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STATE-OF-THE-ART REVIEW

Sacubitril/Valsartan

Neprilysin Inhibition 5 Years After PARADIGM-HF

Kieran F. Docherty, MBChB,[a,*] Muthiah Vaduganathan, MD, MPH,[b,*] Scott D. Solomon, MD,[b]
John J.V. McMurray, MBChB, MD[a]

HIGHLIGHTS

- In PARADIGM-HF, sacubitril/valsartan reduced morbidity and mortality compared to enalapril in patients with chronic HFrEF.
- A series of subsequent analyses of PARADIGM-HF have provided further insight into the benefits of sacubitril/valsartan compared to enalapril.
- Subsequent smaller mechanistic trials have highlighted the favorable effects of sacubitril/valsartan in attenuating adverse myocardial remodeling.
- Other trials have advanced potential pathways for therapeutic implementation (including during hospitalization for heart failure).
- Ongoing trials may provide evidence of new indications for sacubitril/valsartan.

ABSTRACT

Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has been shown to reduce the risk of cardiovascular death or heart failure hospitalization and improve symptoms among patients with chronic heart failure with reduced ejection fraction compared to enalapril, the gold standard angiotensin-converting enzyme inhibitor. In the 5 years since the publication of the results of PARADIGM-HF, further insight has been gained into integrating a neprilysin inhibitor into a comprehensive multidrug regimen, including a renin-angiotensin aldosterone system (RAS) blocker. This paper reviews the current understanding of the effects of sacubitril/valsartan and highlights expected developments over the next 5 years, including potential new indications for use. Additionally, a practical, evidence-based approach is provided to the clinical integration of sacubitril/valsartan among patients with heart failure with reduced ejection fraction. (J Am Coll Cardiol HF 2020;8:800–10) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

From the [a]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, United Kingdom; and the [b]Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, Boston, Massachusetts. *Drs. Docherty and Vaduganathan contributed equally to this work and are joint first authors. Dr. Vaduganathan is supported by the KL2/Catalyst Medical Research Investigator Training award from Harvard Catalyst, The Harvard Clinical and Translational Science Center (NIH/NCATS Award UL 1TR002541); and serves on advisory boards for Amgen, AstraZeneca, Baxter Healthcare, Bayer AG, Boehringer Ingelheim, Cytokinetics, and Relypsa. Dr. Solomon has received research grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Celladon, Gilead, GlaxoSmithKline, Ionis Pharmaceutics, Lone Star Heart, Mesoblast, MyoKardia, National Institutes of Health/NHLBI, Novartis, Sanofi Pasteur, and Theracos; and has consulted for Alnylam, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Corvia, Gilead, GlaxoSmithKline, Ironwood, Merck, Novartis, Pfizer, Takeda, and Theracos. Prof. McMurray's employer, Glasgow University, has been paid by Novartis (who manufacture sacubitril/valsartan) for his time spent as committee member for the trials listed (using sacubitril/valsartan), meetings related to these trials and other activities related to sacubitril/valsartan e.g., lectures, advisory boards and other meetings. Novartis has also paid his travel and accommodation for some of these meetings. These payments were made through a Consultancy with Glasgow University and he has not received personal

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In 2014, the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure [PARADIGM-HF]; NCT01035255) established that the combination of the neprilysin inhibitor pro-drug sacubitril and valsartan, an angiotensin II type 1 receptor blocker [ARB], was superior to the angiotensin-converting enzyme (ACE) inhibitor, enalapril, in reducing morbidity and mortality in patients with chronic heart failure with reduced ejection fraction (HFrEF) (1). Clinical practice guidelines have since afforded sacubitril/valsartan a Class I recommendation as a replacement for an ACE inhibitor (Supplemental Refs. 1,2).

Subsequent analyses of PARADIGM-HF and new trials have provided new information about how neprilysin inhibition works and how sacubitril/valsartan can be used in practice. Further trials are currently underway, examining whether neprilysin inhibition may be valuable in other groups of patients such as after an acute myocardial infarction.

HOW DOES NEPRILYSIN INHIBITION WORK?

NEPRILYSIN SUBSTRATES. Despite the findings of PARADIGM-HF, the exact mechanisms underlying the therapeutic benefit of neprilysin inhibition are not entirely certain. The substrates for neprilysin are multifarious and include the biologically active natriuretic peptides, adrenomedullin, endothelin, angiotensin II, and substance P, among others, and it is unclear which of those substrates or combination of substrates is responsible for the benefit observed (**Figure 1**).

Recent biomarker-based mechanistic studies have provided further insight into potential pathways that may be relevant to the benefits observed with angiotensin receptor-neprilysin inhibitor (ARNI). Compared with enalapril, treatment with sacubitril/valsartan in PARADIGM-HF was associated with an increase in B-type natriuretic peptide (BNP) and urinary levels of cyclic guanosine monophosphate (cGMP), the latter reflecting the increase in intracellular second-messenger levels resulting from the action of natriuretic peptides and other direct and indirect effects of mediators increased by neprilysin inhibition (2). However, the increase in BNP levels after initiation of sacubitril/valsartan was modest in most treated patients (3).

In contrast, A-type natriuretic peptide (ANP), for which neprilysin has a greater affinity than BNP, increased more consistently and robustly after sacubitril/valsartan initiation (Supplemental Refs. 3,4). It may be that ANP or, indeed, other neprilysin substrates (e.g., C-type natriuretic peptide, urodilatin, bradykinin, adrenomedullin, substance P, vasoactive intestinal peptide [VIP], calcitonin gene-related peptide [CGRP], glucagon-like peptide-1 [GLP-1], and apelin) (**Figure 1**) play a predominant role in the mechanism of action of sacubitril/valsartan, and further mechanistic studies are ongoing to elucidate the processes underlying the clinical benefits observed in PARADIGM-HF.

Levels of the N-terminal prohormone of BNP, N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is not a direct substrate of the neprilysin enzyme, and troponin were significantly lowered by treatment with sacubitril/valsartan, reflecting a reduction in cardiac wall stress and cardiac injury, respectively (2). This reduction in NT-proBNP occurred within 4 weeks of therapy in PARADIGM-HF and earlier in other studies. NT-proBNP reduction was strongly and directly related to the observed benefit and represented a near perfect surrogate for benefit in PARADIGM-HF (4). In PARADIGM-HF, treatment with sacubitril/valsartan led to significant reductions in levels of aldosterone, soluble ST2, matrix metalloproteinase (MMP)-9, and its specific inhibitor, tissue inhibitor of metalloproteinases (TIMP)-1, reflecting a reduction in profibrotic signaling (Supplemental Ref. 5). Procollagen amino-terminal propeptide types I (PINP) and III (PIIINP) levels also were reduced compared with enalapril, reflecting reduced collagen synthesis. It is uncertain whether neprilysin inhibition has a direct effect on extracellular matrix homeostasis or if these profibrotic benefits reflect hemodynamic improvement. The completed PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular

ABBREVIATIONS AND ACRONYMS

ACE inhibitors = angiotensin-converting enzyme inhibitors

ARB = angiotensin II receptor blockers

ARNI = angiotensin receptor-neprilysin inhibitor

BNP = B-type natriuretic peptide

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

NYHA = New York Heart Association

payments in relation to these trials/this drug. The trials include PARADIGM-HF: co-PI; PARAGON-HF: co-PI; PERSPECTIVE, PARADISE-MI and UK HARP III Trial: executive/steering committees. Prof. McMurray and Dr. Docherty are conducting an investigator originated study funded by the British Heart Foundation (Project Grant no. PG/17/23/32850) using sacubitril/valsartan supplied by Novartis.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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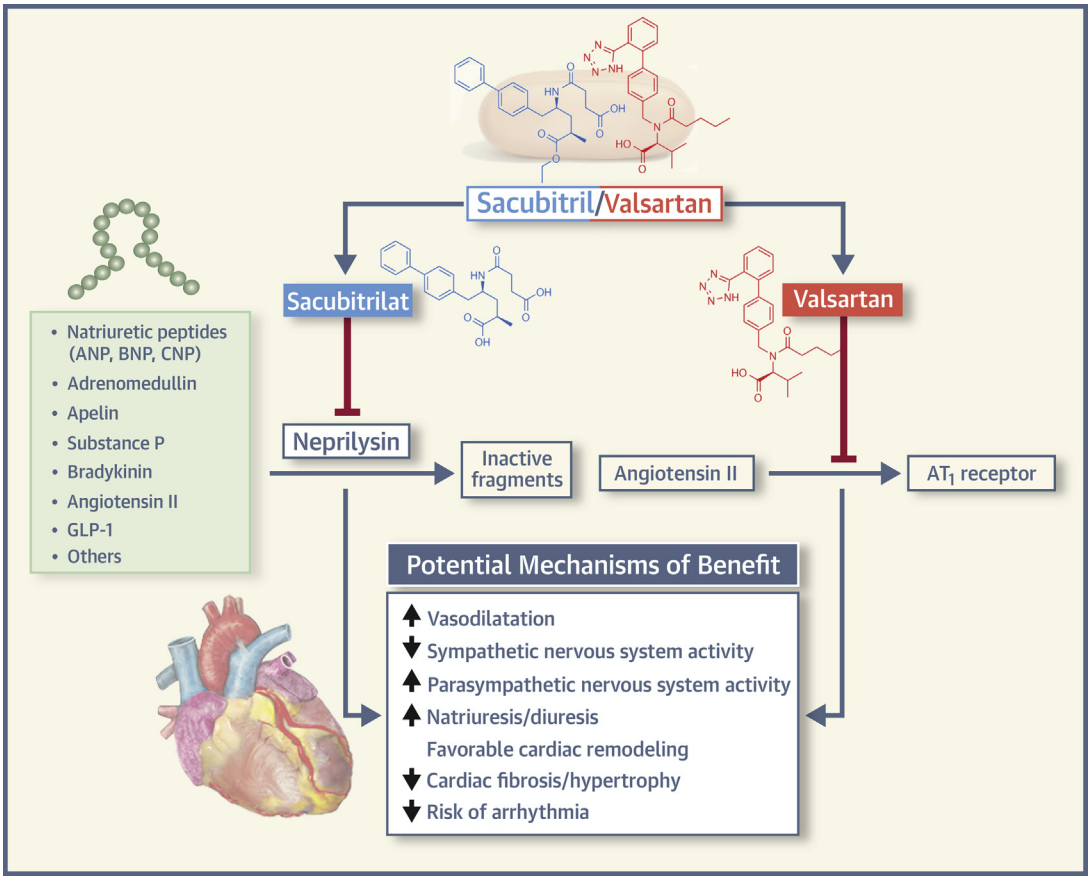
FIGURE 1 Mechanism of Action of Sacubitril/Valsartan



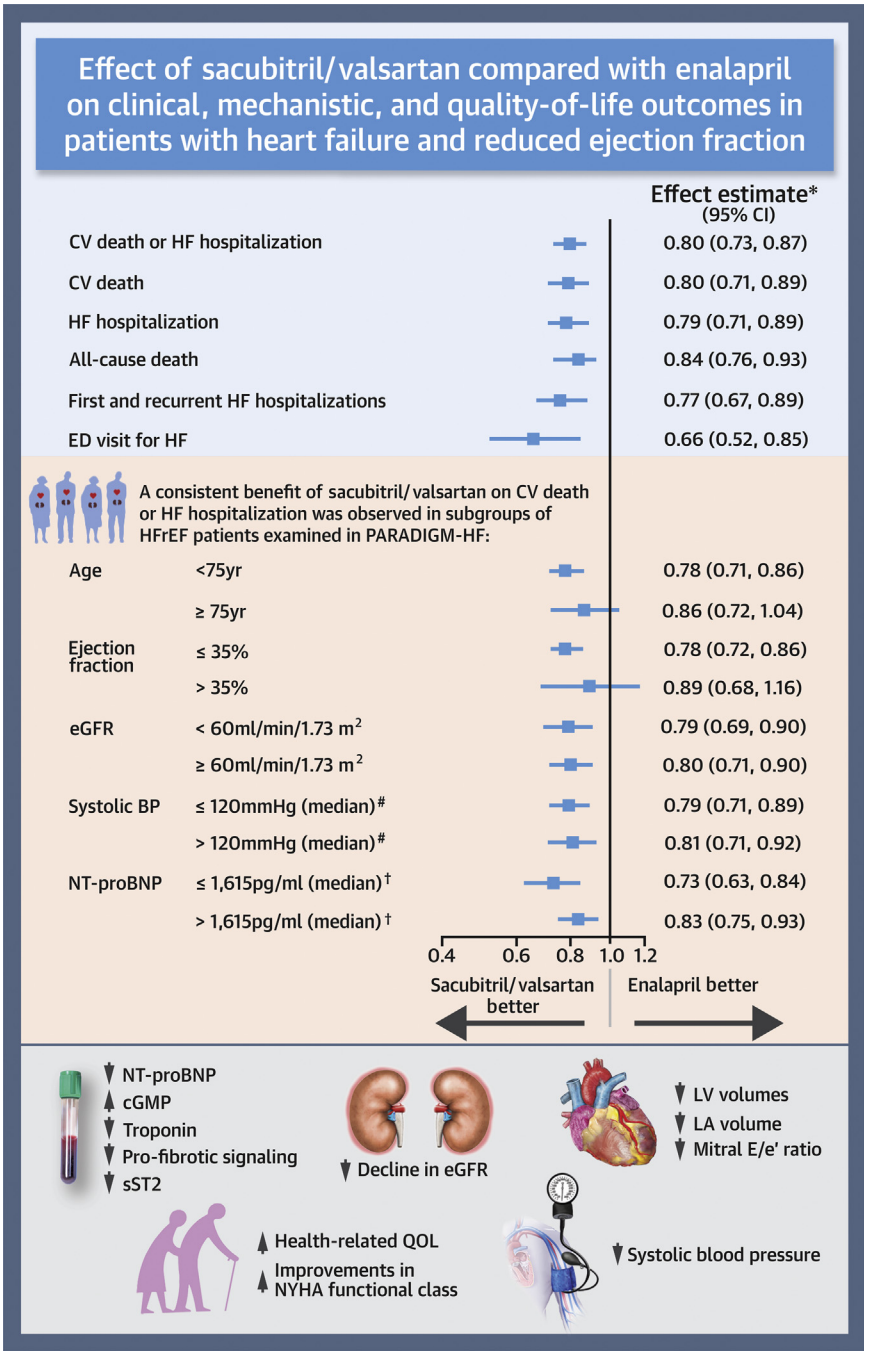
Sacubitril/valsartan is a combination of an angiotensin receptor blocker (valsartan) and a neprilysin inhibitor pro-drug (sacubitril). In binding to the AT1 receptor, valsartan attenuates the vasoconstrictive, sodium-retaining, and pro-fibrotic and pro-mitotic effects of angiotensin II. Neprilysin is responsible for the breakdown of a variety of vasoactive peptides. Sacubitrilat inhibits neprilysin activity, thereby increasing endogenous levels of these peptides, resulting in increased vasodilation, natriuresis, and diuresis, along with a reduction in cardiac fibrosis and hypertrophy. **Red lines** denote inhibitory actions. ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CNP = C-type natriuretic peptide.

Remodeling During Sacubitril/Valsartan Therapy for Heart Failure; [PROVE-HF]; NCT02887183) will continue to examine a broad range of biomarkers, including markers of collagen homeostasis, in 795 patients with HFrEF treated with open-label sacubitril/valsartan (Supplemental Ref. 6).

REVERSE MYOCARDIAL REMODELING. The clinical benefits of ACE inhibitor, ARB, β-blockers, and cardiac resynchronization therapy are due, in part, to beneficial effects on maladaptive ventricular dilation and hypertrophy, along with reductions in systolic function, in HFrEF, and it has been suggested that neprilysin may reverse this adverse remodeling (Supplemental Ref. 7). Prior to the publication of PARADIGM-HF, the phase II PARAMOUNT (Prospective Comparison of ARNI With ARB on Management of Heart Failure with Preserved Ejection Fraction) trial in patients with HF with preserved ejection fraction (HFpEF) demonstrated a significant reduction in left atrial size and volume in patients randomized to sacubitril/valsartan compared with patients who underwent valsartan therapy after 36 weeks of treatment (Supplemental Ref. 8).

Preclinical acute myocardial infarction and heart failure models have shown improvements in ventricular remodeling with neprilysin inhibition, and nonrandomized observational studies have reported favorable reverse-remodeling in HFrEF patients treated with sacubitril/valsartan (Supplemental Refs. 9-11). In patients with HF and significant functional mitral regurgitation, a significant reduction in both the degree of mitral regurgitation and the left

CENTRAL ILLUSTRATION **Effect of Sacubitril/Valsartan Compared With Enalapril on Clinical, Mechanistic, and Quality-of-Life Outcomes in Patients With Heart Failure With Reduced Ejection Fraction**



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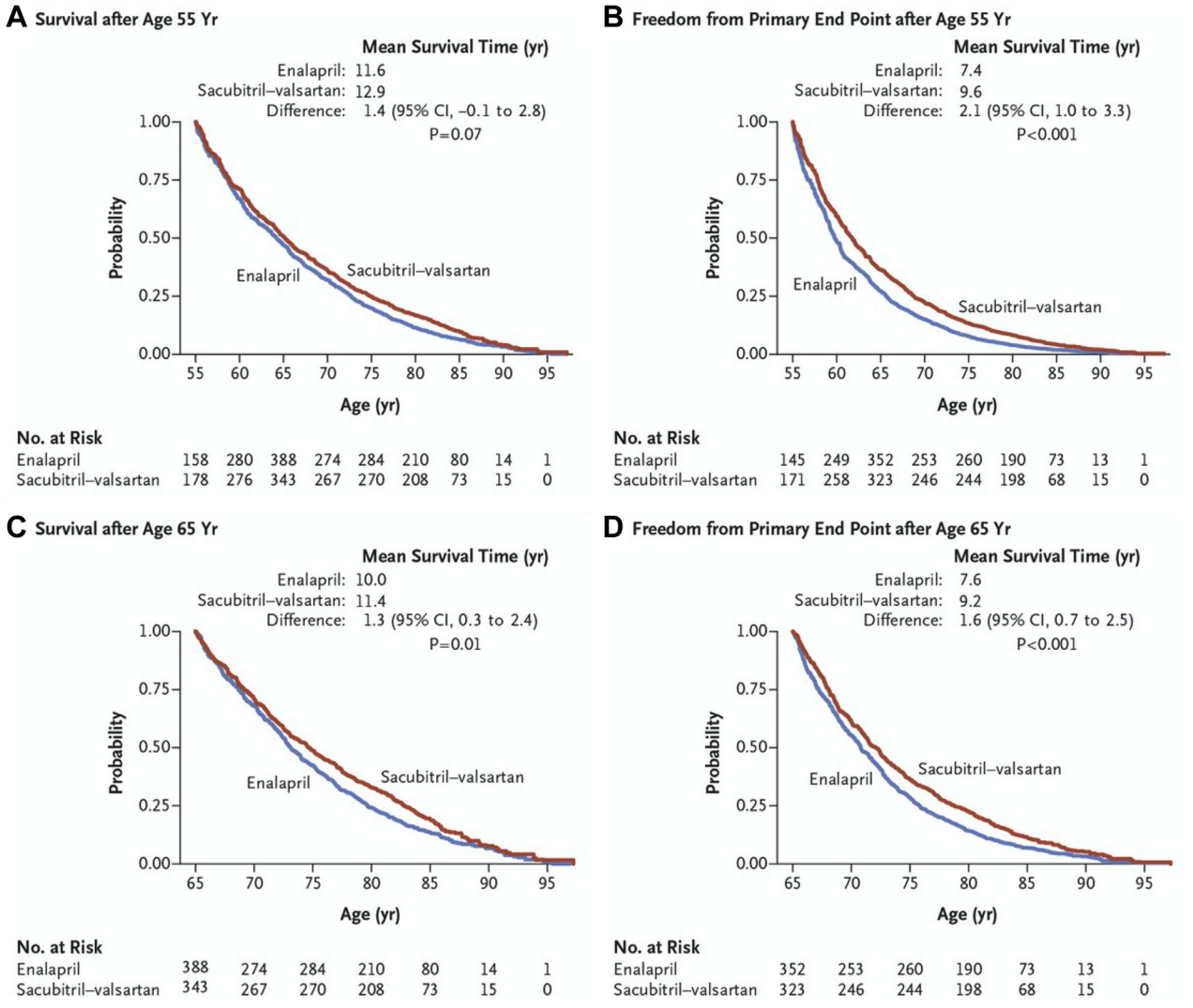
*Effect estimate is presented as a hazard ratio except for first and recurrent heart failure (HF) hospitalizations (rate ratio calculated using the negative-binomial method). #Median systolic blood pressure at randomization = 120 mm Hg. †Median NT-proBNP at screening = 1,615 pg/ml. BP = blood pressure; cGMP = cyclic guanosine monophosphate; CI = confidence interval; CV = cardiovascular; ED = emergency department; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LA = left atrium; QOL = quality of life; LV = left ventricle; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; sST2 = soluble suppression of tumorigenesis-2.

FIGURE 2 Estimation of the Extension of Life Expectancy With Sacubitril/Valsartan Versus Enalapril Based on Projections From the PARADIGM-HF Trial



Age-based Kaplan-Meier curves by randomized treatment in PARADIGM-HF at the age of 55 years **(A, B)** and 65 years **(C, D)**. The primary endpoint was a composite of first occurrence of hospitalization for heart failure or cardiovascular death **(B, D)**. **(A, C)** Freedom from death from any cause. The between-treatment differences represent the differences in mean survival time free from the endpoint. Reprinted from Claggett et al. (7) with permission.

ventricular (LV) end-diastolic volume, as measured by echocardiography, was observed with sacubitril/valsartan, compared with valsartan, in a randomized controlled trial of 118 patients (Supplemental Ref. 12). PROVE-HF, a prospective, single-group, open-label study of sacubitril/valsartan in patients with HFrEF, reported a significant 9.4% (95% confidence interval [CI]: 8.8 to 9.9; $p < 0.001$) absolute improvement in LV ejection fraction (LVEF) as measured by echocardiography, which correlated with changes in NT-proBNP over 12 months of follow-up (5). Favorable changes in LV volumes and indices of LV filling pressures (left atrial volume and E/e′ ratio) were also reported. In the randomized, double-blind EVALUATE-HF (Study of Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction), no beneficial effect of sacubitril/valsartan on the primary endpoint of central aortic stiffness or the prespecified secondary endpoint of LVEF was reported compared with enalapril (6). However, significant favorable changes with sacubitril/valsartan in the prespecified secondary endpoints of LV and left atrial volumes were observed after 12 weeks of follow-up. These

aged data suggest that the beneficial clinical effects of neprilysin inhibition in HFrEF may be partly due to a reverse remodeling mechanism of action.

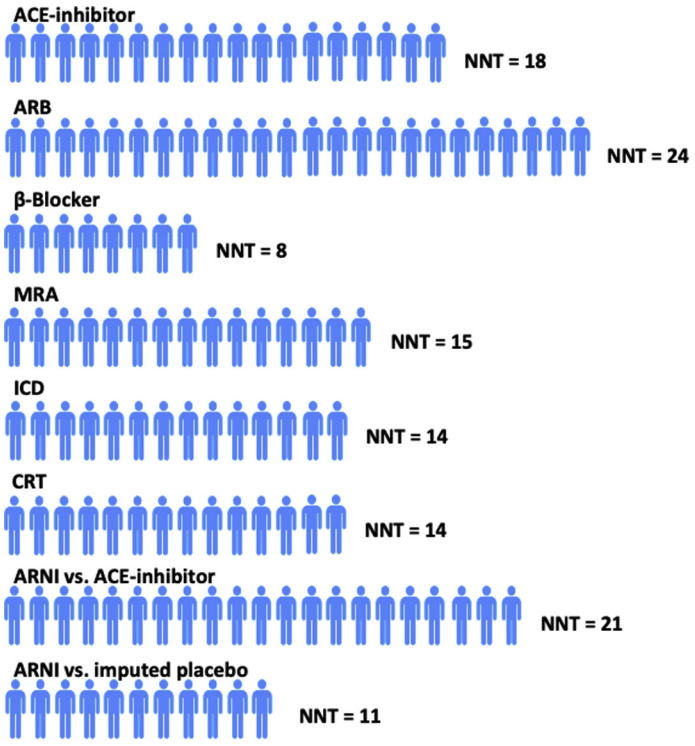
The currently enrolling PARADISE-MI (Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI; NCT02924727) trial includes an echocardiographic substudy and will provide information on the remodeling effect of neprilysin inhibition in patients with LV systolic dysfunction or HF or both following an acute myocardial infarction (Supplemental Table 1). Another dedicated, randomized, cardiac magnetic resonance-based trial comparing sacubitril/valsartan to valsartan in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, RECOVER-LV (Effects of Sacubitril/Valsartan Compared to Valsartan on LV Remodeling in Asymptomatic LV Systolic Dysfunction After MI; NCT03552575) will provide further insight into the potential remodeling effects of ARNI.

CLINICAL BENEFITS OF SACUBITRIL/VALSARTAN VERSUS RAS BLOCKADE ALONE

After the publication of the primary results of PARADIGM-HF, a series of subsequent prespecified and post hoc analyses have provided detailed insight into the clinical and quality-of-life benefits of sacubitril/valsartan compared to enalapril (**Central Illustration**).

ESTIMATING EFFECTS OF LONG-TERM THERAPY. The estimated long-term effects of a treatment are a helpful adjunct to clinical trial results in providing easy-to-understand information to patients regarding the potential benefits of 1 treatment compared to another. Leveraging follow-up data from PARADIGM-HF, using actuarial methods and assuming consistent long-term benefits, patients randomized to sacubitril/valsartan aged 55 and 65 years were estimated to have an average survival benefit, compared to enalapril, of 1.4 years (95% CI: −0.1 to 2.8) and 1.3 years (95% CI: 0.3 to 2.4), respectively (**Figure 2**) (7). On a U.S. population level, assuming similar treatment effects and application of the therapy provided by PARADIGM-HF, >28,000 deaths may be averted by switching eligible patients with HFrEF from an ACE inhibitor/ARB to an ARNI (Supplemental Ref. 13). In PARADIGM-HF, the estimated 5-year number needed to treat (NNT) for the primary outcome of cardiovascular mortality or HF hospitalization was 14 (8) (**Figure 3**). For all-cause mortality, the NNT was 21 for sacubitril/valsartan versus enalapril (i.e., adding a neprilysin inhibitor to a renin-angiotensin aldosterone system (RAS) blocker, compared with a RAS blocker alone). This is compared to NNTs for all-cause mortality of 18 for an ACE inhibitor, 8 for a β-blocker, 15 for a mineralocorticoid receptor antagonist, 14 for an implantable cardioverter-defibrillator, and 14 for cardiac resynchronization therapy (CRT) for all-cause mortality.

FIGURE 3 Estimated 5-Year Number Needed to Treat for All-Cause Mortality



The estimated 5-year number needed to treat for all-cause mortality using data from landmark trials in HFrEF from Srivastava et al. (8). ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; NNT = number needed to treat.

REDUCING THE BURDEN OF HOSPITALIZATIONS. Another goal of treating patients with HFrEF is to reduce the occurrence of often multiple hospitalizations for worsening HF and to maximize the time patients spend out of hospital. In PARADIGM-HF, more than a median follow-up of 27 months, approximately a one-third of patients with a first HF hospitalization had at least 1 additional admission. In an analysis of recurrent events, compared with enalapril, sacubitril/valsartan reduced both first and recurrent events for both HF hospitalization and the combined endpoint of recurrent HF hospitalizations and cardiovascular death (9). The risk of readmission for decompensated HF was

highest in the early period after discharge and was associated with a high mortality rate. In the United States, 30-day readmission rate is a quality-of-care metric which, if higher than expected, may lead to financial penalty. In PARADIGM-HF, the rates of investigator-reported readmission for HF at 30 days were 9.7% and 13.4% in patients randomized to sacubitril/valsartan and enalapril, respectively (odds ratio: 0.62; 95% CI: 0.45 to 0.87; p = 0.006) (10). The benefit was also seen at 60 days.

WORSENING HF AND CLINICAL DETERIORATION. Beyond the reductions in mortality and reports of HF hospitalization in PARADIGM-HF, the addition of a neprilysin inhibitor to a RAS blocker reduced other nonfatal manifestations of clinical deterioration, including the need to intensify medical treatment for HF and visits to an emergency department for worsening HF (2). Even among patients hospitalized with worsening HF, sacubitril/valsartan reduced the rate of admission to intensive care (risk reduction [RR]: 18%; p = 0.005), the use of intravenous inotropes (RR 31%; p < 0.001), and a composite of implantation of ventricular assist devices, cardiac transplantations, and CRT (RR 22%; p = 0.07). Investigator-assessed symptomatic limitation, as measured by New York Heart Association (NYHA) functional class, was also improved, with fewer sacubitril/valsartan-treated patients deteriorating by ≥1 class at 8 and 12 months following randomization, compared with enalapril (2).

Adding neprilysin inhibition to a RAS blocker, compared with a RAS blocker alone, reduced both major modes of CV death among patients with HFrEF, sudden cardiac death, and death due to worsening HF (11). The incremental benefit of neprilysin inhibition compared with RAS inhibition alone in reducing the risk of CV death was observed despite high levels of effective medical and device therapy. Among the potential mechanisms underlying this benefit are reduced wall stress, ventricular dilation, cardiomyocyte injury and hypertrophy, and fibrosis, each of which may reduce the substrate for episodes of arrhythmia. The possible vagoexcitatory and sympathoinhibitory actions of natriuretic peptides may also improve electric stability (Supplemental Ref. 14).

IMPROVING QUALITY OF LIFE. Compared with enalapril in PARADIGM-HF, sacubitril/valsartan improved health-related quality of life in patients with HFrEF. Specifically, sacubitril/valsartan reduced symptom burden and physical limitations related to heart failure, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), and this benefit extended to nearly all domains of the score when examined individually (1,12,13). A significantly smaller proportion of patients randomized to sacubitril/valsartan reported a clinically meaningful deterioration in the KCCQ overall summary score (≥5 points decrease) compared with those randomized to enalapril (27% vs. 31%, respectively; p = 0.01) (12).

Furthermore, compared to individuals randomized to enalapril, patients receiving sacubitril/valsartan reported a significantly attenuated decline in the EQ-5D-3L non disease-specific outcome measurement, an evaluation of 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), regardless of baseline NYHA functional class, and this benefit persisted at 36-months follow-up (Supplemental Ref. 15).

SAFETY OF SACUBITRIL/VALSARTAN

RUN-IN PHASES AND TOLERABILITY. In PARADIGM-HF, patients were required to tolerate target doses of both enalapril and sacubitril/valsartan during sequential run-in phases, with approximately 10% of participants discontinuing each treatment phase because of intolerance or other reasons. This design element may limit the generalizability of the study findings. Several factors were associated with a higher risk of discontinuation of either enalapril or sacubitril/valsartan during the run-in period, including higher natriuretic peptide levels, lower blood pressure, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 and an ischemic cause (Supplemental Ref. 16). An inverse probability-weighted reanalysis of PARADIGM-HF, giving additional weight to those randomized patients with similar characteristics to those who did not complete the run-in, showed a similar benefit of sacubitril/valsartan compared to enalapril, suggesting that the run-in period and related discontinuations did not alter the interpretation of the results of the trial (Supplemental Ref. 16).

RENAL FUNCTION AND POTASSIUM. Renal dysfunction and hyperkalemia are factors limiting attainment of target doses of RAS antagonists. In PARADIGM-HF, both renal dysfunction (serum creatinine: ≥2.5 mg/dl [221 μmol/l]) and severe hyperkalemia (>6 mmol/l) occurred less frequently with sacubitril/valsartan than with enalapril (1). Furthermore, the decline in eGFR over time was attenuated with sacubitril/valsartan compared to enalapril, despite a small increase in urinary albumin/creatinine ratio with neprilysin inhibition (14). Moreover, patients with chronic kidney disease at baseline, who were at particularly high risk of adverse outcomes, had a similar relative risk reduction with sacubitril/valsartan compared with enalapril and, thus, a large absolute benefit from the addition of a neprilysin inhibitor to RAS blockade.

The combination of a mineralocorticoid receptor antagonist (MRA) with a RAS blocker increases the risk of hyperkalemia. Patients taking an MRA at baseline in PARADIGM-HF randomly assigned to enalapril were more likely to experience severe hyperkalemia than those randomized to sacubitril/valsartan, suggesting that the addition of neprilysin inhibition to dual RAS blockade may reduce the risk of hyperkalemia associated with this combination (15).

HEMODYNAMIC INTOLERANCE. In PARADIGM-HF, symptomatic hypotension occurred more frequently in the sacubitril/valsartan group than in those receiving enalapril, although this did not lead to a difference in discontinuation between the treatment arms (1). Hypotension was more likely to occur in older patients, those with a lower systolic blood pressure at screening, and patients taking doses lower than target doses of ACE inhibitor/ARB prior to enrolment (Supplemental Ref. 17). Importantly, there was no interaction between the occurrence of hypotension, either during the run-in phase or following randomization, and the beneficial treatment effect of sacubitril/valsartan. These results, along with the observation that patients who received subtarget doses of sacubitril/valsartan due to intolerance of higher doses derived similar benefit to those who tolerated higher doses, emphasizing that hypotension should not dissuade clinicians from commencing or continuing sacubitril/valsartan therapy at a lower-than-target dose (Supplemental Ref. 18).

In PARADIGM-HF, discontinuation of a diuretic was more common in those treated with sacubitril/valsartan, and the number of diuretic dose increases were fewer than in those treated with enalapril (Supplemental Ref. 19).

ANGIOEDEMA. Because only 1 bradykinin-metabolizing enzyme (neprilysin) is inhibited with sacubitril/valsartan, the risk of angioedema should be low compared with combined ACE and neprilysin inhibition (e.g., using omapatrilat) (Supplemental Ref. 20). Angioedema was independently adjudicated in PARADIGM-HF by a blinded committee with a small number of confirmed cases and no major imbalance between treatment arms. Consistent with prior reports that African-American patients are at increased risk of treatment-related angioedema, black patients in PARADIGM-HF did experience a higher risk of sacubitril/valsartan-related angioedema than non-black patients (Supplemental Ref. 21).

AMYLOID DEPOSITION. Because neprilysin is partially responsible for the clearance of certain amyloid-β peptides from the brain, an ARNI may, theoretically, increase cerebral deposition of these peptides and, in the long term, potentially have an adverse impact on cognition. Two weeks treatment with sacubitril/valsartan compared with placebo increased concentrations of amyloid-β1-38 in the cerebrospinal fluid of healthy volunteers, although concentrations of amyloid-β1-40 and the toxic amyloid-β1-42 were unaltered (Supplemental Ref. 22). Moreover, rates of dementia-related adverse events in PARADIGM-HF were similar in the sacubitril/valsartan and enalapril treatment arms and similar to rates observed with other contemporary trials of HFrEF (Supplemental Ref. 23). A dedicated mini-mental state examination is embedded in the large PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; PARAGON; NCT01920711) trial. Similarly, the PERSPECTIVE (Efficacy and Safety of LCZ696 Compared to Valsartan on Cognitive Function in Patients With Chronic Heart Failure and Preserved Ejection Fraction; NCT02884206) trial is comprehensively evaluating the effects of sacubitril/valsartan compared with valsartan on cognitive function employing a battery of validated neurocognitive instruments and advanced imaging for amyloid deposition in over 550 patients with HFpEF (Supplemental Table 1).

SACUBITRIL/VALSARTAN ACROSS THE HF SPECTRUM

In PARADIGM-HF, consistent benefits of sacubitril/valsartan compared to enalapril were observed across a range of prespecified and other subgroups, including race and geographic region (with patients enrolled in 47 countries on 6 continents) (1) (Supplemental Ref. 24). Sacubitril/valsartan was also beneficial across the whole spectrum of age (patients between 18 and 96 years of age were enrolled in PARADIGM-HF), and there was no interaction between age and the risk of any adverse events (Supplemental Ref. 25). Moreover, the benefits of the addition of neprilysin inhibition were evident regardless of the cause of HFrEF (Supplemental Ref. 26).

PARADIGM-HF also encompassed patients with a broad spectrum of baseline risk and severity of LV dysfunction. The incremental benefit of ARNI was consistent regardless of baseline risk as assessed by the MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Study in Heart Failure) risk scores and ejection fraction (Supplemental Refs. 27,28). The mean baseline LVEF was 29.5 ± 6.2%. A lower LVEF was associated with a higher

risk of all outcomes, with a 5-point reduction in LVEF associated with a 9% higher risk of the composite of cardiovascular death or HF hospitalization and each of its components (Supplemental Ref. 28). The beneficial treatment effect of sacubitril/valsartan was not modified by LVEF (p interaction = 0.95 with LVEF modeled as a continuous variable).

The treatment benefits of sacubitril/valsartan were not influenced by the clinical stability of patients at baseline, as determined by the occurrence of or time from a hospitalization for HF prior to screening (Supplemental Ref. 29). Overall, 37% of patients in PARADIGM-HF were "clinically stable" at baseline with no history of HF hospitalization prior to randomization. The risk of all endpoints was lower in that subgroup than in less stable patients (those with a history of HF hospitalization), although 20% of "stable" patients had a primary endpoint, and 17% died during follow-up. Of those who died, 51% had a cardiovascular death, with no preceding HF hospitalization, and 60% of those deaths occurred suddenly. These data highlight that perceived "stability" is not a reason to withhold the incremental benefits of neprilysin inhibition from patients with HFrEF.

Diabetes mellitus occurs in 30% to 45% of patients with HFrEF and is associated with higher morbidity and mortality than in patients without diabetes. One of the substrates for neprilysin is glucagon-like peptide (GLP)-1, and inhibition of the breakdown of this peptide may result in reduction in blood glucose (Supplemental Ref. 30). In PARADIGM-HF, treatment with sacubitril/valsartan resulted in a greater reduction in glycated hemoglobin (HbA1c) than treatment with enalapril in patients with known diabetes mellitus or an HbA1c concentration ≥6.5% at screening (between-group reduction 0.14%; 95% CI: 0.06 to 0.23; p = 0.0055) (Supplemental Ref. 31). Furthermore, there was less initiation of insulin or oral glucose-lowering medications in patients randomized to sacubitril/valsartan compared with those receiving enalapril. Additionally, the reduction in decline of eGFR over time, which was more marked in patients with diabetes than in those without, was attenuated with sacubitril/valsartan (to at least as great an extent as in individuals without diabetes) (p for interaction = 0.038) (Supplemental Ref. 32).

PRACTICAL CONSIDERATIONS WITH SACUBITRIL/VALSARTAN

PATIENT SELECTION. Ambulatory or hospitalized patients with HFrEF and a systolic blood pressure ≥100 mm Hg are potential candidates for sacubitril/valsartan. The safety and efficacy of sacubitril/valsartan among patients with advanced HFrEF (defined as patients with NYHA functional class IV symptoms, an LVEF ≤35%, elevated natriuretic peptide levels, established on evidence-based HFrEF therapy for at least 3 months [or intolerant of this] and at least one of the following criteria: current or recent use of inotropes; HF hospitalization in the previous 6 months; LVEF ≤25%; or reduced functional capacity measured by either peak VO_2 or 6-min walk test) is being studied in the HFN-LIFE (Entresto [LCZ696] in Advanced Heart Failure [LIFE STUDY]; NCT02816736) trial (Supplemental Table 1). Although U.S. and European guidelines differ regarding the need for optimization of background medical therapies (namely β-blockers and MRAs), the efficacy of ARNI appears consistent regardless of background therapy (Supplemental Ref. 33). Implementation of multidrug regimens of therapies known to alter disease course and mortality in HFrEF (ARNI, β-blockers, MRAs, and most recently the sodium-glucose cotransporter-2 inhibitor dapagliflozin) is expected to afford substantial extension of life expectancy and survival free from heart failure events (16).

IN-HOSPITAL INITIATION. Although most patients in PARADIGM-HF were in NYHA functional class II, the analyses described above showed many of those patients were at high risk and far from "stable." The efficacy of sacubitril/valsartan was consistent across risk strata and similar whether patients were recently hospitalized or not (Supplemental Ref. 29). Patients in hospital because of decompensated HF face the highest risks of near-term readmission and mortality and, thus, potentially stand most to benefit from therapeutic optimization. Although these patients were excluded from evaluation in PARADIGM-HF, in the PIONEER-HF (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) study, the safety and efficacy of in-hospital initiation of sacubitril/valsartan and enalapril were compared in 881 patients stabilized after admission with decompensated HFrEF. The concentration of NT-proBNP (the primary endpoint) was reduced more by sacubitril/valsartan than by enalapril, from baseline through weeks 4 and 8 after randomization, whereas the rates of key safety outcomes (worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema) were not different between treatment groups (17). Although PIONEER-HF was not powered to assess clinical endpoints, in-hospital initiation of sacubitril/valsartan reduced the composite outcome of

death, rehospitalization for HF, implantation of a LV assist system, or listing for cardiac transplantation by 46%, compared with enalapril. This benefit was due, principally, to an observed reduction in HF rehospitalization. A post hoc exploratory analysis reported a 42% (95% CI: 13% to 61%; p = 0.007) reduction in clinical endpoint committee-adjudicated cardiovascular death or HF hospitalization with sacubitril/valsartan compared to enalapril (Supplemental Ref. 34). A reduction in adjudicated HF hospitalization was evident as early as 30 days after randomization (hazard ratio [HR]: 0.72; 95% CI: 0.42 to 1.25) with a 39% (95% CI: 7% to 60%; p = 0.021) reduction at 8 weeks. In patients who were randomized to sacubitril/valsartan, increased natriuretic peptide bioactivity was evident by significant increases in urinary cGMP levels at 1 week following randomization (Supplemental Ref. 35). Early, favorable changes in levels of biomarkers of both hemodynamic stress (NT-proBNP and soluble ST2) and myocardial injury (high-sensitivity troponin T) were also observed in patients randomized to sacubitril/valsartan compared to enalapril.

The results of PIONEER-HF demonstrate that, in hospitalized patients stabilized from an acute decompensation of HFrEF, the addition of a neprilysin inhibitor to a RAS antagonist and standard therapy was safe and effective compared to standard therapy alone. Furthermore, it provides evidence of benefit in groups of patients who were not enrolled in PARADIGM-HF. At randomization approximately one-half of patients were RAS antagonist-naïve, and one-third of patients were presenting with de novo HF. A strategy for in-hospital initiation may promote persistence with treatment after discharge and help overcome "therapeutic inertia" in the care of ambulatory patients mistakenly considered to be "stable." The open-label TRANSITION (Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event; NCT02661217) trial compared a strategy of sacubitril/valsartan initiation before discharge compared to 1 to 14 days after hospital discharge among 1,002 patients stabilized after hospitalization for HFrEF. Similar proportions of patients in each group achieved predefined target doses of the therapy by 10 weeks after randomization (Supplemental Ref. 36).

DATA-DRIVEN APPROACH TO CLINICAL USE OF SACUBITRIL/VALSARTAN. To minimize risks of angioedema, a washout period of at least 36 h after the last dose of an ACE inhibitor should be allowed prior to initiation of sacubitril/valsartan (this is not necessary if the patient has been taking an ARB). Sacubitril/valsartan is an oral therapy given twice daily, with 3 doses available in most countries: 24/26 mg, 49/51 mg, and 97/103 mg (target dose). In some countries, these doses are described as 50 mg, 100 mg, and 200 mg. Prior dosing and tolerance of an ACE inhibitor/ARB helps guide selection of the appropriate starting dose of ARNI. Based on the American College of Cardiology Expert Consensus Decision Pathway, patients should be started on the 49/51 mg dose if tolerating the equivalent of enalapril 10 mg twice daily, or valsartan 160 mg twice daily. Patients who are RAS-blocker naïve, tolerating less than this dose, or who have severe renal dysfunction or moderate hepatic dysfunction should start with the 24/26 mg dose (Supplemental Ref. 37).

The TITRATION (Safety and Tolerability of Initiating LCZ696 in Heart Failure Patients; NCT01922089) trial assessed strategies for up-titrating and optimizing the dose of sacubitril/valsartan, randomizing 498 patients to a "condensed" regimen (49/51 mg twice daily for 2 weeks followed by 97/103 mg twice daily for 10 weeks) or a "conservative" regimen (24/26 mg twice daily for 2 weeks, 49/51 mg twice daily for 3 weeks, followed by 97/103 mg twice daily for 7 weeks) (Supplemental Ref. 38). Rates of hypotension, renal dysfunction, and hyperkalemia at 12 weeks were similar in the 2 treatment groups. Overall, attainment of the target dose of 97/103 mg twice daily was similar between arms, and three-fourths of patients were successfully maintained on this dose. However, among patients taking lower preinitiation doses of ACE inhibitor/ARB, the conservative up-titration regimen resulted in greater attainment of target dosing than with the condensed regimen (Supplemental Ref. 38). In clinical practice, dose increases toward the target dose of 97/103 mg may be made every 2 to 4 weeks, depending on tolerability assessed by symptoms of hypotension, blood pressure, renal function, and potassium. Sacubitril/valsartan seems to be "diuresis-sparing," and loop diuretic dose may need to be reduced during or after up-titration (Supplemental Ref. 19). Indeed, in euvolemic patients, consideration should be given to reducing diuretic dose before initiating or switching to sacubitril/valsartan. Similarly, stopping other treatments with a blood pressure-lowering effect that has not been demonstrated to improve clinical outcomes in HFrEF (e.g., nitrates, calcium channel blockers, and alpha-adrenoceptor antagonists) may facilitate the introduction of sacubitril/valsartan.

CONCLUSIONS

Sacubitril/valsartan is an efficacious, safe, and cost-effective therapy that improves quality of life and longevity in patients with chronic HFrEF and reduces hospital admission. An in-hospital initiation strategy offers a potentially new avenue to improve the clinical uptake of sacubitril/valsartan.

The recently completed PARAGON-HF trial showed that sacubitril/valsartan modestly reduced the risks of total heart failure hospitalizations and cardiovascular death than valsartan in patients with HFpEF, although this finding narrowly missed statistical significance (18), Clinical benefits were observed in secondary endpoints including quality of life and kidney endpoints; women and patients at the lower end of the LVEF spectrum appeared to preferentially benefit. The safety profile of sacubitril/valsartan was largely consistent with prior trial experiences. Regulatory review of sacubitril/valsartan for the treatment of HFpEF is currently under way. Ongoing trials are evaluating the clinical utility of sacubitril/valsartan among patients with HFpEF (PARALLAX) and acute myocardial infarction (PARADISE-MI) (Supplemental Table 1).

In the last 5 years, sacubitril/valsartan has been established as a cornerstone component of comprehensive disease-modifying medical therapy in the management of chronic HFrEF. The next 5 years should see its wider implementation in practice and potential expansion of its therapeutic indications.

ADDRESS FOR CORRESPONDENCE: Prof. John J.V. McMurray, Institute of Cardiovascular and Medical Sciences, BHF Cardiovascular Research Centre, University of Glasgow, Glasgow G12 8TA, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk.

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APPENDIX For supplemental tables, please see the online version of this paper.