change from baseline (SD)	6.2 (16.8)	3.9 (17.4)
Win ratio dapagliflozin versus placebo (95% CI)[a]	1.18 (1.10 to 1.25)	Reference
P value[b,c]	< 0.0001	

CI = confidence interval; FAS = full analysis set; KCCQ = Kansas City Cardiomyopathy Questionnaire; SD = standard deviation.

[a] "The win ratio represents the odds of having a more favourable outcome versus a less favourable outcome when assigned to the dapagliflozin 10 mg treatment group as opposed to placebo. This was accomplished by creating all possible pairs of patients across arms and labelling patients on dapagliflozin 10 mg in each pair as 'winner', 'loser' or 'tied', based on their ranks. The crude win ratio is defined as the ratio of the number of 'winner' pairs divided by the number of 'loser' pairs and an estimated win ratio greater than 1 favours dapagliflozin."[7]

[b] P value based on rank analysis of covariance adjusted for baseline KCCQ score and stratified by type 2 diabetes status at baseline for the FAS population. Change from baseline converted to ranks, with patients who died being assigned the worst ranks.

[c] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

Source: Clinical Study Report for DAPA-HF.[7]

Table 35: Efficacy Outcomes: DEFINE-HF Study

	DEFINE-HF (mITT)	
	Dapagliflozin N = 131	Placebo N = 132
Mortality and cardiovascular events		
All-cause death, n (%)	1 (0.8)	1 (0.8)
CV death, n (%)	1 (0.8)	1 (0.8)
Non-fatal myocardial infarction, n (%)	0	4 (3.0)
Stroke, n (%)	0	1 (0.8)
Time to first HF hospitalization or HF urgent visit[a]		
n (%)	12 (9.1)	13 (9.8)
HR (95% CI)	0.84 (0.36 to 1.97)	Reference
P value	0.68[b]	
Proportion of patients with ≥ 5-point increase in KCCQ overall score at 12 weeks[c]	**N = 126**	**N = 126**
n (%)	54 (43)	41 (33)

	DEFINE-HF (mITT)	
	Dapagliflozin N = 131	Placebo N = 132
OR (95% CI)	1.73 (0.98 to 3.05)	Reference
P value	0.06[b]	
KCCQ overall score at 12 weeks[d]		
Number of patients included in analysis	NR	NR
Baseline mean (SD)	NR	NR
Adjusted mean score at 12 weeks (95% CI)	72.6 (70.2 to 75.0)	68.9 (66.5 to 71.4)
Mean difference (95% CI)	NR	Reference
P value	0.04[b]	
6MWD (m) at 12 weeks[d]		
Number of patients included in analysis	NR	NR
Baseline mean (SD)	NR	NR
Adjusted mean metres at 12 weeks (95% CI)	303.7 (291.2 to 316.7)	301.3 (289.1 to 313.9)
Mean difference versus placebo (95% CI)	NR	
P value	0.79[b]	

6MWD = 6-minute walk distance; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; mITT = modified intention to treat; NR = not reported; OR = odds ratio; SD = standard deviation.

[a] Cox proportional hazards model adjusted for type 2 diabetes status at baseline, age, and baseline estimated glomerular filtration rate for the mITT population.

[b] P value has not been adjusted for multiple testing (i.e., the type I error rate has not been controlled).

[c] Logistic regression model adjusted for baseline value, type 2 diabetes status at baseline, age, and baseline estimated glomerular filtration rate for the mITT population.

[d] Generalized linear mixed model adjusted for baseline value, type 2 diabetes status at baseline, age, and baseline estimated glomerular filtration rate for the mITT population.

Source: Nassif et al. (2019).[19]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the outcome measures KCCQ, EQ-5D-5L, and 6MWD and review their measurement properties, including validity, reliability, responsiveness to change, and MID.

Findings

Table 36: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
KCCQ	KCCQ is a 23-item, disease-specific HRQoL questionnaire	**Validity:** Convergent validity was demonstrated through correlation of the KCCQ domain and summary scores, with a variety of external indicators of clinical status. Overall, moderate correlations were found for the KCCQ-tss, the KCCQ-os, and the KCCQ-cs.[20,36-38] The KCCQ individual domains were also assessed for convergent validity and presented correlations of varying strengths, which are further described in the text. Concurrent validity for the KCCQ domains was demonstrated with a moderate level of agreement between the KCCQ domains and external indicators of clinical status (Cohen kappa statistic = 0.36).[39] **Reliability:** Internal consistency reliability was demonstrated in a number of studies where the KCCQ summary scores and KCCQ domains (with the exception of the self-efficacy domain) had Cronbach alpha values > 0.7.[36,37,39-41] Test-retest reliability has been demonstrated (ICC > 0.7) for the KCCQ symptom domain, physical limitation domain, and social limitation domain, but not for the KCCQ self-efficacy and QoL domains (ICC < 0.7).[21,36,39] **Responsiveness:** High responsiveness of the KCCQ domains and the KCCQ-cs and KCCQ-os was found when the external indications of clinical status were NYHA class, MLHFQ,	The MID of the KCCQ-os and the KCCQ-cs were evaluated with 2 anchor-based methods in patients with HF. Estimates were approximately 5 points for the KCCQ-os, 5 points for the KCCQ-tss, and 6 points for the KCCQ-cs.[21] When the anchor used to assess the MID of the KCCQ-os was assessment of clinical change by a cardiologist using a validated Likert scale, an MID of 5.7 points was calculated.[42] When the PGA was used as the clinical anchor, “little improvement” in the PGA scale was associated with an MID ranging from 3.6 to 4.7, depending on the time point evaluated.[20]

Outcome measure	Type	Conclusions about measurement properties	MID
		SF-36, and 6MWD.[39] The KCCQ-os, and the KCCQ-cs were not responsive to changes in NT-proBNP levels.[37]	
EQ-5D-5L	Generic, preference-based measure of HRQoL	There was no evidence of validity, reliability, or responsiveness of this outcome in patients with HF.	3-point difference in the EQ VAS is clinically meaningful.[21]
6MWD	A supervised test measuring the greatest distance a patient is able to walk on level ground in 6 minutes	**Validity:** Distance walked showed good validity and was moderately correlated with CPET measurements, but not other measures of HF status. **Reliability:** The 6MWD has consistently been reported as having good test-retest reliability in patients. **Responsiveness:** There was good responsiveness when calculating observed change, effect size, and responsiveness coefficient for distance walked.	30 to 37 m for patients with HF.[27,28]

6MWD = 6-minute walk distance; CPET = cardiopulmonary exercise testing; EQ-5D-5L = EuroQol 5-Dimensions 5-Levels questionnaire; EQ VAS = EuroQol Visual Analogue Scale; HF = heart failure; HRQoL = health-related quality of life; ICC = interclass correlation coefficient; KCCQ = Kansas City Cardiomyopathy Questionnaire; KCCQ-cs = KCCQ clinical summary score; KCCQ-os = KCCQ overall summary score; KCCQ-tss = KCCQ total symptom score; MID = minimal important difference; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PGA = Patient Global Assessment; QoL = quality of life; SF-36 = Short Form (36) Health Survey.

Kansas City Cardiomyopathy Questionnaire

The KCCQ is a self-administered, 23-item, disease-specific health-related quality of life questionnaire that was originally developed in 2000 to measure the patient's perception of their health status within a 2-week recall period.[39,43] The items on the KCCQ can be categorized into the following domains: physical limitation, symptoms (frequency, severity, and recent change over time), social limitation, self-efficacy, and health-related quality of life. All items are measured using a Likert scale with 5 to 7 response options. Responses are scored using ordinal values, beginning with 1 for the response that implies the lowest level of functioning. Domain scores are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale, and multiplying by 100. Missing values within each domain are assigned the average of the answered items within the same domain. Various combinations of the KCCQ domains create 3 KCCQ summary scores: the KCCQ total symptom score, the KCCQ-cs and the KCCQ-os. The KCCQ total symptom score combines the symptom burden and symptom frequency domains and evaluates patient-reported swelling in feet, ankles, or legs; fatigue; shortness of breath; and disturbed sleep.[40] The KCCQ-cs includes the physical limitation and total symptom domains, and the KCCQ-os combines the physical limitation, total symptom, social limitation, and health-related quality of life domains into a single score. Summary scores are then transformed to a 0 to 100 range, where larger scores represent a better outcome.[10]

Validity

The KCCQ was originally validated in patients with a clinical diagnosis of congestive HF and an ejection fraction of less than 40%.[39] A cohort of patients (N = 39; mean age 64 years; 69% male; mean NYHA 2.0 ± 0.59) with stable disease was used to assess the validity of the KCCQ. Convergent validity was demonstrated through correlations of the KCCQ physical limitation domain with the NYHA class (r = –0.65) and with the 6MWD (r = 0.48). The symptom frequency and symptom severity domains correlated with the NYHA classification, and the quality of life domain correlated with the NYHA class (r = –0.64). The social limitation domain correlated with the NYHA class and the Short Form (36) Health Survey social limitation scale (r = 0.62). No adequate criterion standard was available for the self-efficacy domain.[39]

Convergent validity has also been assessed in a variety of other publications.[20,36-38,41] Napier et al. assessed convergent validity in patients with HF (N = 110). The KCCQ-os and the total symptom score showed moderate correlations with NYHA class and the 6MWD (range of r = 0.30 to 0.37; P < 0.001 for each).[37] These findings were corroborated in a publication assessing the convergent validity of the KCCQ in a population of patients in the FAIR-HF trial with HF (N = 459). There were moderate correlations between the Patient Global Assessment and the KCCQ-os (week 4: r = 0.31, P < 0.001; week 24: r = 0.42; P < 0.001), the KCCQ-cs (week 4: r = 0.36, P < 0.001; week 24: r = 0.4, P < 0.001), and the KCCQ physical limitation score (week 4: r = 0.31, P < 0.001; week 24: r = 0.39, P < 0.001).[20] Convergent validity was further analyzed in a cohort of patients with stable compensated HF (N = 41; mean age 68 ± 12 years; 100% male). The KCCQ total symptom score moderately correlated (r = 0.30) with peak VO_2.[38] The evidence bundle presented supports the presence of convergent validity of the KCCQ-os and the total symptom score. However, in a publication by Tucker et al., the authors assessed the presence of convergent validity in a population of patients hospitalized with chronic HF (N = 233). The authors found no evidence of convergent validity when the KCCQ domain scores and summary scores were correlated with NYHA class (either class III or IV), B-type natriuretic peptide levels, and the Charlson Comorbidity Index scores. The authors explain that this may be due to the presence of an alternate population in the current study compared to previous studies analyzing the convergent validity of the KCCQ.[44] Nevertheless, these findings taken together support the presence of convergent validity for the KCCQ-os and the total symptom score.

Ten years after the original publication assessing the validity of the KCCQ, Masterson Creber et al. retrospectively assessed the validity of the KCCQ in a cohort of chronic stage-C HF patients (N = 280). Confirmatory factor analysis explained 67.2% of the variance and had high-factor loading coefficients (> 0.7) for all but 5 items that loaded differently across 3 KCCQ domains and no items that loaded onto the quality of life domain.[40] This finding was corroborated by a 2016 paper that analyzed hospitalized patients with HF (N = 223), where 63.6% of the variance was explained within the KCCQ domains with confirmatory factor analysis.[44]

Concurrent validity of the KCCQ was assessed by administration of the KCCQ and the Minnesota Living with Heart Failure Questionnaire to patients with HF with preserved ejection fraction (N = 110) at baseline, 6 weeks, and 12 weeks in the NEAT trial. The level of agreement of change was moderate (Cohen kappa statistic: 0.36; 95% CI, 0.2 to 0.52), supporting the presence of concurrent validity.[37]

Reliability

The internal consistency reliability of the KCCQ domains and summary scores has been assessed in a number of studies and has demonstrated consistent results across all studies.[36,37,39,40,44] In a number of publications, the KCCQ domains, with the exception of the self-efficacy domain, have consistently presented Cronbach alpha values greater than 0.7.[37,39,40,44] The KCCQ self-efficacy domain has been evaluated in a number of studies and has demonstrated Cronbach alpha values in the range of 0.61 to 0.63,[39,40] with 1 publication calculating the Cronbach alpha value as greater than 0.7 for this domain.[44] The KCCQ-cs, KCCQ-os, and total symptom score have demonstrated Cronbach alpha values greater than 0.7, 0.93 to 0.95, and 0.8, respectively.[37,39] These findings were confirmed in a meta-analysis performed by Garin et al., where Cronbach alpha values were greater than 0.7 for all KCCQ domains, with the exception of the self-efficacy domain (Cronbach alpha = 0.62 to 0.66).[36]

The test-retest reliability of the KCCQ has been evaluated in multiple studies.[21,36,39] In the original paper evaluating the KCCQ, among those with stable HF who remained stable (N = 39), mean changes in KCCQ domains and summary scores over the 3 months of observation were 0.8 to 4.0 points, none of which were statistically significant.[39] A meta-analysis that summarized the test-retest reliability of the KCCQ domains found an acceptable ICC (> 0.7) for the KCCQ symptom domain, the physical limitation domain, and the social limitation domain, but an ICC less than 0.7 for the KCCQ self-efficacy domain and the quality of life domain.[36] Furthermore, in a cohort of 280 patients with chronic stage-C HF, test-retest reliability was assessed at baseline and at 6 months, and ICCs greater than 0.7 were demonstrated for the physical limitation domain and the symptom domain, but not for the self-efficacy domain.[40] Taken together, these findings suggest that the KCCQ symptom, physical limitation, and social limitation domains have acceptable test-retest reliability, while the KCCQ self-efficacy and quality of life domains do not demonstrate acceptable test-retest reliability.

Responsiveness

In the original study validating the KCCQ, a cohort of patients with HF who had been admitted to the hospital for HF exacerbations was used to assess the responsiveness of the KCCQ. The KCCQ exhibited high responsiveness, with Guyatt responsiveness statistics ranging from 0.62 for the social limitation domain to 3.19 for the symptoms domain and, specifically, 2.77 for the KCCQ-cs and 1.74 for the KCCQ-os.[39] In a separate study evaluating the responsiveness of the KCCQ in patients with stable chronic HF with preserved ejection fraction (N = 110), none of the KCCQ domains were responsive to changes in NT-proBNP. Of the KCCQ scores evaluated, the KCCQ-os and the KCCQ-cs were ranked as the most responsive to improvement and deterioration, respectively, in distance walked in the 6MWD.[37] These findings were corroborated in a study completed by Eurich et al., which evaluated the responsiveness of the KCCQ-cs and the KCCQ-os in a cohort of HF patients (N = 298). Irrespective of the responsiveness index used, the KCCQ-cs and the KCCQ-os were consistently ranked as the most responsive measures.[45] Furthermore, a meta-analysis that evaluated the responsiveness of 5 domains of the KCCQ (physical limitation, social limitation, symptom, health-related quality of life, and self-efficacy) produced very large effect sizes (0.6 to 3.2), indicating high responsiveness of the KCCQ domains.[36] Taken together, these findings indicate that the KCCQ domains and the KCCQ summary scores exhibit evidence of high responsiveness to change.

Clinical Relevance

Baseline data from a large RCT (HF-ACTION; N = 2,331; mean age 59.1 years; 71.6% male; 63.4% NYHA class II, 35.7% class III, 1% class IV) were used to examine associations between the KCCQ domain and summary scores and the clinical indicators of disease severity, including the 6MWD and peak VO_2.[21] In this study, a 1-SD difference in 6MWD and peak VO_2 was found to be associated with an approximately 5-point difference in the KCCQ-os, a 6-point difference in the KCCQ-cs, and a 5-point difference in the KCCQ total symptom score. The authors considered a 1-SD difference in 6MWD and peak VO_2 to represent a meaningful difference in HF patients, citing that it is a more stringent criterion used for these indicators than in previous studies.[21] This finding was corroborated when the KCCQ-os was associated with clinical change as assessed by a cardiologist (15-point Likert scale, from extremely worse to extremely better and grouped into categories of change) in a study (N = 476; mean age 61 years; 75% male; 11% NYHA class I, 41% class II, 44% class III, 5% class IV) in patients with HF and an ejection fraction less than 40%.[42] When the KCCQ-os was administered at baseline and at 6 weeks, a mean improvement of 5.7 points in the KCCQ-os was associated with a small improvement in HF. A mean decrease of 5.4 points in the KCCQ-os was associated with a small deterioration in HF.[42] Furthermore, the minimal clinically important difference for various KCCQ domain scores was evaluated in the FAIR-HF trial (N = 459) in patients with HFrEF, using the Patient Global Assessment scale at 4 and 24 weeks as an anchor.[20] At week 4, all the KCCQ domains had a less than 5-point MID based on "little improvement" in the Patient Global Assessment. At weeks 4 and 24, the MID estimates ranged from 3.6 to 4.3 for the KCCQ-os, were 4.5 for the KCCQ-cs, and ranged from 4.7 to 4.9 for the total symptoms score.[20] These findings taken as a whole support an approximately 5-point change in the KCCQ-os and the total symptom score and a 6-point change in the KCCQ-cs as an MID to patients.

EQ-5D-5L Questionnaire

The EQ-5D-5L was developed by the EuroQol Group as an improvement to the EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) to measure small and medium health changes and reduce ceiling effects.[22,46,47] The instrument comprises 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension is rated on 5 levels: level 1: "no problems"; level 2: "slight problems"; level 3: "moderate problems"; level 4: "severe problems"; and level 5: "extreme problems" or "unable to perform."[22,46,47] A total of 3,125 unique health states are possible, with 55555 representing the worst health state and 11111 representing the best state. The corresponding scoring of EQ-5D-5L health states is based on a scoring algorithm that is derived from preference data obtained from interviews using choice-based techniques (e.g., time trade-off) and discrete choice experiment tasks.[22,46,47] The lowest and highest score vary depending on the scoring algorithm used. The anchors are 0 (dead) and 1 (full health); however, negative values are also allowed to represent health states that a population considers worse than death. As an example, a Canadian scoring algorithm results in a score of –0.148 for health state 55555 (worst health state) and a score of 0.949 for health state 11111 (best health state).[22,46,47] Another component of the EQ-5D-5L is a visual analogue scale (EQ VAS), which asks respondents to rate their health on a visual scale from 0 (worst health imaginable) to 100 (best health imaginable).[22,46,47]

The literature search completed by CADTH did not find any evidence on the validity, reliability, responsiveness, and MID of the EQ-5D-5L questionnaire in patients with HF. However, there is evidence for these metrics for the EQ-5D-3L and the EQ VAS in an HF

population. Since this is an exploratory outcome for the DAPA-HF trial under review, CADTH will provide a high-level summary of the EQ-5D-3L and the EQ VAS in an HF population.

The discriminant validity of the EQ-5D-3L was determined in a North American cohort study (N = 476) in patients with HF and an ejection fraction less than 40%.[42] The EQ-5D index and the EQ VAS C-statistic ranged from 0.56 and 0.58 for small clinical improvements to 0.69 and 0.76 for moderate to large improvements.[42] From this study, the EQ-5D-3L was found to show less-discriminative abilities than the KCCQ or the NYHA class, but similar discriminative abilities to the Short Form (12) Health Survey (SF-12). In addition, the EQ-5D and the SF-12 did not exhibit much sensitivity to the magnitude of observed clinical change.[42]

The responsiveness of the EQ-5D-3L was compared with the KCCQ and the SF-12 in patients with HF and an ejection fraction less than 40% (N = 298).[48] Patients were administered questionnaires at baseline and 6 weeks in addition to a 6MWD. Overall, the EQ-5D index and the EQ VAS were less responsive than the KCCQ but showed similar responsiveness to the SF-12.[48]

A systematic review of studies looking at the validity and reliability of the EQ-5D-3L in patients with CV disease identified 10 studies.[49] When EQ-5D-3L scores were stratified by disease severity in the HF studies, the mean EQ-5D index scores decreased from 0.78 (SD = 0.18) for mild states to 0.51 (SD = 0.21) for moderate or severe health states.[49]

Baseline data from a large RCT (HF-ACTION; N = 2,331) were used to examine associations between the EQ VAS and clinical indicators of disease severity, including the 6MWD and peak VO_2.[21] In this study, a 1-SD difference in 6MWD and peak VO_2 was found to be associated with an approximate 3-point difference in the EQ VAS. The 1-SD change in 6MWD and peak VO_2 was considered by Flynn et al.[21] to be a clinically meaningful difference to HF patients and is a more stringent criterion than typically used in previous studies.[21] Moreover, a Canadian-specific MID of 0.037 has been reported for the EQ-5D-5L.[50,51]

Thus, overall, the EQ-5D-3L and the EQ VAS have demonstrated discriminant validity and responsiveness in HF patients, but not to the same extent as disease-specific measures such as KCCQ.

6-Minute Walk Distance

The 6MWD is a supervised test in which the patient walks on level ground covering the greatest distance possible in 6 minutes.[52] The American Thoracic Society provides guidelines for standardization to maximize the reliability of this test.[53] It is often preferred for its simplicity, low cost, minimal equipment, and high safety profile compared to the cardiopulmonary exercise test.[54] Despite these advantages, it is not recommended as a replacement for the cardiopulmonary exercise test as a prognostic tool.[38,54] Studies have shown it has consistently good test-retest reliability, as determined by the ICC (ICC > 0.75 considered adequate [24] and ICC > 0.9 considered excellent [25]).[26-29] Studies have also examined the possibility of a learning effect from 1 attempt to the next where there is an observable improvement with the second test. Conducting only 1 walk could result in a falsely low distance for many patients, with the exception of those who had a poor first distance of less than 300 m.[29] Others have observed no significant learning effect and suggest that only 1 test is necessary.[26,55] For validity testing, the distance walked showed

good to moderate correlation with cardiopulmonary exercise test measurements, but not with LVEF, NYHA class, or disease-specific quality of life scores.[25,29,54] Three methods for measuring responsiveness have been identified, including the observed change, effect size, and responsiveness coefficient, though there is no consensus for which is the best.[24] O'Keeffe et al. found that walk distance showed an expected change in direction and magnitude consistent with the Chronic Heart Failure Questionnaire domain scores, that the calculated effect size was large and greater in detecting patient deterioration than improvement, and that the responsiveness coefficient was satisfactory in a study of elderly patients with chronic HF.[24] Tager et al. reported an MID of 35 m after retesting 180 days from baseline and of 37 m after 365 days from baseline in adults ranging from NYHA classes I to III.[28] Shoemaker et al. determined a similar MID of 30 m between 0 and 8 weeks in adults who self-rated as being in NYHA class II or III.[27]

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