Common Drug Review
Clinical Review Report

March 2016

Drug	sacubitril/valsartan (Entresto)
Indication	For the treatment of heart failure with reduced ejection fraction in patients with NYHA Class II or III, to reduce the incidence of cardiovascular death and heart failure hospitalization
Listing request	As per indication
Dosage form(s)	Sacubitril/valsartan 24.3 mg/25.7 mg, 48.6 mg/51.4 mg, and 97.2 mg/ 102.8 mg fixed-dose combination tablets
NOC date	October 2, 2015
Manufacturer	Novartis Pharmaceuticals

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

6MWT	six-minute walk test
ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
ARB	angiotensin receptor blocker
BNP	B-type natriuretic peptide
CI	confidence interval
CRT	cardiac resynchronization therapy
CV	cardiovascular
DB	double-blind
EAIR	exposure-adjusted incidence rate
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol 5-Dimensions Questionnaire
FAS	full analysis set
HF	heart failure
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-cs	Kansas City Cardiomyopathy Questionnaire overall clinical score
KCCQ-os	Kansas City Cardiomyopathy Questionnaire overall summary score
LVEF	left ventricular ejection fraction
MCID	minimal clinically important difference
MD	mean difference
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NYHA	New York Heart Association
OR	odds ratio
RCT	randomized controlled trial
SD	standard deviation
SF-12	Short Form (12) Health Survey
SF-36	Short Form (36) Health Survey
VAS	visual analogue scale
VO_2	volume of oxygen

EXECUTIVE SUMMARY

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] There are an estimated 600,000 Canadians with HF, of which approximately half have a reduced left ventricular ejection fraction (LVEF); it is in this population that the evidence base regarding treatment is more well established.[1,2] The annual mortality rate ranges between 5% and 50%, depending on the severity of symptoms, heart function, age, and other factors.[2] The primary symptoms are dyspnea and fatigue, and may also include fluid retention. Patients report that HF can have a substantial impact on their exercise tolerance and quality of life, limiting their ability to work, participate in recreational activities, and complete activities of daily living.

Entresto is a sodium hydrate complex of two active drugs: sacubitril, a first-in-class neprilysin inhibitor; and valsartan, an angiotensin receptor blocker (ARB). It is available as combination tablets containing sacubitril/valsartan in fixed-dose ratios as follows: 24.3 mg/25.7 mg, 48.6 mg/51.4 mg, and 97.2 mg/102.8 mg, respectively.[3]

Sacubitril/valsartan is indicated for the treatment of HF with reduced ejection fraction in patients with New York Heart Association (NYHA) class II or III HF, to reduce the incidence of cardiovascular (CV) death and HF hospitalization.[3] According to the product monograph, it should be used in clinically stable patients in conjunction with other HF treatments, such as diuretics, beta blockers, and aldosterone antagonists, and in place of angiotensin-converting enzyme inhibitor (ACEI) or ARB therapy. The recommended starting dose for most patients is sacubitril/valsartan 48.6 mg/51.4 mg twice daily orally, increased every two to four weeks, as tolerated, to the target dose of sacubitril/valsartan 97.2 mg/ 102.8 mg twice daily.[3]

Indication under review
For the treatment of heart failure with reduced ejection fraction in patients with NYHA Class II or III, to reduce the incidence of cardiovascular death and heart failure hospitalization
Listing criteria requested by sponsor
As per indication

The objective of this review is to perform a systematic review of the beneficial and harmful effects of sacubitril/valsartan for the treatment of patients with NYHA class II or III HF and reduced ejection fraction.

Results and Interpretation

Included Studies

A single randomized, double-blind (DB), active-controlled superiority trial met the inclusion criteria. The PARADIGM-HF trial (N = 8,442) compared the safety and efficacy of sacubitril/valsartan versus enalapril in patients with HF and reduced ejection fraction (≤ 40% or ≤ 35%) with NYHA functional class II to IV who were treated with an ACEI or ARB plus a beta blocker (unless contraindicated) at stable doses for the past four weeks. Prognostic enrichment criteria were also applied and patients were required to

have B-type natriuretic peptide (BNP) plasma levels ≥ 150 pg/mL or N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels ≥ 600 pg/mL unless the patient had been hospitalized for HF in the past year, in which case the following criteria applied: BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL.

The enrolled patients received enalapril (10 mg twice daily) and then sacubitril/valsartan (97.2 mg/102.8 mg twice daily) in sequential two- to six-week run-in periods. Those who were able to tolerate the study drugs were randomized to DB treatment with enalapril or sacubitril/valsartan, and continued on background HF medications (except for prior ACEI or ARB therapy). The median treatment duration was 24 months and the median follow-up time was 27 months. Three interim analyses were performed for the primary composite outcome and the study was stopped at the third interim analysis based on pre-specified efficacy-stopping criteria and a one-sided alpha of 0.001.

The enrolled patients had a mean age of 64 years, LVEF of 29%, were predominantly male (78%), and classified as NYHA functional class II (70%). The primary outcome was time to CV death or first HF hospitalization, and secondary outcomes included all-cause mortality, change in Kansas City Cardiomyopathy Questionnaire (KCCQ) physical limitations and symptom clinical summary score, and new onset atrial fibrillation.

Efficacy

In the PARADIGM-HF trial, sacubitril/valsartan showed a statistically significant difference over enalapril in all-cause mortality (17% versus 20%, respectively). There were fewer CV-related deaths in the sacubitril/valsartan versus enalapril groups (13% versus 17%, respectively; hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.71 to 0.89), including fewer sudden deaths (6.0% versus 7.4%) and pump failures (3.5% versus 4.4%).

The trial showed statistically significant differences in CV mortality or first HF hospitalization for sacubitril/valsartan (22%) compared with enalapril (27%) (HR 0.80; 95% CI, 0.73 to 0.87). There were similar statistically significant reductions in hospitalizations (whether due to HF worsening, another CV cause, or any cause) in favour of sacubitril/valsartan, with reported HRs ranging from 0.79 to 0.88. The incidence of other CV outcomes — myocardial infarction, stroke, or new onset atrial fibrillation — were similar in the sacubitril/valsartan and enalapril groups.

The subgroup analysis by NYHA functional class showed [redacted] sacubitril/valsartan and enalapril groups in the time to first HF hospitalization ([redacted]) in patients with class III/IV symptoms, [redacted] functional class I/II patients showed a statistically significant treatment effect (HR 0.70; 95% CI, 0.61 to 0.82). A similar pattern was observed for the composite end point of CV death or first HF hospitalization. Of note, patients with NYHA class II HF represented 70% the total study population while 24% were NYHA class III. The treatment effects for CV mortality, first HF hospitalization and the primary composite outcome were generally similar across subgroups based on LVEF (≤ 35% or > 35% to ≤ 40%), implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) use (yes/no), or region, although in some subgroups the effects were not statistically significant. Caution is warranted when interpreting the subgroup analyses, considering that some analyses were likely under-powered due to the smaller sample sizes (N = 602 for North America; N = 961 for LVEF > 35% to ≤ 40%), or the analyses were post hoc (N = 1,379 for ICD/CRT use) and randomization was stratified by site only. No control of multiplicity was considered for the subgroup analyses.

The use of sacubitril/valsartan was not associated with clinically important differences for the outcomes that affect patients' day-to-day lives. Most patients (78%) did not show a change in NYHA functional class, with only 2% more patients showing improvement, and 2% fewer worsening in the sacubitril/valsartan versus enalapril groups. Two quality of life instruments were used in PARADIGM-HF: the disease-specific KCCQ and the generic EuroQol 5-Dimensions Questionnaire (EQ-5D). For both instruments, the differences between treatments in the change from baseline to eight months were small and of uncertain clinical importance. The differences between sacubitril/valsartan and enalapril for the overall KCCQ score were below a minimal clinically important difference of five points (mean difference [MD] 1.9 points). Similar treatment effects were observed for the KCCQ clinical summary score (MD 1.6) and across the individual domains of the KCCQ (MD range 1.4 to 2.6). No data were reported for the EQ-5D index scores; however, the MD in the visual analogue scale (VAS) was 0.8, which may be considered clinically unimportant on this 0- to 100-point scale.

The key limitation of the PARADIGM-HF trial relates to the external validity. The trial used an enrichment design, with specific criteria for LVEF, comorbidities, BNP, and NT-proBNP levels. Of the 18,000 patients screened, 42% were excluded. Enrolment was further restricted to patients who demonstrated adequate tolerability to the study drugs (20% excluded). The clinical expert consulted for this review stated that the enrolled population differed in a number of key characteristics from Canadian HF patients seeking treatment. Moreover, practice patterns differ across regions, and a limited number of North American patients were enrolled (N = 602). The proportion of patients who had an ICD or CRT device implanted was low in the overall PARADIGM-HF population (16%) compared with the US patients enrolled (60%). Given the more prevalent use of device therapy in North America, there is some uncertainty that the same mortality benefits, as observed in the PARADIGM-HF trial, may be achieved in the real-world North American setting. In the PARADIGM-HF trial, the median follow-up was 27 months; additional data are needed to determine if the benefits of sacubitril/valsartan extend beyond this time frame.

Harms

During the (DB) period of the PARADIGM-HF study, 81% and 83% of patients reported an adverse event (AE), 46% and 51% reported a serious adverse event (SAE), and 11% and 12% stopped treatment due to AEs in the sacubitril/valsartan and enalapril groups, respectively. Besides cardiac failure, the most commonly reported AEs in both groups were cough, hyperkalemia, renal impairment, and hypotension (10% to 18%). Hypotension was reported more frequently among patients who received sacubitril/valsartan than enalapril (exposure-adjusted incidence rate 13.2 versus 9.5 events/100 patient-years, respectively); however, the incidence of serious hypotensive events was similar between groups. Renal dysfunction, hyperkalemia, and cough were reported more frequently in the enalapril group than in the sacubitril/valsartan group.

In the PARADIGM-HF trial, a total of 54 confirmed angioedema events were reported, of which 25 occurred during treatment with enalapril (run-in: 15 events; DB: 10 events) and 29 occurred during sacubitril/valsartan treatment (run-in: 10 events; DB: 19 events). Five patients required hospitalization to manage angioedema (enalapril group: two; sacubitril/valsartan group: three), but no events resulted in airway compromise. Data from the DB period suggest that angioedema may be more frequent with sacubitril/valsartan; however, additional information is required.

The AE data from PARADIGM-HF should be interpreted with caution due to the design of trial, which underestimates the incidence of AEs. The study inclusion criteria selected patients who were previously receiving ACEI or ARB therapy, and required that patients demonstrate the ability to tolerate the study

drugs at specific doses. During the run-in periods, an additional 20% of patients withdrew, mainly due to tolerability issues. While the average treatment duration was two years, longer-term safety data are needed. A safety assessment in the broader HF population is also required to determine the tolerability of this new drug once deployed in clinical practice.

Potential Place in Therapy

According to the clinical expert involved in the review, there is an unmet need to further reduce morbidity and mortality events in HF patients. While the addition of a new class of medications would be a potentially important advance, the clinical expert noted that other avenues exist to address this unmet need, which, if optimized, could perhaps reduce the need for new pharmacotherapies for HF. These would include ensuring that patients receive:

- appropriate non-pharmacologic advice on their illness
- appropriate use of medications (diuretics, digitalis, ACEIs, ARBs, beta blockers, and aldosterone antagonists)
- medical devices (ICDs, CRT) in appropriate patient subgroups

and especially

- ready access to health professionals with medical and para-medical expertise in HF.

According to the clinical expert consulted, sacubitril/valsartan is likely to have utility in meeting this unmet need, although some uncertainty remains despite the fact that a large randomized controlled trial (RCT) (PARADIGM-HF) has shown a statistically significant decrease in the combined end point of CV mortality and HF hospitalization. The main area of uncertainty is the generalizability of the study results to the Canadian HF population, as previously described.

The clinical expert consulted by CADTH suggested that, based on the clinical evidence available and the existing unmet need, the patient subpopulations that may benefit most are those with an ejection fraction of less than 35% and NYHA functional class II HF. However, the clinical expert suggested that ideally the results for the effects of sacubitril/valsartan should be replicated in another large and longer-duration RCT, given the evidence for these subgroups comes from a single RCT with relatively small sample sizes in certain subgroups (and reduced precision), and the aforementioned concerns regarding generalizability.

Conclusions

Sacubitril/valsartan was associated with statistically significant differences in CV mortality or HF hospitalizations compared with enalapril, in a select population of stable HF patients with reduced ejection fraction, who were also receiving background therapies for HF. Sacubitril/valsartan did not show any clinically important differences over enalapril in terms of other CV outcomes (myocardial infarction, stroke or new onset atrial fibrillation), quality of life, or functional status, based on data from a single RCT.

Sacubitril/valsartan was associated with an increased frequency of hypotension compared with enalapril. Additional data are required to determine if the risk of angioedema is increased with sacubitril/valsartan, and to determine the longer-term safety of this first-in-class therapy.

The enrichment criteria applied in the selection of patients for study inclusion, and restriction to patients with tolerability to both the study and comparator drugs during the run-in phases, underestimates the incidence of AEs and limits the external validity of the findings.

TABLE 1: SUMMARY OF RESULTS

	PARADIGM-HF			
Outcome	**Enalapril N = 4,212**	**Sacubitril/ Valsartan N = 4,187**	**Treatment effect sacubitril/valsartan versus enalapril**	***P* value**
Mortality	**n (%)**	**n (%)**	**HR (95% CI)**	
All-cause mortality	835 (20)	711 (17)	0.84 (0.76 to 0.93)	0.0005[a]
CV mortality	693 (17)	558 (13)	0.80 (0.71 to 0.89)	< 0.0001[b]
Primary outcome				
CV death or HF hospitalization[c]	1,117 (27)	914 (22)	0.80 (0.73 to 0.87)	< 0.0001[a]
Hospitalization[c]				
All-cause hospitalization	1,827 (43)	1,660 (40)	0.88 (0.82 to 0.94)	0.0001[d]
HF hospitalization	658 (16)	537 (13)	0.79 (0.71 to 0.89)	< 0.0001[b]
CV hospitalization	1,344 (32)	1,210 (29)	0.88 (0.81 to 0.95)	0.0008[d]
Other CV Outcomes				
MI (fatal or non-fatal)	119 (2.8)	115 (2.8)	0.96 (0.74 to 1.24)	0.73[d]
Stroke (fatal or non-fatal)	110 (2.6)	109 (2.6)	0.99 (0.76 to 1.29)	0.92[d]
Resuscitated sudden death	28 (0.7)	16 (0.4)	0.56 (0.31 to 1.04)	0.068[d]
New onset AF[e]	83/2,638 (3.2)	84/2,670 (3.2)	0.97 (0.72 to 1.31)	0.42
KCCQ overall score	**N = 3,638**	**N = 3,643**	**LS mean difference (95% CI)**	***P* value**
Change from baseline to 8 months, LS mean (SE)	–4.17 (0.36)	–2.35 (0.36)	1.91 (0.92 to 2.91)	0.0002[d]
Withdrawals	**N = 4,212**	**N = 4,187**		
Discontinued study during double-blind period	862 (20)	741 (18)	NR	NR
WDAE	**N = 4,229**	**N = 4,203**		
Stopped treatment due to adverse events	516 (12)	450 (11)	NR	NR
SAE				
Patients with 1 or more SAE	2,142 (51)	1,937 (46)	NR	NR
Notable Harms				
Angioedema	10 (0.24)	19 (0.45)	NR	NR
Hypotension	786 (18.6)	1,027 (24.4)	NR	NR
Hyperkalemia	605 (14.3)	500 (11.9)	NR	NR
Renal impairment	746 (17.6)	682 (16.2)	NR	NR
Cough	601 (14.2)	474 (11.3)	NR	NR

AF = atrial fibrillation; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; KCCQ = Kansas City Cardiomyopathy Questionnaire; LS = least squares; MI = myocardial infarction; NR = not reported; SAE = serious adverse event; SE = standard error; WDAE = withdrawal due to adverse event.

[a] Statistical significance (*P* values are one-sided), according to multiple testing procedure at overall alpha level of 0.001.

[b] Statistical testing of the individual components of the primary composite outcome was not part of the planned statistical analysis or multiple testing procedures. One-sided *P* values were reported.

[c] First hospitalization event.

[d] Exploratory outcomes; two-sided *P* value with alpha of 0.05.

[e] This secondary outcome was based on a subgroup of patients without AF at baseline (*P* value one-sided).

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

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 underlying etiologies include disorders of the pericardium, myocardium, endocardium, heart valves, great vessels, or certain metabolic abnormalities.[1] The primary symptoms are dyspnea and fatigue, and may also include fluid retention. Patients report that HF can have a substantial impact on their exercise tolerance and quality of life, limiting their ability to work, participate in recreational activities, and to complete activities of daily living.

There are an estimated 600,000 Canadians with HF and roughly 50,000 new cases are diagnosed each year.[2] Approximately half of HF patients have a reduced left ventricular ejection fraction (LVEF) (which may be defined as LVEF ≤ 40%); it is in this population that the evidence base regarding treatment is more well established.[1] The annual mortality rate for HF ranges between 5% and 50%, depending on the severity of symptoms, heart function, age, and other factors.[2] Among those with HF, the most common causes of death are arrhythmias, including sudden death and pump failure.[2] In the US, one in nine deaths are associated with HF, according to information from death certificates.[1] 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 four or more times.[1]

The New York Heart Association (NYHA) functional classification provides a means to classify patients with HF according to functional capacity, as described in Table 2.

TABLE 2: NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Description
I	No limitations of physical activity
II	Slight limitation of physical activity, but no symptoms at rest
III	Marked limitation of physical activity, but no symptoms at rest
IV	Inability to perform any physical activity without discomfort; symptoms may be present at rest

Source: HF Guideline.[1]

1.2 Standards of Therapy

Non-pharmacologic therapies for HF include sodium restriction, exercise programs, and education on disease management.[1]

The key pharmacotherapies for patients with HF and reduced ejection fraction include angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), beta blockers, and aldosterone antagonists (also known as mineralocorticoid receptor antagonists). Canadian and US guidelines recommend an ACEI plus a beta blocker for all patients, unless contraindicated, as these therapies have been shown to reduce morbidity and mortality.[1,4] ARBs are usually recommended as second-line therapy in patients who are intolerant to ACEIs. Aldosterone antagonists may also reduce morbidity and mortality, and are recommended as add-on therapy in select patients with NYHA functional class II to IV HF.[1,4] Diuretics may provide symptomatic relief of dyspnea or edema in patients

with fluid retention. A subset of patients may receive benefits from implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) devices.[1,4]

1.3 Drug

Entresto is a sodium hydrate complex of two active drugs: sacubitril, a neprilysin inhibitor; and valsartan, an ARB. It is available as combination tablets that contain sacubitril/valsartan in the following fixed-dose ratios: 24.3 mg/25.7 mg, 48.6 mg/51.4 mg, and 97.2 mg/102.8 mg, respectively.[3] Sacubitril is a first-in-class neprilysin inhibitor that increases levels of peptides degraded by neprilysin (also known as neutral endopeptidase). Valsartan blocks the angiotensin type 1 (AT_1) receptor, inhibiting angiotensin II. The result is vasodilation, natriuresis, diuresis, and inhibition of renin and aldosterone release.[3]

Sacubitril/valsartan is indicated for the treatment of heart failure with reduced ejection fraction in patients with NYHA class II or III HF, to reduce the incidence of cardiovascular (CV) death and HF hospitalization.[3] According to the product monograph, it should be used in clinically stable patients in conjunction with other HF treatments, such as diuretics, beta blockers, and aldosterone antagonists, and in place of ACEI or ARB therapy. Concurrent use of sacubitril/valsartan with an ACEI or another ARB is contraindicated and a 36-hour washout period between stopping and starting therapies is recommended to reduce the risk of angioedema.[3] Sacubitril/valsartan treatment should not be initiated in patients with acute decompensated HF, clinically relevant ischemic events (e.g., acute myocardial infarction or cerebral infarction), or those with significant hypotension, elevated serum potassium, or reduced renal function.[3] The recommended starting dose for most patients is sacubitril 48.6 mg/valsartan 51.4 mg twice daily orally, increased every two to four weeks, as tolerated, to the target dose of sacubitril 97.2 mg/valsartan 102.8 mg twice daily. Lower initial doses may be necessary for patients at risk for hypotension or those on lower doses of ACEI or ARB prior to starting sacubitril/valsartan.[3]

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The key characteristics of ACEI and ARB, which may be replaced by sacubitril/valsartan, are listed in Table 3.

TABLE 3: KEY CHARACTERISTICS OF PHARMACOTHERAPIES FOR HEART FAILURE (BY DRUG CLASS)

	ARNI	ACEI	ARB
Mechanism of Action	Inhibits the breakdown of peptides by neprilysin and blocks the binding of angiotensin II to the AT_1 receptor	Inhibits the conversion of angiotensin I to angiotensin II, thereby inhibiting the RAAS.	Selectively blocks the binding of angiotensin II to the angiotensin type 1 (AT_1) receptor and thereby inhibit the RAAS.
Indication	HFrEF in patients with NYHA Class II or III HF	symptomatic congestive HF, essential hypertension	chronic heart failure, essential hypertension

	ARNI	ACEI	ARB
Route of Administration	oral	oral	oral
Maximum Recommended Dose	Sacubitril 24.3 mg/valsartan 25.7 mg to sacubitril 97.2 mg/valsartan 102.8 mg twice daily	Captopril: 50 mg three times daily Enalapril: 10 to 20 mg twice daily Fosinopril: 40 mg daily Lisinopril: 20 to 40 mg daily Perindopril: 8 to 16 mg daily Quinapril: 20 mg twice daily Ramapril: 10 mg daily[a] Trandolapril: 4 mg daily[a]	Candesartan: 32 mg daily Losartan: 50 to 150 mg daily[a] Valsartan: 160 mg twice daily
Serious Side Effects/ Safety Issues	Hypotension, renal dysfunction, hyperkalemia, angioedema Contraindicated with ACEI, ARB or aliskiren, and in patients with symptomatic hypotension, history of angioedema, or pregnancy Caution in patients with renal artery stenosis	Hypotension, renal dysfunction, hyperkalemia, angioedema, cough, neutropenia/agranulocytosis, impaired liver function Contraindicated with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment, patients with history of angioedema, pregnancy Caution in patients with renal artery stenosis	Hypotension, renal dysfunction, hyperkalemia, angioedema Contraindicated with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment, patients with history of angioedema, pregnancy Caution in patients with renal artery stenosis, severe liver impairment
Other	36-hour washout period required between ACEI and ARNI therapy		Generally reserved for use in patients who cannot tolerate ACEI

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor and neprilysin inhibitor; AT_1 = angiotensin type 1; HFrEF = heart failure with reduced ejection fraction; HF = heart failure; NYHA = New York Heart Association; RAAS = renin-angiotensin-aldosterone system.

[a] Not approved for use in HF in Canada.

Source: Yancy et al.,[1] Entresto Product monograph (Novartis),[3] Canadian Pharmacists Assocation.[5,6]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of sacubitril/valsartan combination therapy tablets for the treatment of patients with NYHA class II or III HF and reduced ejection fraction.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	NYHA Class II or III HF with reduced ejection fraction Subgroups: • NYHA functional class • Ejection fraction • Region • ICT/CRT • Ischemic cardiomyopathy
Intervention	Sacubitril plus valsartan in combination with other HF therapies
Comparators	Standard HF therapies, such as ACEI (or ARB) + BB (may also include eplerenone, spironolactone, digoxin, diuretics etc.)
Outcomes	**Key efficacy outcomes:** All-cause mortality **Other efficacy outcomes:** Death from cardiovascular causes Sudden cardiac death Fatal or non-fatal myocardial infarction Fatal or non-fatal stroke All-cause hospitalizations • HF-related • cardiovascular-related Development of new or worsening atrial fibrillation Implantation of cardiac defibrillator or CRT LVEF Quality of Life Change in NYHA class **Harms outcomes:** AEs, SAEs, WDAEs, notable harms (angioedema, hyperkalemia, hypotension, renal impairment, cough)
Study Design	Published and unpublished phase 3 RCTs

ACEI = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin receptor blocker; BB = beta blocker; CRT = cardiac resynchronization therapy; DB = double-blind; HF = heart failure; ICD = implantable cardiac defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Entresto (sacubitril/ valsartan).

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on October 19, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on February 17, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), and Internet search. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) 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 one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in APPENDIX 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

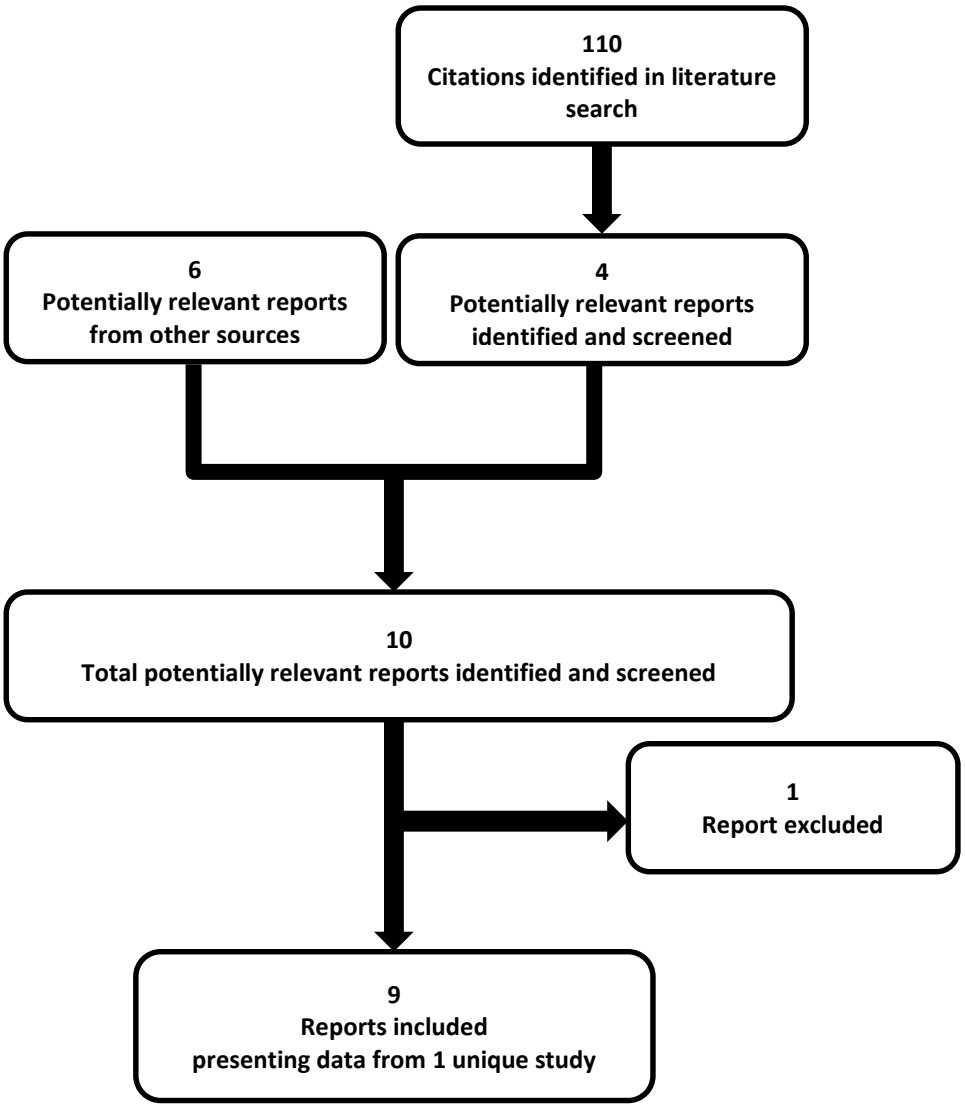


TABLE 5: DETAILS OF INCLUDED STUDIES

		PARADIGM-HF
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	North, South and Central America; Europe; Asia; South Africa
	Randomized (N)	8,442
	Inclusion Criteria	• ≥ 18 years with HF and EF ≤ 40% (or ≤ 35% with protocol amendment) • NYHA class II, III or IV symptoms • Plasma BNP ≥ 150 pg/mL or NT-proBNP ≥ 600 pg/mL[a] • On a stable dose of ACEI or ARB plus BB for past 4 weeks (ACEI/ARB dose equivalent to ≥ 10 mg enalapril per day)
	Exclusion Criteria	• Symptomatic hypotension • Systolic BP < 100 mm Hg at screening or 95 mm Hg at randomization • eGFR < 30 mL/min/1.73 m^3 or decrease in eGFR > 25% (amended to > 35%) between screening and randomization • Serum potassium level > 5.3 mmol/L • History of angioedema • Unacceptable adverse effects with ACEI or ARB
DRUGS	**Run-in**	Patients switched from previous ACEI or ARB to: • single-blind enalapril 10 mg twice daily for 2 to 4 weeks; If therapy tolerated, then switched to: • single-blind sacubitril/valsartan; titrated from sacubitril 48.6 mg/valsartan 51.4 mg twice daily to sacubitril 97.2 mg/valsartan 102.8 mg twice daily, for 3 to 6 weeks If no unacceptable adverse effects, patients were randomized to DB treatment.
	Intervention	sacubitril 97.2 mg/valsartan 102.8 mg twice daily
	Comparator(s)	enalapril 10 mg twice daily
DURATION	**Phase**	3
	Enalapril Run-in	2 to 4 weeks
	Sacubitril/valsartan Run-in	3 to 6 weeks
	DB	Event-driven (planned to be stopped once 2,410 primary outcome events occurred)
OUTCOMES	**Primary End Point**	Composite of cardiovascular death or first HF-related hospitalization
	Other End Points	• time to death (all-cause) • change from baseline to 8 months in KCCQ clinical summary score • time to new onset atrial fibrillation • time to first decline in renal function • harms
NOTES	**Publications**	McMurray 2014[7]

ACEI = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin receptor blocker; BB = beta blocker; BNP = B-type natriuretic peptide; BP = blood pressure; CDR = CADTH Common Drug Review; DB = double-blind; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal prohormone B-type natriuretic peptide; NYHA = New York Heart Association; RCT = randomized controlled trial.

[a] Plasma BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL levels if patient had been hospitalized for HF within the past 12 months.

Note: Six additional reports were included (FDA Medical and Statistical reports,[8,9] Desai 2015,[10] Packer 2015,[11] CDR Submission,[12] Health Canada Reviewers Report.[2]).

Source: Clinical Study Report,[13,14] McMurray.[7]

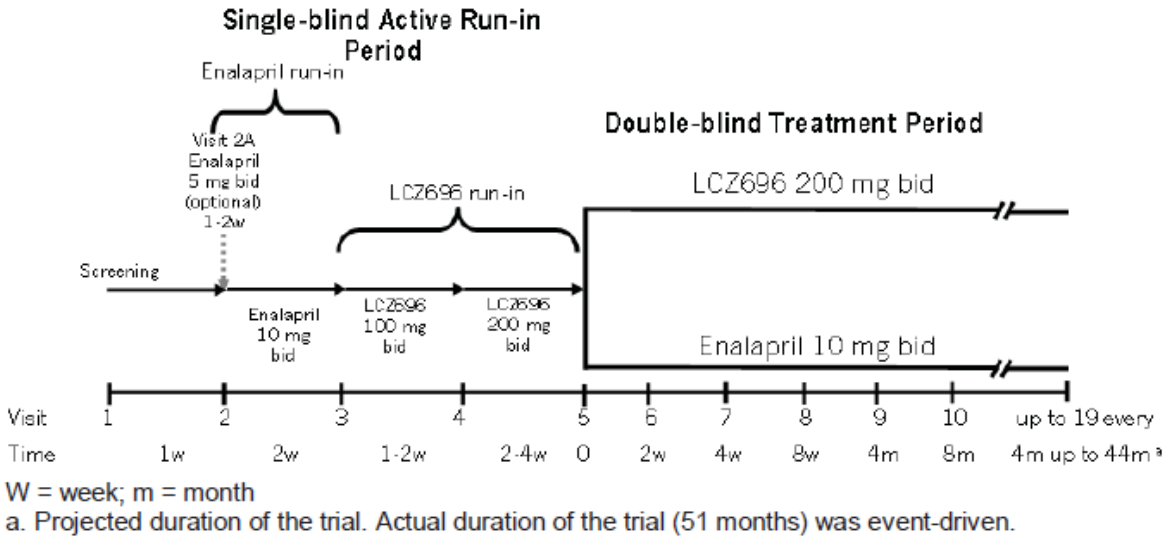
3.2 Included Studies

3.2.1 Description of studies

PARADIGM-HF was a randomized, double-blind (DB), active-controlled trial designed to test the superiority of sacubitril/valsartan versus enalapril in patients with heart failure and reduced ejection fraction.

The trial used an enrichment enrolment design. Those who met the study's eligibility criteria were enrolled in two consecutive run-in periods during which all patients received single-blind enalapril (two to four weeks), and if no unacceptable adverse events (AEs) occurred, were switched to single-blind sacubitril/valsartan (three to six weeks) (Figure 2). The total run-in period was five to 10 weeks in duration. Patients who tolerated both active treatments were then randomized 1:1 (stratified by site) to DB, double-dummy enalapril (10 mg twice daily) or sacubitril/valsartan (97.2 mg/102.8 mg twice daily). The study was event-driven, thus patients remained in the trial (regardless of whether they received study medication) until the projected number of events (2,410) was reached or early study termination if pre-specified efficacy or safety criteria were met. PARADIGM-HF was stopped on March 2014 based on the results of the third interim analysis (1,744 adjudicated events), which met efficacy-stopping criteria for the primary outcome of CV death or HF hospitalization. The median follow-up time was 27 months (maximum 51 months) after randomization.

FIGURE 2: STUDY DESIGN OF PARADIGM-HF TRIAL



bid = twice daily; LCZ696 200 mg = sacubitril 97.2 mg /valsartan 102.8 mg; m = month; w = week.
Source: Clinical Study Report, p. 185.[13]

3.2.2 Populations

a) Inclusion and exclusion criteria

PARADIGM-HF enrolled adults with HF and a reduced ejection fraction who had NYHA class II, III, or IV symptoms. Initially, those with an LVEF ≤ 40% were included, but a protocol amendment changed this to ≤ 35% after 1,285 patients had been enrolled. This change was made after the EMPHASIS-HF trial (eplerenone versus placebo) was published,[15] and the sponsor anticipated that an increase in the use of aldosterone antagonists could lower the incidence of HF-related events. The lower LVEF threshold was expected to increase the number of primary outcome events in PARADIGM-HF.

The inclusion criteria specified that all patients were treated with an ACEI or ARB plus a beta blocker (unless contraindicated) at stable doses for at least four weeks prior to enrolment. In addition, all patients should have been considered for aldosterone antagonist therapy, taking into account their renal function, serum potassium, and tolerability. If given, the dose of aldosterone antagonists should be stable for the four weeks prior to enrolment. The study also set minimum B-type natriuretic peptide (BNP) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) serum levels as part of the prognostic enrichment criteria. The study excluded patients who had a history of intolerance to ACEI or ARBs, or were more likely to be intolerant of the study drugs. The study also excluded those with acute coronary syndrome or a cerebrovascular event, and those with cardiac, carotid, or other major CV surgery or intervention, including an ICD or CRT device, within the past three months.

b) Baseline characteristics

The patients randomized to the DB period had a mean age of 63.8 years, were predominantly male (78%), and had a mean LVEF of 29.5% (Table 6). The majority of patients (69% to 72%) were NYHA functional class II, and 23% to 25% were class III. Approximately one-third of patients had been diagnosed with HF within the past year, one-third within one to five years, and one-third over five years ago. As per the inclusion criteria, all patients were treated with either an ACEI or ARB prior to enrolment and 93% were receiving beta blockers.

The patient characteristics at the start of the DB period were generally balanced between the enalapril and sacubitril/valsartan treatment groups. The characteristics of those who entered the run-in periods and those randomized in the DB period were similar, with the exception of functional class. More patients with functional class I or II HF entered the DB period than the run-in periods.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic	Run-in period 1[a]	Run-in period 2[a]	DB period[b] FAS	
Treatment	**Enalapril**	**Sacubitril/valsartan**	**Enalapril**	**Sacubitril/valsartan**
N	10,513	9,419	4,212	4,187
Age, mean years (SD)	64.0 (11.5)	63.9 (11.5)	63.8 (11.3)	63.8 (11.5)
Female, n (%)	2,345 (22)	2,072 (22)	953 (23)	879 (21)
Systolic BP, mean mm Hg (SD)	128 (17)	128 (17)	121 (15)	122 (15)
BMI, mean kg/m^2 (SD)	28.0 (5.6)	28.0 (5.6)	28.2 (5.5)	28.1 (5.5)
LVEF, mean % (SD)	29.3 (6.3)	29.4 (6.3)	29.4 (6.3)	29.6 (6.1)
BNP, median pg/mL (IQR)[c]	261 (156 to 491)	259 (156 to 483)	251 (154 to 465)	255 (155 to 474)
NT-proBNP, median pg/mL (IQR)[c]	1,684 (908 to 3,466)	1,650 (897 to 3,369)	1,594 (886 to 3,306)	1,631 (886 to 3,156)
eGFR, mean mL/min/1.73 m^2 (SD)	67.3 (20.1)	67.7 (19.6)	67.8 (20.3)	67.6 (19.9)
NYHA functional class, n (%)				
I	41 (< 1)	33 (< 1)	209 (5)	180 (4)
II	6,707 (64)	6,059 (64)	2,921 (69)	2,998 (72)
III	3,581 (34)	3,166 (34)	1,049 (25)	969 (23)
IV	168 (2)	149 (2)	27 (1)	33 (1)

Characteristic	Run-in period 1[a]	Run-in period 2[a]	DB period[b] FAS	
Time since diagnosis of HF, n (%)				
≤ 1 year	3,116 (30)	2,822 (30)	1,248 (30)	1,275 (30)
> 1 to 2 years	1,471 (14)	1,317 (14)	590 (14)	588 (14)
> 2 to 5 years	2,553 (24)	2,298 (24)	1,021 (24)	1,033 (25)
> 5 years	3,372 (32)	2,982 (32)	1,353 (32)	1,291 (31)
Medical history, n (%)				
Ischemic cardiomyopathy	6,378 (61)	5,662 (60)	2,530 (60)	2,506 (60)
Hypertension	7,333 (70)	6,593 (70)	2,971 (71)	2,969 (71)
Diabetes	3,667 (35)	3,266 (35)	1,456 (35)	1,451 (35)
Atrial fibrillation	3,769 (36)	3,400 (36)	1,557 (37)	1,501 (36)
Hospitalization for HF	6,590 (63)	5,917 (63)	2,667 (63)	2,607 (62)
Myocardial infarction	4,582 (44)	4,096 (43)	1,815 (43)	1,817 (43)
Stroke	928 (9)	830 (9)	370 (9)	355 (8)
Pre-trial use of ACEI	8,131 (77)	7,327 (78)	3,266 (78)	3,266 (78)
Pre-trial use of ARB	2,405 (23)	2,120 (23)	963 (23)	929 (22)
Treatments at study start or randomization				
Beta blocker	9,866 (94)	8,868 (94)	3,912 (93)	3,899 (93)
Diuretic	8,705 (83)	7,787 (83)	3,375 (80)	3,363 (80)
Aldosterone antagonist	6,201 (60)	5,527 (59)	2,400 (57)	2,271 (54)
ICD[d]	1,105 (11)	966 (10)	417 (10)	417 (10)
Pacemaker[d]	1,412 (13)	1,239 (13)	532 (13)	556 (13)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; BP = blood pressure; DB = double-blind; eGFR = estimated glomerular filtration rate; FAS = full analysis set; HF = heart failure; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation. NT-ProBNP = N-terminal prohormone B-type natriuretic peptide.

[a] Patient characteristics for the run-in groups were based on measurements at the screening visit.

[b] Patient characteristics for the double-blind period were based on the last available measurement during the run-in phase.

[c] Converted from pmol/L to pg/mL by multiplying by 3.47 for BNP and 8.46 for NT-proBNP.[13]

[d] Based on data collected at screening visit.

Source: Clinical Study Report,[13] McMurray 2014.[7]

3.2.3 Interventions

In PARADIGM-HF, enalapril 10 mg twice daily and sacubitril 97.2 mg/valsartan 102.8 mg twice daily were the target study dosages. Based on pharmacokinetic analysis, a sacubitril 97.2 mg/valsartan 102.8 mg tablet delivers the equivalent of 160 mg valsartan.[12,13] For the enalapril run-in period, investigators could initiate enalapril at a lower dose (5 mg twice daily) in patients who were previously taking an ARB or were on a lower dose of ACEI before the study start. In the sacubitril/valsartan run-in period, the initial dose was sacubitril 48.6 mg/valsartan 51.4 mg twice daily, increased to sacubitril 97.2 mg/valsartan 102.8 mg twice daily after one to two weeks. During the run-in, sacubitril/valsartan could be temporarily down-titrated to sacubitril 48.6 mg/valsartan 51.4 mg twice daily with a subsequent re-challenge using the target dose. Patients who could not tolerate enalapril 10 mg or sacubitril 97.2 mg/valsartan 102.8 mg twice daily for the last two weeks of the run-in periods were withdrawn from the study.

Patients that completed both run-in periods entered the DB period and were randomized to enalapril 10 mg or sacubitril 97.2 mg/valsartan 102.8 mg twice daily. In the DB period, patients who were unable to tolerate the target study doses could be down-titrated to a lower dose at the investigator's discretion (enalapril 2.5 mg or 5 mg twice daily; sacubitril 24.3 mg/valsartan 25.7 mg or sacubitril 48.6 mg/valsartan 51.4 mg twice daily). Modification of other non–disease-modifying HF medications was recommended before study drug dosages were reduced. Any patients whose study drug dose was reduced were to be re-challenged with higher study drug doses as soon as possible at the investigator's discretion. Those who could not tolerate higher doses could continue receiving treatment with the lower doses. Patients who permanently stopped study drug treatment continued study visits and study measurements until the end of the trial.

A double-dummy design was used to maintain blinding, and patients received active treatment tablets as well as placebo tablets matching the opposite study drug in the single-blind run-in periods and the DB period. There were two washout periods of approximately 36 hours after each run-in period to minimize the risk of angioedema due to overlapping angiotensin-converting enzyme neprilysin inhibition.

All patients stopped ACEI or ARB therapy before receiving any study drug in the run-in or DB periods, but continued all other HF medications. The proportion of patients on key HF medications was similar in the enalapril and sacubitril/valsartan groups throughout the DB period (Table 7). In the overall population, approximately 16% of patients had either an ICD or CRT device implanted.

TABLE 7: USE OF KEY CONCOMITANT TREATMENTS DURING DOUBLE-BLIND PERIODS

	PARADIGM-HF			
	Enalapril		**Sacubitril/valsartan**	
Drug class, n (%)	**At randomization N = 4,229**	**Year 3 N = 1,003**	**At randomization N = 4,203**	**Year 3 N = 1,002**
Aldosterone antagonists	2,417 (57)	445 (44)	2,292 (55)	423 (42)
Beta blockers	3,946 (93)	916 (91)	3,929 (94)	914 (91)
Digoxin derivatives	1,330 (31)	304 (30)	1,233 (29)	275 (27)
Diuretics	3,418 (81)	823 (82)	3,395 (81)	785 (78)
Statins	2,365 (56)	608 (61)	2,374 (57)	601 (60)
ICD[a]	620 (15)	NR	623 (15)	NR
CRT[b]	282 (7)	NR	292 (7)	NR
ICD and/or CRT[c]	687 (17)	NR	692 (16)	NR

CRT = cardiac resynchronization therapy; FAS = full analysis set; ICD = implantable cardioverter-defibrillator; NR = not reported.
[a] Includes any use of ICD including CRT-defibrillator in the FAS.
[b] Includes CRT-pacemaker and CRT-defibrillator in the FAS.
[c] The proportion of US patients with any ICD or CRT use was 60% and 62% in the sacubitril/valsartan and enalapril groups, respectively. Data not reported for Canadian participants.
Source: Clinical Study Report,[13] McMurray 2014.[7]

Median daily doses of key medications were similar in the treatment groups at the start of the DB period (Appendix 4, Table 16). Of those receiving beta blockers, 47% and 49% were on a dosage ≥ 50% of the recommended target beta blocker dose in the enalapril and sacubitril/valsartan groups, respectively. The proportion receiving ≥ 50% of the recommended target aldosterone antagonist dose was higher (enalapril: 82%, sacubitril/valsartan: 84%), but similar between treatment groups.

3.2.4 Outcomes

The primary outcome was the time to CV death or first HF hospitalization.
Secondary outcomes were as follows:

- time to all-cause mortality
- change from baseline to eight months in the clinical summary score (HF symptom and physical limitations) of the Kansas City Cardiomyopathy Questionnaire (KCCQ)
- time to new onset atrial fibrillation
- time to renal dysfunction defined as:
  - 50% decline in estimated glomerular filtration rate (eGFR) compared with baseline
  or
  - > 30 mL/min/1.73 m^2 decline in eGFR versus baseline to a value below 60 mL/min/1.73 m^2
  or
  - end-stage renal disease.

Other outcomes of interest in this review were reported as exploratory outcomes, including sudden cardiac death, myocardial infarction, stroke, all-cause or CV-related hospitalization, and quality of life (EuroQol 5-Dimensions Questionnaire [EQ-5D] and KCCQ overall and individual domain scores).

A blinded adjudication committee evaluated efficacy outcome events to determine if pre-specified end point criteria were met. The events assessed included all deaths, unplanned hospitalizations for HF, unplanned hospitalization for suspected myocardial infarction, non-fatal stroke, resuscitated sudden death, new onset atrial fibrillation, and renal dysfunction. All events were reviewed independently by two committee members, with disagreements resolved by the committee chairman.

The KCCQ is a self-administered 23-item quality of life questionnaire that measures HF-related physical limitations, symptoms (recent change over time, frequency, and severity), quality of life, self-efficacy, and social limitations.[16] Domain and summary scores range from 0 to 100 with higher scores indicating better health status or quality of life.[16] The clinical summary score reported in the PARADIGM-HF study was computed as the mean of the total HF symptom domain (frequency and severity) and the physical function domain. A minimally important clinical difference (MCID) of five points has been reported in the literature for the KCCQ overall score, which includes the physical function, symptom frequency and severity, quality of life, and social limitation domains.[17]

A serious adverse event (SAE) was defined as an event that resulted in death, was life-threatening, was a congenital anomaly or birth defect, required or prolonged hospitalization, or was a medically important event. All SAEs that occurred until 30 days after the patients stopped study participation were reported.

An independent Angioedema Adjudication Committee reviewed all potential angioedema events in a blinded manner and determined if the event met the criteria for an angioedema event. The severity of the event was rated as follows:

- no treatment administered or antihistamines only
- treated with catecholamines or steroids
- hospitalized but no mechanical airway protection
  - no airway compromise
  - airway compromise
- mechanical airway protection or death from airway compromise.

3.2.5 Statistical analysis

For the primary efficacy analysis, the time to first occurrence of either CV death or HF hospitalization, was analyzed using a Cox regression model with treatment group and region as fixed factors. Patients with no events were censored at the date of withdrawal of consent, date of last visit prior to loss to follow-up, analysis cut-off date, or date of death from non-CV causes, whichever came first. Kaplan–Meier survival curves were presented for each treatment group.

Secondary outcomes were tested only if the primary outcome was statistically significant. A sequentially rejective multiple-test procedure was used to control the alpha level across the primary and secondary endpoints. Secondary and exploratory time-to-event outcomes were also analyzed using a Cox regression model with treatment group and region as fixed factors. Time to new onset atrial fibrillation was analyzed for the subset of patients without atrial fibrillation at baseline. Change from baseline to eight months for the clinical summary score of the KCCQ questionnaire was analyzed using a repeated measures analysis of covariance (ANCOVA) model in which treatment, region, visit (month 4 and 8), and treatment-by-visit interaction were included as fixed effect factors, and the baseline value was included as a covariate. Patients whose language did not have a validated translation of the KCCQ were exempt from completing the questionnaire. All patients with at least one KCCQ data point during the DB period were included in the analysis. Missing data after death for the KCCQ questionnaire were imputed with zero (worst score) and other data were assumed missing at random. Sensitivity analyses were conducted using a pattern mixture model to impute missing KCCQ data or data that excluded patients who died before eight months. The post hoc analysis of the change in NYHA functional class was based on Cochran-Mantel-Haenszel test with modified ridit assessments and stratified by region. Patients who died or had missing data were excluded from the analysis of the change in functional class. A secondary analysis was conducted where patients who died were recorded as worsened (i.e., class V).

Several pre-specified subgroup analyses were conducted for the primary and secondary outcomes using the same models but also including treatment-by-subgroups interaction terms. In addition, numerous exploratory outcomes were analyzed. There was no multiplicity adjustment for subgroup or exploratory analyses.

Efficacy analyses included all events that occurred in the DB period up to March 31, 2014. Patients who permanently stopped study treatment continued to be followed in the trial unless the patient withdrew consent.

PARADIGM-HF was an event-driven trial, with sample size estimations based on a 1:1 randomization and a one-sided significance level of 0.02314, which was adjusted for interim efficacy analyses. A total of 1,229 CV deaths were needed for 80% power to detect a 15% hazard reduction using the log-rank test. Assuming an annual 7% CV death rate in the enalapril group, an enrolment period of 18 to 22 months, and a minimum follow-up of 21 months, a sample size of 7,980 patients was needed. This sample size would provide 97% power to detect a 15% hazard reduction in the primary composite outcome, assuming the annual event rate was 14.5% (based on the CHARM-Added trial)[18] in the enalapril group (a total of 2,410 CV deaths or HF hospitalizations). The study was to end once 2,410 CV deaths or HF hospitalizations occurred unless the study was terminated early due to statistically significant interim efficacy analyses or critical safety concerns. Three interim analyses were planned for the primary composite outcome and CV deaths once one-third, one-half, and two-thirds of events occurred. One-sided testing was performed for the primary outcome with adjustment to control the overall type I error of 0.025. The Haybittle-Peto type of boundary was used in the interim analyses to assess superiority, producing an alpha of 0.0001, 0.001, and 0.001 (one-sided) at the first, second, and third interim

analyses. The study was stopped early if statistically significant results above the planned boundary were observed for both the primary composite outcome and for CV deaths. Interim analyses were conducted by an independent statistician and the results reviewed by an independent data monitoring committee. As the study was stopped at the third interim analysis, a one-sided alpha of 0.001 was used for the formal significance test.

a) Analysis populations

The enrolled set included all patients who received at least one dose of run-in study drug. The randomized set included all patients who completed the run-in periods and who received a randomization number.

The efficacy analyses were based on the full analysis set (FAS), which included all randomized patients except:

- patients who were inadvertently randomized (those who had not qualified for randomization and had not received study drug)
- patients whose site was excluded based on serious Good Clinical Practice violations.

The exclusion of patients from the FAS was done in a blinded manner prior to the database lock. Patients were analyzed according to the treatment assigned at randomization.

The safety set included all randomized patients who received at least one dose of study drug during the DB period. The per-protocol set included FAS patients who did not have any major protocol deviations during the DB period.

3.3 Patient Disposition

Of the patients screened for entry into PARADIGM-HF, 42% were excluded. The most common reasons for screen failure were low BNP/NT-proBNP levels (62%), hyperkalemia (19%), eGFR < 30 mL/min/1.73m^2 (6%), and withdrawal of consent (6%).

A total of 10,513 patients entered study treatment, and of these, 10% were excluded in each of the run-in periods, leaving 8,442 patients who were randomized to start the DB treatment period (Table 8). The primary reasons for exclusion during the enalapril and sacubitril/valsartan run-in periods were AEs or abnormal test results (6%), and withdrawal of consent (1%) (Appendix 4, Table 17).

Among those who entered the DB period, 20% and 18% did not complete the study and the primary reason for discontinuation was death for 20% and 17%, in the enalapril and sacubitril/valsartan groups, respectively. The number of patients who withdrew for reasons other than death was similar between groups. Overall, 30% of patients stopped treatment during the DB period but continued to be followed. The reasons for stopping treatment are described in Section 3.4. The vital status was unknown for nine patients in the enalapril group and 11 patients in the sacubitril/valsartan group.

TABLE 8: PATIENT DISPOSITION

	PARADIGM-HF	
	Enalapril	**Sacubitril/valsartan**
Screened, N	18,071	
Enalapril run-in period, N	10,513[a]	
Sacubitril/valsartan run-in period, N (%)	9,419 (90)[b]	
Randomized, N (%)	8,442 (80)[b]	
	4,233	4,209
Excluded from efficacy analysis, n (%)	21 (< 1)	22 (< 1)
Mis-randomized[c]	2	4
GCP violations[d]	19	18
Discontinued study during double-blind period, n (%)	862 (20)	741 (18)
Death	844 (20)	724 (17)
Lost to follow-up	5 (< 1)	2 (< 1)
Patient request	13 (< 1)	15 (< 1)
Unknown final status, n (%)	9 (0.2)	11 (0.3)
Median (IQR) duration of follow-up, years	2.25 (1.57 to 2.97)	2.27 (1.61 to 2.98)
FAS, n	4,212	4,187
PP, n	4,187	4,166
Safety, n	4,229	4,203

FAS = full analysis set; GCP = Good Clinical Practice; IQR = interquartile range; PP = per-protocol.
[a] Among the patients screened, 42% were excluded. The most common reasons for screen failure were low B-type natriuretic peptide/N-terminal prohormone B-type natriuretic peptide levels (62%), hyperkalemia (19%), eGFR < 30 mL/min/1.73m^2 (6%), and withdrew consent (6%).
[b] Per cent based on the number of patients who entered enalapril run-in phase.
[c] Six patients failed the sacubitril/valsartan run-in period but were randomized erroneously but never received study drug.
[d] 37 patients excluded from efficacy analyses because they were randomized at sites that were later closed due to serious GCP violations. Of these, 33 patients received study drug and were included in the safety analyses.
Source: Clinical Study Report.[13]

3.4 Exposure to Study Treatments

PARADIGM-HF was designed with a longer run-in period for sacubitril/valsartan (median 29 days) than enalapril (median 15 days).

During the DB period, the median treatment duration was similar for the enalapril and sacubitril/valsartan treatments groups (23.5 and 24.4 months, respectively) (Table 9). Approximately one-third of patients had at least one treatment interruption during the DB period. Of these, 27% of patients in the sacubitril/valsartan and 30% in the enalapril group had a treatment interruption that was seven days or longer.

Among patients who were taking study medications at the final visit, the mean daily dose of enalapril was 18.9 mg, and for sacubitril/valsartan was 374.9 mg. The distribution of dosages was similar between treatments (Table 9).

TABLE 9: TREATMENT DURATION AND EXPOSURE DURING DOUBLE-BLIND PERIOD

	PARADIGM-HF	
	Enalapril	**Sacubitril/valsartan**
	N = 4,229	**N = 4,203**
Duration of treatment (months), median (IQR)	23.5 (16.3 to 33.5)	24.4 (17.0 to 33.8)
Daily dose per patient (mg), mean (SD)	18.9 (2.9)	374.9 (62.4)
Proportion of patients at each daily dose level on last available record, n (%)		
Enalapril 20 mg or sacubitril 194.4/valsartan 205.6 mg	2,856 (68)	2,927 (70)
Enalapril 10 mg or sacubitril 97.2 mg/valsartan 102.8 mg	251 (6)	282 (7)
Enalapril 5 mg or sacubitril 48.6 mg/valsartan 51.4 mg	71 (2)	83 (2)
No drug	1,051 (25)	911 (22)

IQR = interquartile range; SD = standard deviation.
Source: Clinical Study Report.[13]

During the DB period, 32% and 28% of patients in the enalapril and sacubitril/valsartan groups, respectively, permanently discontinued treatment (Table 10). AEs (10% to 12%) and death (10% to 12%) were the most common reasons for discontinuation followed by patient's request (5%).

TABLE 10: PRIMARY REASON FOR TREATMENT DISCONTINUATION DURING DOUBLE-BLIND PERIOD

	PARADIGM-HF (Randomized set)	
	Enalapril	**Sacubitril/valsartan**
Randomized to double-blind period, n	4,233	4,209
Never received study drug	4 (0.1)	6 (0.1)
Permanently discontinued study drug, n (%)	1,353 (32.0)	1,182 (28.1)
Reason for discontinuation, n (%)		
Adverse event	510 (12.1)	437 (10.4)
Abnormal laboratory value	6 (0.1)	7 (0.2)
Unsatisfactory treatment effect	1 (<0.1)	0
Patients condition no longer required drug	4 (0.1)	3 (0.1)
Lost to follow-up	8 (0.2)	8 (0.2)
Administrative problems	9 (0.2)	12 (0.3)
Death	512 (12.1)	430 (10.2)
Protocol deviation	3 (0.1)	5 (0.1)
Patients request	219 (5.2)	208 (4.9)
Other	81 (1.9)	72 (1.7)
Missing end of treatment	3 (0.1)	5 (0.1)

Source: Clinical Study Report.[13]

3.5 Critical Appraisal

3.5.1 Internal validity

The study used accepted methods to randomize patients and conceal allocation (interactive voice or web response system) and patient groups appeared similar at the start of the DB period. A double-

dummy placebo design was used to maintain blinding. The dose of the active control, enalapril, was consistent with clinical trials that have shown a mortality benefit, and with clinical guidelines.[1,19] In addition, the use of other recommended therapies for HF (e.g., beta blockers, aldosterone antagonists, ICD or CRT devices) was similar between groups. The median treatment duration was similar between groups (enalapril: 23.5, sacubitril/valsartan: 24.5 months) and those who permanently stopped study drugs continued to be evaluated in the trial. A total of 1,603 patients (19%) did not complete the study; however, death was reported as the reason for withdrawal for most patients (n = 1,568). Overall, few threats to internal validity were identified.

The study included mortality, morbidity, and quality of life outcomes that were relevant to patients with HF. The key outcomes (deaths, hospitalizations or cardiac events) and angioedema-like AEs were adjudicated by a blinded committee.

The study was an event-driven trial, powered for an estimated 2,410 events (CV deaths or HF hospitalizations) to signal the end of the trial. The decision to stop the trial early was based on pre-specified stopping criteria for the primary composite outcome as well as CV mortality, analyzed by an independent statistician. The overall alpha error was controlled across the interim analyses and for the primary and secondary end points. The manufacturer analyzed multiple exploratory outcomes and subgroups, but did not institute procedures to control for multiplicity of statistical testing. Thus, the interpretation of statistically significant results should be made with caution due to the inflated type I error.

The efficacy analyses used a modified intention-to-treat population that excluded patients who were randomized in error and those from sites excluded due to clinical practice violations. The number of exclusions was small (n = 43) and they were distributed equally between groups. The treatment effect estimates for the change in KCCQ scores showed some sensitivity to the methods used to handle missing data; however, in all analyses, the differences between groups were small and the clinical importance was uncertain.

The study underestimates the incidence of adverse events, due to the study design, which excluded patients (through the selection criteria and run-in periods) who were unable to tolerate specific dosages of the study drugs.

3.5.2 External validity

The enrichment design applied in the screening phase to the selection of patients for inclusion, and exclusion of patients during the run-in phases, limits the external validity of the trial. Less than 60% of patients screened for the trial entered the treatment phase, with most patients excluded due to low BNP or NT-proBNP levels. Furthermore, 20% of patients who entered the run-in phase were excluded, mainly due to tolerability issues. According to the clinical expert consulted for this review, the randomized population was not representative of the HF population currently being treated in Canada.

Those enrolled represent a select subset of stable HF patients, with a younger mean age (64 years), who are predominantly male (78%), and with NYHA functional class II HF (70%) and LVEF < 35% (89%). The prognostic enrichment criteria selected patients with high BNP or NT-proBNP levels (or recent HF hospitalization), which likely represent a higher-risk HF population with a poorer prognosis. The trial excluded those with acute decompensated HF, clinically relevant ischemic events (e.g., acute myocardial infarction or cerebral infarction), or those with significant hypotension, elevated serum potassium, or reduced renal function. Thus the efficacy and safety in these patients is unclear. Moreover, patients

were all receiving established first-line pharmacologic treatments shown to reduce mortality and morbidity in HF. In general practice, the proportion of patients receiving an ACEI or ARB plus a beta blocker for HF is lower than reported in PARADIGM-HF. Further practice pattern differences were noted, with 16% of the overall PARADIGM-HF population having ICD or CRT devices, which may be considered low for North America (in PARADIGM-HF 60% of US patients had a device). Overall, a limited number of North American patients were enrolled in PARADIGM-HF (N = 602, 7%). As stated above, the PARADIGM-HF trial underestimates the incidence of AEs, due to the exclusion of patients at risk of, or with demonstrated poor tolerability to, an ACEI or sacubitril/valsartan.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

No data were available for the outcomes of implantation of ICD or CRT devices, or changes in LVEF.

3.6.1 Mortality

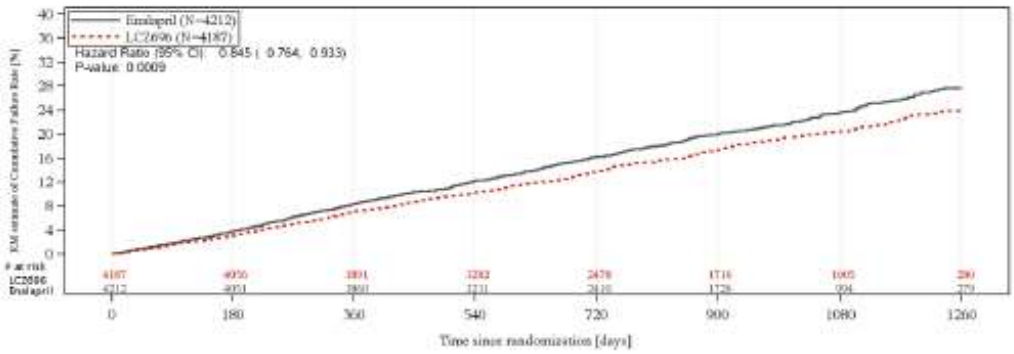
All deaths were adjudicated in a blinded manner by two members of the clinical end points committee. The between-reviewer agreement with regards to the cause of death (i.e., CV, non-CV, or other cause) was 93.5% (kappa 0.78) and for the specific cause of CV death was 74% (kappa 0.67).[10] The vital status of all patients was known except for 20 patients (enalapril: nine; sacubitril/valsartan: 11).

a) All-cause mortality

During the DB period, 835 deaths (20%) occurred in the enalapril group compared with 711 deaths (17%) in the sacubitril/valsartan group (Table 11). Sudden death (7.4% versus 6.0%), pump failure (4.4% versus 3.5%), and presumed CV death (2.2% versus 1.6%) were the most common causes of death in the enalapril and sacubitril/valsartan groups, respectively (Appendix 4, Table 18). The proportion of patients with a non-CV cause of death was similar between treatment groups (Appendix 4, Table 18).

The risk of death was statistically significantly lower in the sacubitril/valsartan versus the enalapril group (hazard ratio [HR] 0.84; 95% confidence interval [CI], 0.76 to 0.93) (Figure 3).

FIGURE 3: KAPLAN–MEIER PLOT FOR ALL-CAUSE MORTALITY BY TREATMENT GROUP (FULL ANALYSIS SET)

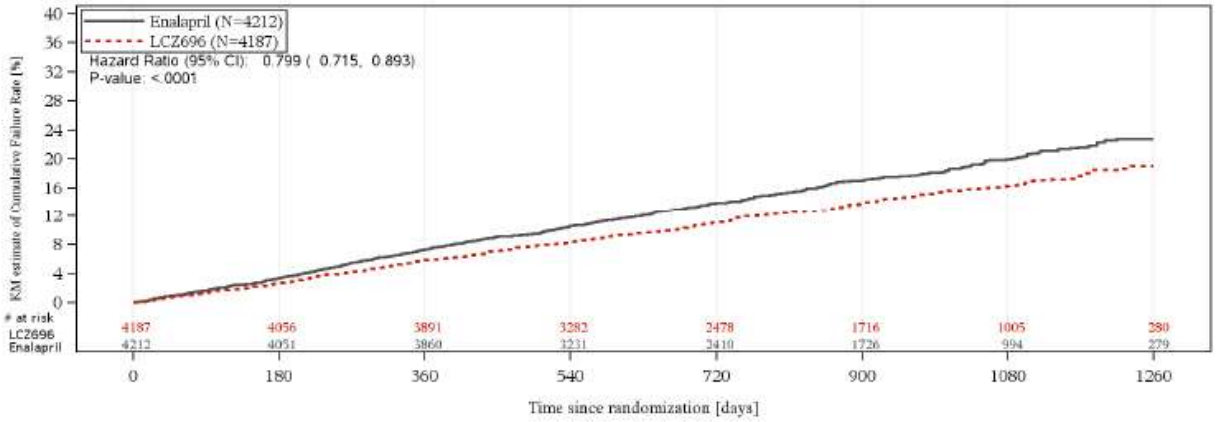


CI = confidence interval; LCZ696 = sacubitril/valsartan; KM = Kaplan–Meier.
Source: Clinical Study Report, p. 271.[13]

b) Cardiovascular mortality

There were 693 deaths (17%) due to CV causes in the enalapril group and 558 (13%) in the sacubitril/valsartan group during the DB period (HR 0.80; 95% CI, 0.71 to 0.89) (Table 11). The differences between groups were statistically significant; however, analysis of CV mortality alone (i.e., not as part of the primary composite outcome) may be considered exploratory, as it was not part of the statistical analysis plan or multiple testing procedures (Figure 4).

FIGURE 4: KAPLAN–MEIER PLOT FOR CONFIRMED CARDIOVASCULAR DEATH BY TREATMENT GROUP (FULL ANALYSIS SET)

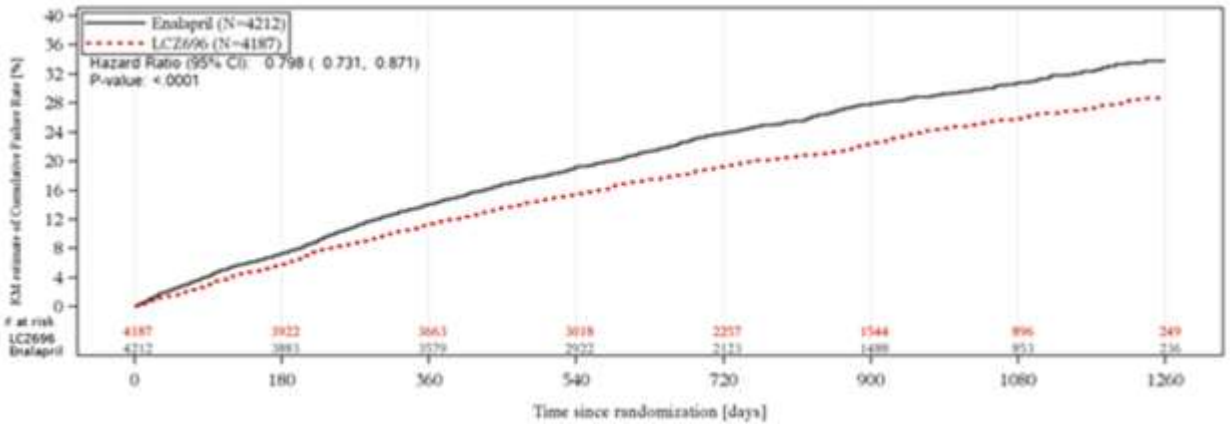


CI = confidence interval; LCZ696 = sacubitril/valsartan; KM = Kaplan–Meier.
Source: Clinical Study Report, p. 268.[13]

3.6.2 Mortality or hospitalization

The primary outcome in PARADIGM-HF was a composite of CV mortality or first HF hospitalization. The composite outcome was reported more frequently in the enalapril versus sacubitril/valsartan groups (27% versus 22%, respectively) and the differences were statistically significant (HR 0.80; 95% CI, 0.73 to 0.87) (Table 11). Differences between treatments were noted early on and were sustained throughout the study (Figure 5).

FIGURE 5: KAPLAN–MEIER PLOT FOR FIRST CONFIRMED HEART FAILURE HOSPITALIZATION OR CARDIOVASCULAR DEATH BY TREATMENT GROUP (FULL ANALYSIS SET)



CI = confidence interval; LCZ696 = sacubitril/valsartan; KM = Kaplan–Meier.
Source: Clinical Study Report, p. 268.[13]

a) Subgroup analyses

Five subgroups of interest were identified in the protocol: NYHA functional class, LVEF, use of ICD/CRT device, region, and HF due to ischemic cardiomyopathy. No data were available for patients with ischemic cardiomyopathy.

New York Heart Association functional class

Subgroup data for patients with NYHA functional class I and II (n = 6,308) or III and IV (n = 2,078) HF were reported (note: less than 5% of patients were functional class I, and 1% were class IV) (Appendix 4, Table 19).

The absolute risk of death (all-cause) was lower in the functional class I/II subgroup (sacubitril/valsartan 15% versus enalapril 18%) than the class III/IV subgroup (sacubitril/valsartan 22% versus enalapril 25%). However, the relative treatment effects were similar in each subgroup (HR 0.84 and 0.85) (interaction term *P* value = 0.94). Similar patterns were noted for CV mortality.

The proportion of patients with the primary outcome was lower in those in NYHA functional class I/II (enalapril: 25%, sacubitril/valsartan: 19%) than in the functional class III/IV subgroup (enalapril: 32%, sacubitril/valsartan: 30%), and the interaction between the subgroups was statistically significant (interaction term *P* value 0.03), indicating a possible effect modification by functional class on the primary outcome. The HR for sacubitril/valsartan versus enalapril was 0.75 (95% CI, 0.68 to 0.84) in the class I/II subgroup compared with 0.92 (95% CI, 0.79 to 1.08) in the class III/IV subgroup (Appendix 4, Table 19).

[redacted] between subgroups was also noted in the time to first HF hospitalization ([redacted]). In patients with NYHA class I/II HF the HR was [redacted], and in those in class III/IV, the HR was [redacted].

Left ventricular ejection fraction

Data were reported for patients with a baseline LVEF > 35% and ≤ 40% (n = 961) and ≤ 35% (n = 7,437) (Appendix 4, Table 20). For all four outcomes (all-cause mortality, CV mortality, primary composite outcome, and HF hospitalization), no statistically significant differences were detected among subgroups based on LVEF (interaction *P* values 0.36 to 0.90). The treatment effect point estimates for each subgroup analysis (HR ranging from 0.78 to 0.92) were generally similar to the results of the overall population (HR 0.79 to 0.84). However, for the subgroup with LVEF > 35%, the treatment effect 95% CI included the null value (i.e., did not achieve statistical significance).

Region

In the PARADIGM-HF trial, the number of patients enrolled varied across regions: North America = 602; Latin America = 1,433; Western Europe = 2,051; Central Europe = 2,826; Asia Pacific = 1,487. In total, 168 patients from Canada were included.

For all four outcomes (all-cause mortality, CV mortality, primary composite outcome, and HF hospitalization), no statistically significant differences were detected between subgroups based on region (interaction *P* values 0.37 to 0.81) (Appendix 4, Table 21). The Cox proportional hazard analyses by region showed, in general, a reduced risk of death or hospitalization for the sacubitril/valsartan versus enalapril patients within regional subgroups (HR range 0.67 to 0.97), although for some subgroups the 95% CI included the null value.

Implantable cardioverter-defibrillator and cardiac resynchronization therapy use
A post hoc subgroup analysis was reported for patients who had an ICD or CRT device implanted (N = 1,379) or had no device (N = 7,020) (Appendix 4, Table 22). No statistically significant differences were detected between subgroups for CV mortality, HF hospitalization, or the primary composite outcome (interaction term *P* values 0.38 to 0.67). The point estimates for the within-subgroup treatment effects (HR 0.78 to 0.86) were similar to those reported for the overall study population; however, the 95% CI for the effect estimates included the null value for the subgroup with an ICD or CRT device.

3.6.3 Hospitalization

During the DB period, 43% versus 40% of patients had one or more hospitalization (all-cause), 16% versus 13% were hospitalized for HF, and 32% versus 29% were hospitalized for CV reasons in the enalapril versus sacubitril/valsartan groups, respectively (Table 11). Treatment with sacubitril/valsartan delayed all-cause, HF- or CV-related hospitalization relative to enalapril in all three exploratory analyses. Data on hospitalization rates are presented in Appendix 4, Table 23.

3.6.4 Other cardiovascular outcomes

Myocardial infarction, stroke, and resuscitated sudden death were reported as exploratory outcomes in the PARADIGM-HF trial. The incidence of myocardial infarction or stroke was similar in both treatment groups and no statistically significant differences were detected between enalapril and sacubitril/valsartan (Table 11). In the enalapril and sacubitril/valsartan groups, 0.7% and 0.4% of patients experienced a resuscitated sudden death; however, the differences between groups were not statistically significant.

The time to new onset atrial fibrillation was a secondary outcome that was reported for the subset of patients without atrial fibrillation at baseline (N = 5,308). No differences were observed between the enalapril and sacubitril/valsartan treatment groups (Table 11).

3.6.5 Functional class

The change in NYHA functional class was a post hoc analysis that was specified after unblinding of the trial. More patients in the sacubitril/valsartan group showed improvement in functional class from baseline to eight months, and fewer patients worsened, compared with enalapril in the analysis that excluded patients who died, and in a second analysis that classified patients who died as worsened (NYHA class V) (Table 11).

TABLE 11: EFFICACY OUTCOMES

	PARADIGM-HF (FAS)			
	Enalapril N = 4,212	Sacubitril/ valsartan N = 4,187	Treatment effect sacubitril/valsartan versus enalapril	P value
Mortality	**n (%)**	**n (%)**	**HR (95% CI)**	
All-cause mortality	835 (20)	711 (17)	0.84 (0.76 to 0.93)	0.0005[a]
CV mortality	693 (17)	558 (13)	0.80 (0.71 to 0.89)	< 0.0001[b]
Primary outcome				
CV death or HF hospitalization[c]	1,117 (27)	914 (22)	0.80 (0.73 to 0.87)	< 0.0001[a]
Hospitalization[c]				
All-cause hospitalization	1,827 (43)	1,660 (40)	0.88 (0.82 to 0.94)	0.0001[d]
HF hospitalization	658 (16)	537 (13)	0.79 (0.71 to 0.89)	< 0.0001[b]
CV hospitalization	1,344 (32)	1,210 (29)	0.88 (0.81 to 0.95)	0.0008[d]
Other CV Outcomes				
MI (fatal or non-fatal)	119 (2.8)	115 (2.8)	0.96 (0.74 to 1.24)	0.73[d]
Stroke (fatal or non-fatal)	110 (2.6)	109 (2.6)	0.99 (0.76 to 1.29)	0.92[d]
Resuscitated sudden death	28 (0.7)	16 (0.4)	0.56 (0.31 to 1.04)	0.068[d]
New onset AF[e]	83/2,638 (3.2)	84/2,670 (3.2)	0.97 (0.72 to 1.31)	0.42
Change in NYHA functional class at month 8[f]	**N = 3,825**	**N = 3,833**		
Improved	569 (15)	639 (17)	NA	0.0015[c]
Unchanged	2,990 (78)	2,989 (78)		
Worsened	266 (7)	205 (5)		

AF = atrial fibrillation; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MI = myocardial infarction; NA = not applicable; NYHA = New York Heart Association.
[a] Statistical significance (*P* values are one-sided), according to multiple testing procedure at overall alpha level of 0.001.
[b] Statistical testing of the individual components of the primary composite outcome was not part of the planned statistical analysis or multiple testing procedure. One-sided P values were reported.
[c] First hospitalization event.
[d] Exploratory outcomes; two-sided *P* value with alpha of 0.05.
[e] This secondary outcome was based on a subgroup of patients without AF at baseline (*P* value one-sided).
[f] A second post hoc analysis in which deaths were reported as the worst outcome (class V), showed 13% and 10% of patients on enalapril and sacubitril/valsartan, respectively, had their functional class worsen at eight months (73% versus 74% unchanged; 14% versus 16% improved) (*P* = 0.0002). Of note, the FDA Medical Review stated that the analysis that classified patients who died as worsened may bias the findings in favour of sacubitril/valsartan due to the higher number of deaths reported in the control group.[8]
Source: Clinical Study Report.[13]

3.6.6 Health-related quality of life

Two instruments were used to measure health-related quality of life: KCCQ and EQ-5D. According to the statistical analysis plan, EQ-5D index scores were to be analyzed; however, no data for this outcome were reported.

Kansas City Cardiomyopathy Questionnaire

At baseline, the domain and summary scores of the KCCQ ranged from 62.8 to 79.4 points in the enalapril group and from 63.2 to 80.8 points in the sacubitril/valsartan group (Table 12). For both

groups, all scores decreased from baseline to eight months, suggesting that heath status declined during the study. For the enalapril group, scores decreased by 3.1 (self-efficacy) to 7.9 (symptom stability) points, and for the sacubitril/valsartan group, by 1.1 (quality of life) to 6.1 points (symptom stability), with the mean treatment differences ranging from 1.4 to 2.6 points (overall score 1.9 points). For the clinical summary score (a secondary outcome) the differences between treatments (1.6 points) was not statistically significant. Although the *P* value for other domain scores were less than 0.05, these were exploratory outcomes and not part of the multiple testing procedure. Based on the estimated MCID of five points, the clinical relevance of the differences observed is unclear.

The analyses conducted showed some differences in effect size depending on the methods used to handle missing data (6.7% and 5.6% of patients in the enalapril and sacubitril/valsartan groups had missing KCCQ clinical summary scores). The analyses that assigned a zero score to patients who died showed larger treatment effects favouring sacubitril/valsartan than the analysis that excluded patients who died; however, in all analyses the differences between treatments was small (mean difference 1.0 to 1.7).

A post hoc responder analysis was reported for patients with at least a 5-point increase or decrease in KCCQ scores from baseline to eight months. Fewer patients in the sacubitril/valsartan group (31%) reported at least a 5-point decrease in KCCQ overall score compared with enalapril (35%) (odds ratio [OR] 0.84; 95% CI, 0.76 to 0.93). The results were similar for the proportion of patients with a ≥ 5-point decrease in the KCCQ clinical summary score (OR 0.82; 95% CI, 0.74 to 0.90). The proportion of sacubitril/valsartan and enalapril patients with a ≥ 5-point increase in the KCCQ overall score was 33% versus 31% (OR 1.07; 95% CI, 0.97 to 1.18), and a ≥ 5-point increase in the KCCQ clinical summary score was 31% versus 31% (OR 1.02; 95% CI, 0.93 to 1.13).

EuroQol 5-Dimensions Questionnaire

The mean EQ-5D visual analogue scale (VAS) score was 67 and 68 at baseline and increased by 1.7 and 2.6 points at eight months in the enalapril and sacubitril/valsartan groups, respectively (Table 12). The mean difference between groups was 0.8 points, and the clinical importance of this difference is unclear.

TABLE 12: HEALTH-RELATED QUALITY OF LIFE OUTCOMES

	PARADIGM-HF									
	Enalapril N = 3,873				Sacubitril/valsartan N = 3,833				Treatment effect sacubitril/valsartan versus enalapril	
KCCQ DOMAIN	n	Baseline Mean (SD)	n	Change from baseline to 8 months, LS mean (SE)	n	Baseline Mean (SD)	n	Change from baseline to 8 months, LS mean (SE)	LS mean of difference (95% CI)	*P* value
Overall summary score	3,826	72.3 (19.4)	3,638	–4.17 (0.36)	3,797	73.5 (19.5)	3,643	–2.35 (0.36)	1.91 (0.92 to 2.91)	0.0002[a]
Clinical summary score[b]	3,826	75.3 (19.3)	3,638	–4.63 (0.36)	3,797	76.6 (19.3)	3,643	–2.99 (0.36)	1.61 (0.63 to 2.65)	NS[c]
Physical limitation	3,798	71.7 (22.6)	3,589	–4.13 (0.39)	3,771	73.1 (22.5)	3,588	–2.59 (0.39)	1.54 (0.46 to 2.62)	0.0052[a]
Symptom stability	3,823	62.8 (20.8)	3,632	–7.92 (0.40)	3,790	63.2 (21.0)	3,631	–6.10 (0.40)	1.82 (0.71 to 2.93)	0.0014[a]
Symptom frequency	3,822	78.1 (21.0)	3,632	–5.22 (0.40)	3,792	79.0 (20.9)	3,637	–3.00 (0.40)	2.22 (1.10 to 3.33)	0.0001[a]
Symptom burden	3,826	79.4 (20.1)	3,635	–5.29 (0.40)	3,795	80.8 (19.7)	3,640	–3.59 (0.40)	1.70 (0.59 to 2.81)	0.0027[a]
Total symptom score	3,826	78.8 (19.8)	3,635	–5.23 (0.39)	3,795	79.9 (19.5)	3,640	–3.32 (0.39)	1.91 (0.83 to 2.99)	0.0005[a]
Self-efficacy	3,823	78.9 (19.8)	3,632	–3.11 (0.40)	3,793	79.9 (19.7)	3,638	–1.70 (0.40)	1.41 (0.29 to 2.53)	0.0138[a]
Quality of life	3,820	67.2 (22.6)	3,632	–3.23 (0.39)	3,792	68.4 (22.1)	3,635	–1.11 (0.39)	2.11 (1.03 to 3.20)	0.0001[a]
Social limitation	3,705	71.1 (25.2)	3,454	–4.62 (0.43)	3,677	72.2 (25.4)	3,448	–2.06 (0.43)	2.56 (1.36 to 3.76)	0.0000[a]
EQ-5D										
VAS	4,137	67.0 (19.9)	3,684	1.74 (0.26)	4,114	68.1 (19.8)	3,740	2.55 (0.25)	0.81 (0.10 to 1.52)	0.025[a]

CI = confidence interval; EQ-5D = EuroQoL 5-Dimensions Questionnaire; KCCQ = Kansas City Cardiomyopathy Questionnaire; LS = least squares; NS = not statistically significant; SD = standard deviation; SE = standard error; VAS = visual analogue scale.

[a] Exploratory outcome (two-sided, alpha = 0.05)

[b] Calculated as mean of total symptom score (symptom frequency and symptom burden) and physical limitation domain.

[c] Secondary outcome was not statistically significant based on multiple testing procedure (one-sided *P* value with an overall alpha of 0.001, i.e., required $P < 0.0002$ to reach statistical significance).

Source: Clinical Study Report.[13]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse events

During the enalapril and sacubitril run-in periods, 22% and 29% of patients experienced an AE. The most commonly reported AEs during the enalapril run-in period were cough (2.8%), hyperkalemia (2.7%), renal impairment (2.2%), and hypotension (2.0%). During the sacubitril/valsartan run-in period, hypotension (3.1%), hyperkalemia (2.8%), and renal impairment (2.3%) were most common. Due to differences in the treatment duration for the two run-in periods, the AE rates should not be compared.

During the DB period, 83% and 81% of patients in the enalapril and sacubitril/valsartan groups, respectively, experienced an AE (Table 13). Cardiac failure, cough, hyperkalemia, renal impairment, and hypotension were the most frequently reported AEs.

3.7.2 Serious adverse events

SAEs were reported by 2.6% and 3.5% of patients in the enalapril and sacubitril/valsartan run-in periods.

During the DB period, more patients in the enalapril group experienced an SAE than in the sacubitril/valsartan group (51% and 46%, respectively) (Table 13). Cardiac failure was the most frequent SAE (enalapril 15%, sacubitril/valsartan 14%), followed by pneumonia, chronic or congestive cardiac failure, atrial fibrillation, and cardiac death (all < 5%).

3.7.3 Withdrawals due to adverse events

In both the enalapril and sacubitril/valsartan run-in periods, 6% of patients stopped treatment due to AEs. Cough, hyperkalemia, renal impairment, and hypotension led to discontinuation of study treatment in 0.5%, 1.7%, 1.7%, and 1.4% of patients in the enalapril run-in period, and in 0.2%, 1.3%, 1.7%, and 1.8% of patients, respectively, in the sacubitril/valsartan run-in period (Appendix 4, Table 17).

During the DB period, 12% of those in the enalapril and 11% of patients in the sacubitril/valsartan groups stopped treatment due to AEs (Table 13). Death, cardiac failure, hypotension, renal impairment, and cough were the most frequently reported reasons for stopping therapy.

TABLE 13: HARMS REPORTED DURING DOUBLE-BLIND PERIOD

	PARADIGM-HF	
AEs	**Enalapril N = 4,229**	**Sacubitril/valsartan N = 4,203**
Patients with ≥ 1 AE, N (%)	3,503 (83)	3,419 (81)
Most common AEs[a]		
Cardiac failure	832 (20)	730 (17)
Cough	*601 (14)*	*474 (11)*
Hyperkalemia	*592 (14)*	*488 (12)*
Renal impairment	*487 (12)*	*426 (10)*
Hypotension	*506 (12)*	*740 (18)*
Dizziness	206 (5)	266 (6)
Atrial fibrillation	236 (6)	251 (6)
Pneumonia	237 (6)	227 (5)
Peripheral edema	213 (5)	215 (5)
Dyspnea	306 (7)	213 (5)
Nasopharyngitis	175 (4)	204 (5)
Upper respiratory tract infection	201 (5)	203 (5)
Urinary tract infection	195 (5)	199 (5)
Diarrhea	189 (4)	194 (5)
Bronchitis	224 (5)	183 (4)
Anemia	201 (5)	172 (4)
Hypertension	193 (5)	126 (3)
SAEs		
Patients with ≥ 1 SAE, N (%)	2,142 (51)	1,937 (46)
Most common SAEs[b]		
Cardiac failure	649 (15.4)	588 (14.0)
Pneumonia	181 (4.3)	155 (3.7)
Cardiac failure, chronic	135 (3.2)	112 (2.7)
Cardiac failure, congestive	140 (3.3)	112 (2.7)
Atrial fibrillation	113 (2.7)	108 (2.6)
Cardiac death	114 (2.7)	85 (2.0)
WDAEs		
Stopped treatment due to adverse events, N (%)	516 (12)	450 (11)
Notable reasons		
Death	93 (2.2)	81 (1.9)
Cardiac failure	65 (1.5)	63 (1.5)
Hypotension	23 (0.5)	26 (0.6)
Renal impairment	33 (0.8)	18 (0.4)
Cough	30 (0.7)	8 (0.2)
Hyperkalemia	15 (0.4)	11 (0.3)
Renal failure	11 (0.3)	4 (0.1)
Acute renal failure	10 (0.2)	5 (0.1)
Angioedema	5 (0.1)	5 (0.1)
Dizziness	2 (0.1)	7 (0.2)

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] AEs with an incidence of 5% or higher in one of the treatment groups. Italicized events were identified in the protocol as notable AEs.

[b] SAE with an incidence of 2.5% or higher in one of the treatment groups.

Source: McMurray 2014,[7] Clinical Study Report.[13]

3.7.4 Notable harms

a) Angioedema

A total of 147 possible angioedema events (in 144 patients) were reported by investigators, and of these, 54 cases were confirmed angioedema events according to the Angioedema Adjudication Committee (Table 14). Fifteen events and 10 events occurred during the enalapril and sacubitril/valsartan run-in periods, respectively. During the DB period, 10 events occurred in the enalapril group and 19 events in the sacubitril/valsartan group. There were no cases that resulted in airway compromise. In total, five patients were hospitalized, including two who received enalapril and three who received sacubitril/valsartan.

The FDA noted that the incidence of adjudicated angioedema events was higher among black patients (2.3% versus 0.5%, sacubitril/valsartan versus enalapril groups, respectively), compared with non-black patients (0.4% versus 0.2%), during the DB period.[8] The FDA found no clustering of events around the time of transition between ACEI and sacubitril/valsartan therapy, suggesting that the 36-hour washout period was adequate to reduce the risk of angioedema.[8] The median time to first adjudicated angioedema event was four days and 10.5 days in the enalapril and sacubitril/valsartan run-in periods and, in the DB period, most cases occurred within the first 180 days of enalapril or sacubitril/valsartan treatment, with sporadic cases occurring thereafter.

TABLE 14: ADJUDICATED ANGIOEDEMA EVENTS REPORTED DURING PARADIGM-HF

	Paradigm-HF			
Angioedema	**Run-in period 1**	**Run-in period 2**	**DB period**	
	Enalapril N = 10,513	**Sacubitril/valsartan N = 9,419**	**Enalapril N = 4,229**	**Sacubitril/valsartan N = 4,203**
Angioedema (total), n (%)	15 (0.14)	10 (0.11)	10 (0.24)	19 (0.45)
No treatment or use of antihistamine	8 (0.08)	8 (0.08)	5 (0.12)	10 (0.24)
Catecholamine or glucocorticoids without hospitalization	6 (0.06)	2 (0.02)	4 (0.09)	6 (0.14)
Hospitalization without airway compromise	1 (0.01)	0	1 (0.02)	3 (0.07)
Airway compromise	0	0	0	0
Angioedema events that led to drug discontinuation	10 (0.1)	8 (0.1)	4 (0.1)	7 (0.2)

DB = double-blind.
Source: McMurray 2014,[7] FDA Medical Review.[8]

Standardized Medical Dictionary for Regulatory Activities (MedDRA) searches were conducted for specific AEs and their related terms (angioedema, hyperkalemia, hypotension and renal impairment), and exposure-adjusted incidence rates (EAIR) were reported. The rate of unadjudicated angioedema-like events was similar in both groups during the DB period (Table 15).

b) Hypotension

In the DB period, hypotension-related events were reported more frequently in the sacubitril/valsartan (24.4%) than the enalapril groups (18.6%) (Table 15). There were 13.2 exposure-adjusted hypotensive

events/100 patient-years in the sacubitril/valsartan group compared with 9.5 events for the enalapril group. In addition, more patients reported symptomatic hypotension in the sacubitril/valsartan versus enalapril groups (14% versus 9%, respectively),[7] although the incidence of hypotensive-related SAEs was similar between groups (sacubitril/valsartan: 2.8%; enalapril: 3.5%).[8] Either no action (49%) or a reduction in dose or temporary interruption of therapy (42% to 46%) was used to manage hypotensive-related events that occurred during the DB period.[8]

TABLE 15: NOTABLE HARMS IDENTIFIED BY STANDARDIZED MEDDRA QUERY (DOUBLE-BLIND PERIOD)

	Paradigm-HF			
Adverse Events	**Enalapril N = 4,229**		**Sacubitril/valsartan N = 4,203**	
Notable harms	**n (%)**	**Exposure-adjusted incidence rate (95% CI)[a]**	**n (%)**	**Exposure-adjusted incidence rate (95% CI)[a]**
Angioedema	312 (7.4)	3.5 (3.1 to 3.9)	300 (7.1)	3.3 (3.0 To 3.7)
Hyperkalemia	605 (14.3)	7.1 (6.5 to 7.7)	500 (11.9)	5.7 (5.2 to 6.2)
Hypotension	786 (18.6)	9.5 (8.8 to 10.2)	1,027 (24.4)	13.2 (12.4 to 14.0)
Renal impairment	746 (17.6)	8.8 (8.2 to 9.4)	682 (16.2)	7.9 (7.3 to 8.5)
SAE				
Hyperkalemia	42 (1.0)	NR	17 (0.4)	NR
Hypotension	147 (3.5)	NR	117 (2.8)	NR
Renal impairment	188 (4.4)	NR	161 (3.8)	NR

CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; NR = not reported; SAE = serious adverse event.
[a] Incidence per 100 patient-years.
Source: FDA Medical Review,[8] Clinical Study Review.[13]

c) Renal dysfunction

The EAIR of renal impairment-related events was lower in the sacubitril/valsartan versus enalapril groups during the DB period (7.9 and 8.8 events per 100 patient-years, respectively) (Table 15). Similarly, the incidence of renal-related SAEs was also lower for sacubitril/valsartan (sacubitril/valsartan: 3.8%; enalapril: 4.4%). No statistically significant difference was found between treatments for the time to first confirmed renal dysfunction event (HR 0.86; 95% CI, 0.65 to 1.13), which was reported as a secondary efficacy outcome.[13]

d) Hyperkalemia

Hyperkalemia-related AEs were reported in 11.9% of those in the sacubitril/valsartan group versus 14.3% in the enalapril group during the DB period (EAIR sacubitril/valsartan: 5.7 events, enalapril: 7.1/100 patient-years) (Table 15). More patients in the enalapril group (1.0%) reported a hyperkalemia-related SAE than the sacubitril/valsartan group (0.4%).

e) Cough

During the DB period, cough was reported by 14% of patients in the enalapril group and 11% of those in the sacubitril/valsartan group (Table 13). Cough was the reason for stopping treatment in 0.7% and 0.2% of patients in the enalapril and sacubitril/valsartan groups, respectively.

4. DISCUSSION

4.1 Summary of Available Evidence

A single randomized, DB, active-controlled trial met the inclusion criteria. The PARADIGM-HF trial (N = 8,442) compared the safety and efficacy of sacubitril/valsartan versus enalapril in patients with heart failure and reduced ejection fraction (≤ 40% or ≤ 35%) with NYHA functional class II to IV HF, and elevated BNP or NT-proBNP levels (or recent HF hospitalization). The primary outcome was time to CV death or first HF hospitalization, and secondary outcomes included all-cause mortality, change in KCCQ physical limitations and symptom summary score, and new onset atrial fibrillation. The external validity of the trial may be limited by the enrichment criteria applied to the selection of patients for enrolment.

4.2 Interpretation of Results

4.2.1 Efficacy

In the PARADIGM-HF trial, there were fewer all-cause (17% versus 20%), or CV-related deaths (13% versus 17%), in the sacubitril/valsartan versus enalapril groups, respectively, and these differences were statistically significant (CV mortality HR 0.80; 95% CI, 0.71 to 0.89). During the trial (median follow-up 27 months), there were fewer sudden deaths (6.0% versus 7.4%) and pump failures (3.5% versus 4.4%) for sacubitril/valsartan versus enalapril groups. The proportion of patients with a non-CV cause of death was similar between treatment groups.

The trial showed statistically significant differences in CV mortality or first HF hospitalization for sacubitril/valsartan (22%) compared with enalapril (27%), which was associated with a 20% risk reduction as estimated by the hazard risk using Cox proportional hazards model (HR 0.80; 95% CI, 0.73 to 0.87). Considering that enalapril showed a 16% relative risk reduction in mortality and 26% reduction in mortality or HF hospitalization in the pivotal SOLVD trial,[19] the treatment effects observed in the PARADIGM-HF study may be considered clinically important. The analyses of the first HF-related, CV-related, or all-cause hospitalization showed similar absolute (3%) and relative differences between treatments (HR 0.79 to 0.88). The incidence of other CV outcomes — myocardial infarction, stroke, or new onset atrial fibrillation — were similar in the sacubitril/valsartan and enalapril groups.

The subgroup analysis by NYHA functional class showed [redacted] sacubitril/valsartan and enalapril groups in the time to first HF hospitalization ([redacted]) in patients with class III/IV symptoms, [redacted] functional class I/II patients showed a statistically significant treatment effect (HR 0.70; 95% CI, 0.61 to 0.82). A similar pattern was observed for the composite end point of CV death or first HF hospitalization. Of note, patients in NYHA class II represented 70% the total study population, while 24% were in class III. The treatment effects for CV mortality, first HF hospitalization and the primary composite outcome were generally similar across subgroups based on LVEF (≤ 35% or > 35% to 40%), ICD or CRT use (yes/no), or region, although in some subgroups the treatment effects were not statistically significant. Caution is warranted when interpreting the subgroup analyses considering that some analyses were likely under-powered due to the smaller sample sizes (North America N = 602; LVEF > 35%, N = 961), or the analyses were post hoc (ICD or CRT use, N = 1,379) and randomization was stratified by site only. No control of multiplicity was considered for the subgroup analyses.

Despite showing improvement in mortality or hospitalization, sacubitril/valsartan was not associated with clinically important differences in the outcomes that patients' report as affecting their day-to-day lives. Most patients did not show a change in NYHA functional class, with only 2% more patients showing improvement, and 2% fewer worsening in the sacubitril/valsartan versus enalapril groups. Although the

P value for this post hoc analysis was small (*P* = 0.0015) the clinical importance of the differences observed is uncertain. Two quality of life instruments were used in PARADIGM-HF: the disease-specific KCCQ and the generic EQ-5D. For both instruments, the differences between treatments in the change from baseline to eight months were small and of uncertain clinical importance. An MCID of five points has been reported for the KCCQ overall score, and the differences between sacubitril/valsartan and enalapril were below this threshold (mean difference [MD] 1.9 points). Similar treatment effects were observed for the KCCQ clinical summary score (MD 1.6) and across the individual domains of the KCCQ (MD range 1.4 to 2.6). No data were reported for the EQ-5D index scores; however, the MD in the VAS was 0.8, which may be considered clinically unimportant on this 0- to 100-point scale.

The key limitation of the PARADIGM-HF trial relates to the external validity. The trial used an enrichment design, with specific criteria for LVEF, comorbidities, and BNP and NT-proBNP levels. Of the 18,000 patients screened, 42% were excluded. Enrolment was further restricted to patients who demonstrated adequate tolerability to the study drugs (an additional 20% were excluded). The clinical expert consulted for this review stated that the enrolled population differed in a number of key characteristics from Canadian HF patients seeking treatment. The enrichment criteria applied in the selection process enrolled HF patients with elevated BNP or NT-proBNP levels despite medical therapies, which may be considered a higher-risk group. As such, there is uncertainty that the absolute and relative benefits of sacubitril/valsartan would be observed in a lower-risk HF group with normal BNP levels. Moreover, practice patterns differ across regions, and a limited number of North American patients were enrolled (N = 602). The proportion of patients who had an ICD or CRT device implanted was low in the overall PARADIGM-HF population (16%) compared with the US patients enrolled (60%). Given the more prevalent use of device therapy in North America, there is some uncertainty that the same mortality benefits, as observed in the PARADIGM-HF trial, may be achieved in the real-world North American (and particularly Canadian) setting. In the PARADIGM-HF trial, the median follow-up was 27 months; additional data are needed to determine if the benefits of sacubitril/valsartan extend beyond this time frame.

4.2.2 Harms

In the PARADIGM-HF trial, SAEs were reported by 51% and 46% of patients in the enalapril and sacubitril/valsartan groups, respectively, with disease-related events being most common (cardiac failure, atrial fibrillation, cardiac death). The proportion of patients who stopped treatment due to adverse events was similar for both treatments (11% and 12%) during the DB period.

Most patients experienced one or more AEs during the PARADIGM-HF study, with 81% to 83% reporting an event during the DB treatment period. Besides cardiac failure, the most commonly reported AEs were cough, hyperkalemia, renal impairment, and hypotension (10% to 18%), which are known events associated with ACEI or ARBs. Hypotension was reported more frequently among patients who received sacubitril/valsartan than enalapril, and, although symptomatic hypotension was also reported more frequently in the sacubitril/valsartan group, the incidence of serious hypotensive events was similar between groups. Renal dysfunction, hyperkalemia, and cough were reported more frequently in the enalapril than sacubitril/valsartan group.

The incidence of angioedema-related events is of particular interest for sacubitril/valsartan, as the first neprilysin inhibitor, omapatrilat, was not approved by the FDA due to the increased risk of potentially life-threatening angioedema.[20] In the PARADIGM-HF trial, a total of 54 confirmed angioedema events were reported, of which 25 occurred during treatment with enalapril (run-in: 15 events; DB: 10 events) and 29 occurred during sacubitril/valsartan treatment (run-in: 10 events; DB: 19 events). Five patients

required hospitalization to manage angioedema (enalapril: two; sacubitril/valsartan: three), but no events resulted in airway compromise. Given the differences in the length of the run-in periods, and the order in which treatments were administered (i.e., patients with higher risk of angioedema may be excluded prior to receiving sacubitril/valsartan), it is difficult to interpret the angioedema incidence data. The data from the DB period suggest angioedema may be more frequent with sacubitril/valsartan; however, additional information is required.

The AE data from PARADIGM-HF should be interpreted with caution due to the design of the trial, which underestimates the incidence of AEs. The study inclusion criteria selected patients who were previously receiving ACEI or ARB therapy, and required that patients demonstrate the ability to tolerate the study drugs at specific doses. During the run-in periods, an additional 20% of patients withdrew, mainly due to tolerability issues. While the average treatment duration was two years, longer-term safety data are needed to determine the harms associated with this first-in-class pharmacotherapy. Safety assessment in the broader HF population is also required to determine the tolerability of this new drug once deployed in clinical practice.

4.3 Potential Place in Therapy[1]

According to the clinical expert involved in the review, there is an unmet need to further reduce morbidity and mortality events in HF patients. While the addition of a new class of medications would be a potentially important advance, the clinical expert noted that this unmet need could be addressed by other avenues which, if optimized, could perhaps reduce the need for new pharmacotherapies for HF. These would include assuring that patients receive:

- appropriate non-pharmacologic advice on their illness
- appropriate use of medications (diuretics, digitalis, ACEIs ARBs, beta blockers, and aldosterone antagonists)
- medical devices (ICDs, CRT) in appropriate patient subgroups

and especially

- ready access to health professionals with medical and para-medical expertise in HF.

Sacubitril/valsartan, according to the clinical expert consulted, is likely to have utility in meeting this need. A large RCT — PARADIGM-HF — has shown a statistically significant decrease in the combined end point of CV mortality and HF hospitalization, although some uncertainty remains concerning the generalizability of the study results to the Canadian HF population, as described previously in the review.

The clinical expert consulted by CADTH suggested that based on the clinical evidence available and the existing need, the patient subpopulations that may benefit most are those with an ejection fraction of less than 35% and in NYHA functional class II. However, the clinical expert suggested that ideally the results for the effects of sacubitril/valsartan should be replicated in another large and longer-duration RCT, given the evidence for these subgroups comes from a single RCT with relatively small sample sizes in certain subgroups (and reduced precision), and the aforementioned concerns regarding generalizability.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5. CONCLUSIONS

Sacubitril/valsartan was associated with statistically significant differences in CV mortality or HF hospitalizations compared with enalapril, in a select population of stable HF patients with reduced ejection fraction, who were also receiving background therapies for HF. Sacubitril/valsartan did not show any clinically important differences over enalapril in terms of other CV outcomes (myocardial infarction, stroke or new onset atrial fibrillation), quality of life, or functional status, based on data from a single RCT.

Sacubitril/valsartan was associated with an increased frequency of hypotension compared with enalapril. Additional data are required to determine if the risk of angioedema is increased with sacubitril/valsartan, and to determine the longer-term safety of this first-in-class therapy.

The enrichment criteria applied in the selection of patients for study inclusion, and restriction to patients with tolerability to both the study and comparator drugs during the run-in phases, underestimates the incidence of AEs and limits the external validity of the findings.

APPENDIX 1: PATIENT INPUT SUMMARY

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

1. Brief Description of Patient Group Supplying Input
Input was received from one patient group.

The Heart and Stroke Foundation of Canada (HSF) is a national charity run by 125,000 volunteers. The HSF supports heart and stroke research and runs health promotion and advocacy programs across the country with the goal of reducing the impact of and eliminating heart disease and stroke. Over the last 60 years, the HSF has invested more than $1.39 billion in heart and stroke research. Conflict of interest declarations include the receipt of unrestricted financial support from pharmaceutical companies including Novartis. No conflict was declared in the preparation of the submission.

2. Condition-Related Information
Information on the impact of the condition impact on patients and caregivers was collected via an online survey that was advertised using posts through Facebook, pop-ups on heart failure information pages of the HSF website, and through its Community of Survivors mailing list — a list of survivors and caregivers who have consented to receiving directed emails related to recovery. Of the 113 individuals who responded to the survey, 42 indicated that they have been told by a health care professional that they have heart failure, and 13 indicated that they were a caregiver for someone with heart failure. Information was also gathered through literature searches, HSF health information, and guidelines and policies from credible organizations.

Heart failure is a serious health problem affecting an estimated 500,000 Canadians. Every year, 50,000 Canadians are newly diagnosed with heart failure and up to 50% of patients die within five years of diagnosis. Of the 42 survey respondents identified as having heart failure, 38 reported experiencing symptoms. The most common symptoms included: increased shortness of breath (n = 30); fatigue, loss of energy, extreme tiredness or weakness (n = 30); increased swelling of the ankles, feet, legs, or abdomen (n = 20); increased heart rate or irregular heart beat (n = 15); bloating or feeling full all the time (n = 14); increased urination at night (n = 14); sudden gains in weight (n = 13); decreased alertness or difficulty concentrating (n = 13); cough or cold symptoms lasting longer than a week (n = 11); and loss or of change in appetite or nausea (n = 7).

In the online survey, the Minnesota Living with Heart Failure Questionnaire (MLHFQ) was used to assess quality of life in 36 patients with heart failure. The MLHFQ has 21 questions assessing physical symptoms, and the impact on physical and social functions over the previous four weeks. Scores range from 0 to 105, with higher scores indicating greater impacts on quality of life. The mean score of the 36 respondents was 45 (range 0 to 91) with 25%, 28% and 47% classified as having good, moderate, and poor quality of life, respectively. Fifteen patients reported that heart failure was making their sexual activities difficult, 14 patients reported that their recreational activities had become difficult, 12 patients reported that leaving home had become difficult, and 11 patients reported that working to earn a living was difficult. One patient stated that “I can’t do the things I enjoy.”

Caregivers' lives were also affected by having to administer medications multiple times per day and providing additional care because of side effects from treatments, taking time off work and attending frequent medical appointments for their loved one. Some caregivers reported feeling anxious, stressed or overwhelmed, and that caring for someone with heart failure increased their financial burden and reduced their freedom.

3. Current Therapy-Related Information

Of the 42 survey respondents identified as having heart failure, 33 reported that they have been prescribed medication to manage the condition, and 13 reported using a range of medication, including aldosterone inhibitors, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, digoxin, diuretics, oral anticoagulants, and statins. One patient stated that there are "too many to list." Six patients reported experiencing side effects with current medications that included fatigue, dizziness, low blood pressure, diarrhea, and back pain.

Of the 42 survey respondents identified as having heart failure, 22 reported that taking medication at a specific time affected their day-to-day life, 20 reported having to take medication multiple times a day, 19 reported having to visit their health care provider frequently, 10 reported having to take time off work, and eight reported having to manage their condition with other forms of therapy. Patients reported that the ideal therapy would keep the condition stable with no further issues and no major side effects, and allow them to return to their previously active lifestyle.

4. Expectations About the Drug Being Reviewed

Thirteen patients reported having received sacubitril/valsartan through their health care provider or a clinical trial, and 10 of these patients were actively taking sacubitril at the time of the survey. Six patients reported that taking sacubitril helped control their condition, six patients were unsure, and one patient reported that it did not help. Twelve patients had to take at least one additional medication to control their condition. Five patients reported experiencing side effects as a result of taking sacubitril, which included fatigue, respiratory issues, infection, dizziness, and low blood pressure.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 19, 2015
Alerts:	Biweekly (twice monthly) updates until February 17, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
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
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
.kw	Keyword heading
.pt	Publication type
.po	Population group [PsycInfo only]
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	(936623-90-4 or WB8FT61183).rn,nm.
2	(entresto* or LCZ 696 or LCZ696 or "sacubitril/valsartan" or "valsartan/sacubitril" or "sacubitril-valsartan" or "valsartan-sacubitril").ti,ab,rn,nm,sh,hw,ot,kw.
3	or/1-2
4	(149709-62-6 or 17ERJ0MKGI).rn,nm.
5	(sacubitril* or ahu 377 or ahu377 or biphenyl derivative or enkephalinase inhibitor or neprilysin

MULTI-DATABASE STRATEGY	
	inhibitor).ti,ab,rn,nm,sh,hw,ot,kw.
6	or/4-5
7	(137862-53-4 or 80M03YXJ7I).rn,nm.
8	(valsartan* or diovan* or tareg or tazea or kalperss or miten or provas or vals or walsartan or nisis or valtan or valzaar or CGP 48933 or CPG48933 or CPG 49309 or CPG49309).ti,ab,rn,nm,sh,hw,ot,kw.
9	(atennor or Diopass or Dioten or Diovane or Diqvan or Disartan or Exvan or Hiperval or Kovan or Maxdio or Selectan or Starval or Sui Yue or Tabuvan or Valazyd or Valosartan or Valsaone or Valsarect or Valt or Valtensin or Valvex or Varcor or Vector).ti,ab,rn,nm,sh,hw,ot,kw.
10	or/7-9
11	6 and 10
12	3 or 11
13	12 use pmez
14	*"3 (1 biphenyl 4 ylmethyl 3 ethoxycarbonyl 1 butylcarbamoyl)propionic acid plus valsartan"/
15	(entresto* or LCZ 696 or LCZ696 or "sacubitril/valsartan" or "valsartan/sacubitril" or "sacubitril-valsartan" or "valsartan-sacubitril").ti,ab.
16	or/14-15
17	*Sacubitril/
18	(sacubitril* or ahu 377 or ahu377 or biphenyl derivative or enkephalinase inhibitor or neprilysin inhibitor).ti,ab.
19	or/17-18
20	*valsartan/
21	(valsartan* or diovan* or tareg or tazea or kalperss or miten or provas or vals or walsartan or nisis or valtan or valzaar or CGP 48933 or CPG48933 or CPG 49309 or CPG49309).ti,ab.
22	(atennor or Diopass or Dioten or Diovane or Diqvan or Disartan or Exvan or Hiperval or Kovan or Maxdio or Selectan or Starval or Sui Yue or Tabuvan or Valazyd or Valosartan or Valsaone or Valsarect or Valt or Valtensin or Valvex or Varcor or Vector).ti,ab.
23	or/20-22
24	19 and 23
25	16 or 24
26	25 use oemezd
27	conference abstract.pt.
28	26 not 27
29	13 or 28
30	exp animals/
31	exp animal experimentation/ or exp animal experiment/
32	exp models animal/
33	nonhuman/
34	exp vertebrate/ or exp vertebrates/
35	animal.po.
36	or/30-35
37	exp humans/

MULTI-DATABASE STRATEGY	
38	exp human experimentation/ or exp human experiment/
39	human.po.
40	or/37-39
41	36 not 40
42	29 not 41
43	remove duplicates from 42

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	October 2015
Keywords:	Entresto, lcz696, lcz 696, sacubitril/valsartan, valsartan/sacubitril, sacubitril AND valsartan
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (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
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Jhund PS, Fu M, Bayram E, Chen CH, Negrusz-Kawecka M, Rosenthal A, et al. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. Eur Heart J [Internet]. 2015 Oct 7 [cited 2015 Oct 20];36(38):2576-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4595742/pdf/ehv330.pdf.	Subgroup not of interest

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 16: DAILY DOSE OF KEY CONCOMITANT MEDICATIONS DURING DOUBLE-BLIND PERIODS

	PARADIGM-HF			
	Enalapril N = 4,229		**Sacubitril/valsartan N = 4,203**	
Drug class, n (%)	**Proportion treated at randomization, n (%)**	**Median daily dose in mg (IQR)**	**Proportion treated at randomization, n (%)**	**Median daily dose in mg (IQR)**
Beta blockers				
Metoprolol	900 (21)	50 (47.5 to 100)	925 (22)	50 (47.5 to 100)
Bisoprolol	1,116 (26)	5.0 (2.5 to 7.5)	1,120 (27)	5.0 (2.5 to 5.0)
Carvedilol	1,663 (39)	12.5 (6.25 to 25)	1,637 (39)	12.5 (9.4 to 25)
Aldosterone antagonists				
Spironolactone	2,217 (52)	25 (25 to 25)	2,113 (50)	25(25 to 25)
Eplerenone	173 (4)	25 (25 to 25)	158 (4)	25 (25 to 25)

IQR = interquartile range.
Source: Clinical Study Report.[13]

TABLE 17: PRIMARY REASON FOR DISCONTINUATION DURING RUN-IN PERIODS

	PARADIGM-HF	
	Enalapril Run-in	**Sacubitril/valsartan Run-in**
Enrolled in run-in period, N	10,513[a]	9,419[a]
Total withdrawals during run-in, N (%)	1,102 (10)	977 (10)
Reason for discontinuation		
Adverse event, N (%)	591 (5.6)	551 (5.9)
Cough	49 (0.5)	15 (0.2)
Hyperkalemia	174 (1.7)	125 (1.3)
Hypotension	146 (1.4)	164 (1.7)
Renal dysfunction	181 (1.7)	174 (1.8)
Other	102 (1.0)	132 (1.4)
Abnormal laboratory or test result	66 (0.6)	59 (0.6)
Withdrew consent	171 (1.6)	100 (1.1)
Lost to follow-up	39 (0.4)	26 (0.3)
Death	49 (0.5)	47 (0.5)
Protocol deviation	79 (0.8)	92 (1.0)
Administrative problems	20 (0.2)	29 (0.3)
Unsatisfactory treatment effect	4 (0.1)	10 (0.1)
Other	83 (0.8)	68 (0.7)

[a] Median exposure duration was 15 days (interquartile range [IQR] 14 to 21 days) for enalapril run-in period and 29 days (IQR 26 to 35 days) for sacubitril/valsartan run-in period.
Source: Clinical Study Report.[13]

TABLE 18: REASON FOR DEATH DURING DOUBLE-BLIND PERIOD

	Paradigm-HF (Randomized set)	
Adverse Events	**Enalapril N = 4,233**	**Sacubitril/valsartan N = 4,209**
Deaths		
Number of deaths, N (%)	837 (20)	714 (17)
Total CV deaths	694 (16.4)	560 (13.3)
Pump failure	185 (4.4)	147 (3.5)
Sudden death	311 (7.4)	251 (6.0)
Presumed sudden death	23 (0.5)	26 (0.6)
Presumed CV death	95 (2.2)	67 (1.6)
Fatal stroke	34 (0.8)	30 (0.7)
Fatal myocardial infarction	33 (0.8)	25 (0.6)
Pulmonary embolus, CV procedure or other CV death	13 (0.3)	14 (0.3)
Total non-CV deaths	110 (2.6)	120 (2.9)
Infection	34 (0.8)	36 (0.9)
Malignancy	41 (1.0)	41 (1.0)
Gastrointestinal	10 (0.2)	16 (0.4)
Other non-CV cause	25 (0.6)	27 (0.6)
Unknown	33 (0.8)	34 (0.8)

CV = cardiovascular.
Source: Clinical Study Report.[13]

TABLE 19: SUBGROUP ANALYSIS OF EFFICACY OUTCOMES — NYHA FUNCTIONAL CLASS

	Subgroup	PARADIGM-HF			
Outcome	**NYHA functional class**	**Enalapril**	**Sacubitril/ Valsartan**	**Treatment effect Sacubitril/valsartan versus enalapril**	**Interaction term *P* value**
MORTALITY		**n/N (%)**	**n/N (%)**	**HR (95% CI), *P* value**	
All-cause mortality	I/II	566/3,130 (18)	490/3,178 (15)	0.85 (0.75 to 0.96)	0.94
	III/IV	269/1,076 (25)	221/1,002 (22)	0.84 (0.71 to 1.01)	
CV mortality	I/II	462/3,130 (15)	373/3,178 (12)	0.79 (0.69 to 0.91)	0.76
	III/IV	231/1,076 (22)	185/1,002 (19)	0.82 (0.68 to 1.00)	
PRIMARY OUTCOME					
CV death or HF hospitalization[a]	I/II	777/3,130 (25)	611/3,178 (19)	0.75 (0.68 to 0.84)	0.034
	III/IV	340/1,076 (32)	302/1,002 (30)	0.92 (0.79 to 1.08)	
HOSPITALIZATION					
HF hospitalization[a]	I/II	[redacted]	[redacted]	[redacted]	[redacted]
	III/IV				

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NYHA = New York Heart Association.
[a] First hospitalization event.
Source: Clinical Study Report.[13]

TABLE 20: SUBGROUP ANALYSIS OF EFFICACY OUTCOMES — EJECTION FRACTION AT BASELINE

	Subgroup	PARADIGM-HF			
Outcome	**Ejection fraction**	**Enalapril**	**Sacubitril/ Valsartan**	**Treatment effect Sacubitril/valsartan versus enalapril**	**Interaction term *P* value**
MORTALITY		**n/N (%)**	**n/N (%)**	**HR (95% CI), *P* value**	
All-cause mortality	≤ 35%	727/3,722 (20)	621/3,715 (17)	0.84 (0.76 to 0.94)	0.90
	> 35%	108/489 (22)	90/472 (19)	0.86 (0.65 to 1.13)	
CV mortality	≤ 35%	615/3,722 (17)	488/3,715 (13)	0.78 (0.69 to 0.88)	0.36
	> 35%	78/489 (16)	70/472 (15)	0.92 (0.67 to 1.27)	
PRIMARY OUTCOME					
CV death or HF hospitalization[a]	≤ 35%	999/3,722 (27)	811/3,715 (22)	0.78 (0.72 to 0.86)	0.36
	> 35%	118/489 (34)	103/472 (22)	0.89 (0.68 to 1.16)	
HOSPITALIZATION					
HF hospitalization[a]	≤ 35%	595/3,722 (16)	488/3,715 (13)	0.79 (0.70 to 0.89)	0.97
	> 35%	63/489 (13)	49/472 (10)	0.80 (0.55 to 1.16)	

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
[a] First hospitalization event.
Source: Clinical Study Report.[13]

TABLE 21: SUBGROUP ANALYSIS OF EFFICACY OUTCOMES — REGION

	Subgroup	PARADIGM-HF			
Outcome	**Region**	**Enalapril**	**Sacubitril/ Valsartan**	**Treatment effect Sacubitril/valsartan versus enalapril**	**Interaction term *P* value**
MORTALITY		**n/N (%)**	**n/N (%)**	**HR (95% CI), *P* value**	
All-cause mortality	North America	[redacted]	[redacted]	[redacted]	[redacted]
	Latin America	[redacted]	[redacted]	[redacted]	
	Western Europe	[redacted]	[redacted]	[redacted]	
	Central Europe	[redacted]	[redacted]	[redacted]	
	Asia Pacific	[redacted]	[redacted]	[redacted]	
CV mortality	North America	48/292 (16)	38/310 (12)	0.76 (0.49 to 1.16)	0.81
	Latin America	140/720 (19)	100/713 (14)	0.71 (0.55 to 0.92)	
	Western Europe	128/1,025 (13)	114/1,026 (11)	0.88 (0.69 to 1.14)	
	Central Europe	237/1,433 (17)	194/1,393 (14)	0.82 (0.68 to 0.99)	
	Asia Pacific	140/742 (19)	112/745 (15)	0.79 (0.62 to 1.01)	
PRIMARY OUTCOME					
CV death or HF hospitalization[a]	North America	103/262 (35)	77/310 (25)	0.67 (0.50 to 0.90)	0.37
	Latin America	183/720 (25)	131/713 (18)	0.71 (0.56 to 0.88)	
	Western Europe	239/1,025 (23)	217/1,026 (21)	0.89 (0.74 to 1.07)	
	Central Europe	394/4,133 (28)	318/1,393 (23)	0.79 (0.68 to 0.92)	
	Asia Pacific	198/742 (27)	171/745 (23)	0.85 (0.69 to 1.04)	
HOSPITALIZATION					
HF hospitalization[a]	North America	[redacted]	[redacted]	[redacted]	[redacted]
	Latin America	[redacted]	[redacted]	[redacted]	
	Western Europe	[redacted]	[redacted]	[redacted]	
	Central Europe	[redacted]	[redacted]	[redacted]	
	Asia Pacific	[redacted]	[redacted]	[redacted]	

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.

[a] First hospitalization event.

Source: Clinical Study Report.[13]

TABLE 22: SUBGROUP ANALYSIS OF EFFICACY OUTCOMES — IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR/CARDIAC RESYNCHRONIZATION THERAPY (POST HOC)

	Subgroup	PARADIGM-HF			
Outcome	**Use of ICD and/or CRT**	**Enalapril**	**Sacubitril/ Valsartan**	**Treatment effect Sacubitril/valsartan versus enalapril**	**Interaction term *P* value**
Mortality		**n/N (%)**	**n/N (%)**	**HR (95% CI), *P* value**	
CV mortality	Yes	92/687 (13)	81/692 (12)	0.85 (0.63 to 1.15)	0.55
	No	601/3,525 (17)	477/3,495 (14)	0.79 (0.70 to 0.89)	
Primary outcome					
CV death or HF hospitalization[a]	Yes	192/687 (28)	172/692 (25)	0.86 (0.70 to 1.05)	0.38
	No	925/3,525 (26)	742/3,495 (21)	0.78 (0.71 to 0.86)	
Hospitalization					
HF hospitalization[a]	Yes	[redacted]	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]	

CI = confidence interval; CRT = cardiac resynchronization therapy; CV = cardiovascular; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator.
[a] First hospitalization event.
Source: Clinical Study Report.[13]

TABLE 23: EXPLORATORY EFFICACY OUTCOMES DURING DOUBLE-BLIND PERIOD

	PARADIGM-HF			
	Enalapril N = 4,212	**Sacubitril/ Valsartan N = 4,187**	**Treatment effect Sacubitril/valsartan versus enalapril**	***P* value**
Treatment Failure	**n (%)**	**n (%)**	**HR (95% CI), *P* value**	
Time to first treatment failure event (addition of a new drug for worsening HF, IV treatment requirement, or increase in diuretic dose for persistent use > 1 month)	604 (14)	520 (12)	0.84 (0.74 to 0.94)	0.0029[a]
Hospitalization Rate	**Number of hospital admissions per PY (95% CI)[b]**	**Number of hospital admissions per PY (95% CI)[b]**	**Rate ratio (95% CI)[b]**	***P* value**
All-cause hospitalization	0.496 (0.468 to 0.526)	0.419 (0.395 to 0.445)	0.845 (0.781 to 0.913)	< 0.0001[a]
HF-related hospitalization	0.136 (0.123 to 0.151)	0.105 (0.094 to 0.117)	0.77 (0.671 to 0.891)	0.0004[a]

CI = confidence interval; HF = heart failure; HR = hazard ratio; IV = intravenous.
[a] Exploratory outcomes; two-sided *P* value with alpha of 0.05.
[b] Negative binomial regression model adjusted for treatment and region. Log(follow-up duration) is the offset variable.
Source: Clinical Study Report.[13]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity and the minimally clinically important difference (MCID) of the following outcome measures:

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- EuroQoL 5-Dimensions Questionnaire (EQ-5D)

Findings

TABLE 24: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOME MEASURES

Instrument	Type	Validated	MCID	References
KCCQ	KCCQ is a 23-item (15-question), disease-specific health-related quality of life questionnaire.	Yes	5 points in KCCQ-os	Green 2000[16] Spertus 2004[17]
EQ-5D	EQ-5D is a general, non–disease-specific health-related quality of life questionnaire.	Yes	HF: unknown General use: 0.033 to 0.074 for index score	Rabin 2001[21] Sinnott 2007[22]

EQ-5D = EuroQoL 5-Dimensions Questionnaire; KCCQ = Kansas City Cardiomyopathy Questionnaire; KCCQ-os = KCCQ overall score; MCID = minimal clinically important difference.

Kansas City Cardiomyopathy Questionnaire

The KCCQ is a self-administered, 23-item (15-question), disease-specific, health-related quality of life questionnaire that was originally developed in 2000 for use in patients with congestive heart failure (CHF).[16] The items of the KCCQ can be categorized into the following domains: physical limitation (question 1); symptoms (frequency [questions 3, 5, 7, 9], severity [questions 4, 6, 8], and recent change over time [question 2]); social limitation (question 16); self-efficacy (questions 11, 12); and quality of life (questions 13, 14, 15). All items are measured using a Likert scale with five to seven 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. Two summary scores were defined in the original publication by Green et al., 2000.[16]: a functional status score (combination of the physical limitation domain and symptom domain, excluding symptom change over time) and a clinical summary score (combination of the functional status score, quality of life domain, and social limitation domain). The clinical summary score as defined by Green et al., 2000 is more commonly referred to as the overall summary score (KCCQ-os), and the functional status score is referred to as the clinical summary score (KCCQ-cs). The rest of this section will refer to these summary scores as such.

The KCCQ was originally validated in patients with a clinical diagnosis of CHF and an ejection fraction of < 40%.[16] A cohort of patients (n = 39; mean age 64 years; 69% male; mean New York Heart Association [NYHA] 2.0 ± 0.59) with stable disease was used to assess the reliability of the KCCQ, while another cohort of patients (n = 39; mean age 68 years; 62% male; mean NYHA 3.3 ± 0.46) admitted to the hospital for CHF exacerbations was used to assess the responsiveness of the KCCQ. At baseline and at

three months, each patient had his/her NYHA classification assessed, completed the KCCQ, the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and the Short Form (36) Health Survey (SF-36) questionnaire, and had a six-minute walk test (6MWT) administered. The convergent validity of each KCCQ domain and summary score was determined using baseline data from all patients and comparing with other measures that quantify similar concepts.

The domains of the KCCQ generally showed high internal consistency, with Cronbach's alpha ranging from 0.62 for the self-efficacy domain to 0.90 for the physical limitations domain. The lower Cronbach's alpha for the self-efficacy domain may be due to the fact that it is composed of only two questions that acquire slightly different pieces of information. The Cronbach's alpha values for the KCCQ-cs and KCCQ-os were high (0.93 to 0.95). The KCCQ also showed good test-retest reliability, with mean changes of 0.8 to 4.0 points for the various domains and summary scores over three months of observation, none of which were statistically significant. The KCCQ also exhibited high responsiveness, with responsiveness statistics ranging from 0.62 for the social limitation domain to 3.19 for the symptoms domain. The responsiveness statistic for the KCCQ-cs was 2.77 and for the KCCQ-os was 1.74.[16]

There was no universally accepted gold standard for identification of functional status and quality of life in heart failure (HF) patients at the time the KCCQ was developed, so the NYHA class, 6MWT, and domains from the MLHFQ and SF-36 questionnaires were used to validate the domain and summary scores of the KCCQ.[16] The physical limitation domain showed good correlation with NYHA class (r = –0.65) and with the distance walked in the 6MWT (r = 0.48). The symptom stability score was lower in patients admitted to the hospital than those who were stable (25.8 versus 53.8). The symptom frequency and symptom severity domains correlated with NYHA classification; the quality of life domain correlated with NYHA class (r = –0.64). The social limitation domain correlated with NYHA class and the SF-36 social limitation scale (r = 0.62). No adequate criterion standard was available for the self-efficacy domain, although domain scores were significantly lower in patients admitted to the hospital compared with stable outpatients (67.6 versus 83.5). Both the KCCQ-cs (F statistic = 52.3) and KCCQ-os (F statistic = 41.9) correlated with NYHA class, and baseline scores were significantly lower among patients who died or were rehospitalized than those with event-free survival.

The KCCQ-os has been shown to be prognostic of subsequent cardiovascular mortality and hospitalizations in a cohort of patients from the Eplerenone's Neurohormonal Efficacy and Survival Study (EPHESUS) with heart failure after a recent acute myocardial infarction (n = 1,516; mean age 64 years; 73.6% male; 38.9% NYHA class I, 45.9% class II, 13.6% class III, 1.6% class IV). Among those with higher KCCQ-os scores (≥ 75) the one-year event-free survival was 84% compared with 59% for those with lower scores (< 25).[8] In another cohort of the EPHESUS study (n = 1,358; mean age 63.5 years; 73.9% male), a change in KCCQ-os was found to be linearly associated with cardiovascular mortality or hospitalization (hazard ratio for each 5-point decrease in KCCQ-os 1.12; 95% CI, 1.07 to 1.18).[23] Associations of changes in KCCQ-os with clinical change was assessed in a North American cohort study (n = 476; mean age 61 years; 75% male; 11% NYHA class I, 41% class II, 44% class III, 5% IV) in patients with heart failure and an ejection fraction < 40%, by administering the KCCQ and other measures at baseline and week 6.[17] In this study, a mean improvement of 5.7 (standard deviation [SD] 16.1) points in the KCCQ-os was associated with a small improvement in heart failure from baseline as determined by a cardiologist's assessment of change using a validated change question (15-point Likert scale, from extremely worse to extremely better and grouped into categories of change). A mean decrease of 5.4 (SD 10.8) points in the KCCQ-os was associated with a small deterioration in HF.[17]

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) was used to examine associations between the KCCQ domain and summary scores, and clinical indicators of disease severity, including the 6MWT and peak volume of oxygen (VO_2).[24] In this study, a 1-SD difference in 6MWT and peak VO_2 was found to be associated with an approximately 5-point difference in the KCCQ-os and a 6-point difference in the KCCQ-cs. The authors considered a 1-SD difference in 6MWT and peak VO_2 to represent a meaningful difference in heart failure patients, citing that it is a more stringent criteria used for these indicators than previous studies.[24]

EuroQoL 5-Dimensions Questionnaire

The EQ-5D questionnaire is a generic, non–disease-specific measure of health status.[21] The tool is based on self-report of five domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. There are three levels per domain in the original version: 1 (no problems), 2 (some or moderate problems) and 3 (extreme problems). Each combination of the five domains and three levels creates a unique health state description (243 in total). The index score is calculated by applying a country-specific, utility-function–based scoring algorithm to the EQ-5D health states. This algorithm attaches weights reflecting that society's preferences for each health state.[25] An index score of 1 represents best possible health and 0 represents dead, with the possibility of health states being valued as worse than dead (< 0). The EQ-5D is also accompanied by a visual analogue scale (VAS) to provide a self-rating of overall health, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).[21]

The discriminant validity of the EQ-5D was determined in the North American cohort study (n = 476; mean age 61 years; 75% male; 11% NYHA class I, 41% class II, 44% class III, 5% IV) in patients with HF and an ejection fraction < 40%.[17] The c-statistic was used to represent the percentage of the time that the EQ-5D index and VAS correctly identified patients with clinical change for all possible pairs of patients, one experiencing clinical change and one not. A value of 0.5 indicates no discriminative ability while a value of 1.0 indicates perfect discrimination. The EQ-5D index and 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.[17] From this study, the EQ-5D was found to show less discriminative abilities than the KCCQ and NYHA class, but similar discriminative abilities to the Short Form (12) Health Survey (SF-12). In addition, the EQ-5D and SF-12 did not exhibit much sensitivity to the magnitude of observed clinical change.[17]

The responsiveness of the EQ-5D was compared with the KCCQ and SF-12 in patients with HF and an ejection fraction < 40% (n = 298; mean age 60 years; 75% male; 11% NYHA class I, 43% class II, 41% class III, 4% class IV).[26] Patients were administered questionnaires at baseline and six weeks in addition to a 6MWT. Overall, the EQ-5D index and VAS were less responsive than the KCCQ, but showed similar responsiveness to the SF-12.

A systematic review of studies looking at the validity and reliability of the EQ-5D in patients with cardiovascular disease identified 10 studies (three studies in ischemic heart disease, three studies in patients with cerebrovascular disease, two studies in patients with HF, and two studies in patients with peripheral vascular disease).[27] When EQ-5D 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/severe health states.

Baseline data from a large randomized controlled trial (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) was used to examine associations between the EQ-5D VAS and clinical indicators of disease severity, including the 6MWT and peak VO_2.[24] In this study, a 1-SD difference in 6MWT and peak VO_2 was found to be associated with an approximately 3-point difference in the EQ-5D VAS. The authors considered a 1-SD difference in 6MWT and peak VO_2 to represent a meaningful difference in HF patients, citing that it is a more stringent criteria used for these indicators than previous studies.[24]

Conclusion

The KCCQ is a self-reported, disease-specific, health-related quality of life questionnaire with five domains used in patients with HF that can be summarized with an overall score (KCCQ-os) and clinical summary score (KCCQ-cs). The domains and summary scores of the KCCQ have demonstrated good internal consistency, good test-retest reliability, and high responsiveness. The KCCQ-os has been shown to be prognostic of subsequent cardiovascular mortality and hospitalizations. An improvement or decrease of 5 points in the KCCQ-os was found to be associated with a small improvement or small deterioration in patients with HF.

The EQ-5D is a widely-used generic health status measure consisting of five self-reported health domains with three levels per domain. The EQ-5D has demonstrated discriminant validity and responsiveness in HF patients, but not to the same extent as disease-specific measures such as KCCQ. An MCID for EQ-5D index or VAS scores in patients with HF was not identified. The MCID for the EQ-5D index score in general use ranges from 0.033 to 0.074.[22]

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