Title: Sacubitril/Valsartan: Neprilysin inhibition 5 Years after PARADIGM-HF

Brief Title: Updated Perspective on Sacubitril/Valsartan

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DISCLOSURES

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Tweet: A comprehensive review of data supporting the benefits of neprilysin inhibition with sacubitril/valsartan in HFrEF

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, when compared to the gold-standard angiotensin-converting enzyme inhibitor, enalapril. 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 multi-drug regimen, including a renin-angiotensin aldosterone system (RAS) blocker. Here we review current understanding of the effects of sacubitril/valsartan and highlight expected developments over the next 5 years, including potential new indications for use. We additionally provide a practical, evidence-based approach to the clinical integration of sacubitril/valsartan among patients with heart failure with reduced ejection fraction.

Key Words: heart failure; neprilysin inhibition; sacubitril/valsartan.

ABBREVIATIONS LIST

ACEi = 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

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 over 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.

Introduction

In 2014, the PARADIGM-HF trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) 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 inhibitor (ACEi), enalapril, in reducing morbidity and mortality in patients with chronic HFrEF (1). Clinical practice guidelines have since afforded sacubitril/valsartan a class I recommendation as a replacement for an ACEi (Online ref 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, substance P, among others, and it is unclear which of these substrates, or combination of substrates, are 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 observed benefits with 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), which neprilysin has a greater affinity for compared to BNP, increases more consistently and robustly after sacubitril/valsartan initiation (Online ref. 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 (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-9 (MMP-9) and its specific inhibitor, tissue inhibitor of metalloproteinases-1 (TIMP-1), reflecting a reduction in profibrotic signalling (Online ref 5). Procollagen aminoterminal

propeptide type I (PINP) and type III (PIIINP) levels, were also reduced, compared with enalapril, reflecting reduced collagen synthesis. It is uncertain whether neprilysin inhibition has a direct effect on ECM homeostasis or if these profibrotic benefits reflect hemodynamic improvement. The completed PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure; 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 (Online ref 6).

Reverse Myocardial Remodeling. The clinical benefits of ACEi, ARB, β-blockers and cardiac resynchronisation therapy (CRT) are in part, due to beneficial effects on maladaptive ventricular dilatation and hypertrophy, along with reductions in systolic function, in HFrEF and it has been suggested that neprilysin may reverse this adverse remodeling (Online ref 7). Prior to the publication of PARADIGM-HF, the phase II Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) 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 valsartan after 36 weeks of treatment (Online ref 8).

Pre-clinical acute myocardial infarction and heart failure models have shown improvements in ventricular remodeling with neprilysin inhibition, and non-randomized, observational studies have reported favorable reverse-remodeling in HFrEF patients treated with sacubitril/valsartan (Online ref. 9-11). In patients with HF and significant functional mitral regurgitation, a significant reduction in both the degree of mitral regurgitation and LV end-diastolic volume, as measured by echocardiography, was observed with sacubitril/valsartan,

compared with valsartan, in a randomized controlled trial of 118 patients (Online ref. 12). PROVE-HF, a prospective, single-group, open-label study of sacubitril/valsartan in HFrEF, reported a significant 9.4% (95%CI 8.8-9.9, 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) Favourable changes in LV volumes and indices of left ventricular filling pressures (left atrial volume and E/e' ratio) were also reported. In the randomized, double-blind Study of Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction (EVALUATE-HF), 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 favourable changes with sacubitril/valsartan in the prespecified secondary endpoints of LV and left atrial volumes were observed after 12-weeks of follow-up. These data suggest that the beneficial clinical effects of neprilysin inhibition in HFrEF may be, in part, due to a reverse remodelling mechanism of action.

The currently enrolling PARADISE-MI trial includes an echocardiographic substudy and will provide information on the remodeling effect of neprilysin inhibition in patients with left ventricular systolic dysfunction (LVSD), HF, or both following an acute myocardial infarction (**Supplementary Table 1**). Another dedicated randomized, cardiac magnetic resonance imaging-based trial comparing sacubitril/valsartan to valsartan in patients with asymptomatic LVSD and a prior history of myocardial infarction (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 pre-specified and *post-hoc* analyses have provided detailed insight into the clinical and quality-of-life benefits of sacubitril/valsartan over enalapril.

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 one treatment over another. Leveraging follow-up data from PARADIGM-HF using actuarial methods and assuming consistent long-term benefits patients randomised to sacubitril/valsartan aged 55 and 65 years were estimated have an average survival benefit, compared to enalapril, of 1.4 years (95% confidence interval [CI], -0.1-2.8) and 1.3 years (95% CI, 0.3-2.4), respectively (**Figure 2**) (7). On a US population level, assuming similar treatment effects and application of the therapy as in PARADIGM-HF, >28,000 deaths may be averted by switching eligible patients with HFrEF from ACEi/ARB to ARNI (Online ref. 13). In PARADIGM-HF the estimated 5-year number needed to treat (NNT) for the primary outcome of cardiovascular mortality or HF hospitalisation 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 RAS blocker, compared with a RAS blocker alone. This compared to NNTs for all-cause mortality of 18 for an ACEi, 8 for a β-blocker, 15 for a mineralocorticoid receptor antagonist, 14 for an implantable cardioverter-defibrillator, and 14 for cardiac resynchronization therapy for all-cause mortality.

Reducing Burden of Hospitalizations. Another goal of treating HFrEF is to reduce the occurrence of often multiple hospitalizations for worsening HF and maximize the time patients spend out of hospital. In PARADIGM-HF, over a median follow-up of 27 months,

approximately a third of patients with a first HF hospitalization had at least one further admission. In a recurrent events analysis, 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 is highest in the early after discharge and is associated with a high mortality rate. In the US, 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 0.45-0.87; p=0.006) (10). The benefit was also seen at 60 days.

Worsening HF & Clinical Deterioration. Beyond the improvements in mortality and HF hospitalisation reported in PARADIGM-HF, the addition of a neprilysin inhibitor to a RAS blocker reduces other of non-fatal manifestations of clinical deterioration, including of 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 ventricular assist device implantation, cardiac transplantation and cardiac resynchronization therapy (RR 22%, p=0.07). Investigator-assessed symptomatic limitation, as measured by 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 a 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 dilatation, cardiomyocyte injury and hypertrophy, and fibrosis, each of which may reduce the substrate for arrhythmias. The possible vagoexcitatory and sympathoinhibitory actions of natriuretic peptides may also improve electrical stability (Online ref. 14).

Improving Quality of Life. Compared with enalapril in PARADIGM-HF, sacubitril/valsartan improved health-related quality of life (HRQL) 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 randomised to sacubitril/valsartan reported a clinically meaningful deterioration (≥5 points decrease) compared with those randomized to enalapril (27% versus 31%; 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 measure, an evaluation of five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), irrespective of baseline NYHA functional class and this benefit persisted at 36-months follow-up (Online ref 15).

Safety of Sacubitril/Valsartan

Run-In Phases & 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, eGFR <60mL/min/1.73m^2, and an ischemic etiology (Online ref 16). An inverse probability-weighted re-analysis 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 over enalapril, suggesting that the run-in period and related discontinuations did not alter the interpretation of the results of the trial (Online ref 16).

Renal Function and Potassium. Renal dysfunction and hyperkalaemia 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 hyperkalaemia (>6mmol/l) occurred less frequently with sacubitril/valsartan, compared 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 (UACR) with neprilysin inhibition (14). Moreover, patients with CKD 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.

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

Hemodynamic Intolerance. In PARADIGM-HF, symptomatic hypotension occurred more frequently with sacubitril/valsartan group than with enalapril, although this did not lead to a difference in discontinuation between the treatment arms (1). Hypotension was more likely in older patients, those with a lower systolic blood pressure at screening and patients on lower than target dose of ACEi/ARB prior to enrolment (Online 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 sub-target doses of sacubitril/valsartan due to intolerance of higher doses derived similar benefit to those who tolerated higher doses, emphasize that hypotension should not dissuade clinicians from commencing or continuing sacubitril/valsartan at a lower than target dose (Online ref 18). In PARADIGM-HF, discontinuation of diuretic was more common in those treated with sacubitril/valsartan, and the number of diuretic dose increases fewer, compared with enalapril (Online ref 19).

Angioedema. Because only one bradykinin-metabolizing enzyme (neprilysin) is inhibited with sacubitril/valsartan, the risk of angioedema should be low compared with combined ACE and neprilysin inhibitor (e.g. using omapatrilat) (Online 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 patients of African-descent are at increased risk of treatment-related angioedema, black patients in PARADIGM-HF did experience a higher risk of sacubitril/valsartan-related angioedema compared with non-black patients (Online ref 21).

Amyloid Deposition. As 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 amyloid-β1-38 concentrations in the cerebrospinal fluid of healthy volunteers, although concentrations of amyloid-β1-40 and the toxic amyloid-β1-42 were unaltered (Online 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 (Online ref 23). A dedicated mini-mental state examination is embedded in the large PARAGON-HF trial (Efficacy and Safety of LCZ696 Compared to Valsartan on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction; NCT01920711). Similarly, the PERSPECTIVE 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 (**Supplementary Table 1**).

Sacubitril/Valsartan Across the HF Spectrum

In PARADIGM-HF, consistent benefits of sacubitril/valsartan over 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, Online ref 24). Sacubitril/valsartan

was also beneficial across the whole spectrum of age (patients aged between 18 and 96 years were enrolled in PARADIGM-HF) and there was no interaction between age and the risk of any adverse events (Online ref 25). Moreover, the benefits of the addition of neprilysin inhibition were evident irrespective of the etiology of HFrEF (Online ref 26).

PARADIGM-HF also encompassed patients with a broad spectrum of baseline risk and severity of left ventricular dysfunction. The incremental benefit of ARNI was consistent irrespective 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 Survival Study in Heart Failure) risk scores and ejection fraction (Online ref 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 of CV death or HF hospitalization, and each of its components (Online ref 28). The beneficial treatment effect of sacubitril/valsartan was not modified by LVEF (P interaction=0.95 with LVEF modelled 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 (Online 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 this 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 these 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 30-45% of patients with HFrEF and is associated with higher morbidity and mortality, compared with patients without diabetes. One of the substrates for neprilysin is glucagon-like peptide-1 (GLP-1) and inhibition of the breakdown of this peptide may result in reduction in blood glucose (Online 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 ≥6·5% at screening (between-group reduction 0·14%, 95%CI 0·06-0·23, p=0·0055) (Online ref 31). Furthermore, there was less initiation of insulin or oral glucose lowering medications in patients randomized to sacubitril/valsartan, compared with 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) (Online ref 32).

Practical Considerations with Sacubitril/Valsartan

Patient Selection: Ambulatory or hospitalized patients with HFrEF and a systolic blood pressure ≥100 mmHg are potential candidates for sacubitril/valsartan. The safety and efficacy of sacubitril/valsartan among patients with advanced HFrEF (defined as patients with NYHA class IV symptoms, an LVEF ≤35%, elevated natriuretic peptide levels, established on evidenced 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; a HF hospitalization in the past 6 months; LVEF ≤25%; or reduced functional capacity measured by either peak VO_2 or 6-minute walk test) is being studied in the HFN-LIFE trial (**Supplementary Table 1)**.

Although the US & European guidelines differ regarding need for optimization of background medical therapies (namely β-blockers and MRAs), the efficacy of ARNI appears consistent irrespective of background therapy (Online ref 33). Implementation of multi-drug regimens of therapies known to alter disease course and mortality in HFrEF (ARNI, β-blockers, MRAs, and most recently the sodium-glucose co-transporter-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 these 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 (Online 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. While these patients were excluded from evaluation in PARADIGM-HF, in PIONEER-HF (Comparison of Sacubitril–Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode), the safety and efficacy of in-hospital initiation of sacubitril/valsartan and enalapril were compared in 881 patients stabilized after admission with decompensated HFrEF. NT-proBNP level (the primary endpoint) was reduced more by sacubitril/valsartan compared to enalapril, from baseline through weeks 4 and 8 after discharge, while 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 left ventricular 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 13-61%; p=0.007) reduction in clinical endpoint committee-adjudicated CV death or HF hospitalization with sacubitril/valsartan compared to enalapril (Online ref 34). A reduction in adjudicated HF hospitalization was evident as early as 30 days following randomisation (HR 0.72; 95% CI,0.42-1.25) with a 39% (95%CI 7-60%; p=0.021) reduction at 8 weeks. In patients who were randomised to sacubitril/valsartan, increased natriuretic peptide bioactivity was evidenced by significant increases in urinary cGMP levels at 1 week following randomisation (Online ref 35). Early, favourable changes in levels of biomarkers of both haemodynamic stress (NT-proBNP and soluble ST2) and myocardial injury (high-sensitivity troponin T) were also observed in patients randomised to sacubitril/valsartan compared to enalapril.

The results of PIONEER-HF demonstrate that in hospitalized patients stabilised from an acute decompensation of HFrEF, the addition of a neprilysin inhibitor to a RAS antagonist and standard therapy is 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 randomisation around a half of patients were RAS antagonist naïve and a third of patients were de-novo presentations of HF. A strategy of 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 trial initiation sacubitril/valsartan initiated before discharge compared to 1-14 days after hospital discharge, among 1,002 patients stabilized after hospitalization for HFrEF. Similar proportions of patients in each group achieved pre-defined target doses of the therapy by 10 weeks after randomization (Online ref 36).

Data-Driven Approach to Clinical Use of Sacubitril/Valsartan: To minimize risks of angioedema, a washout period of at least 36 hours after the last dose of ACEi 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 dosed twice daily with 3 doses available in most countries: 24/26mg, 49/51mg, and 97/103mg (target dose); in some countries these doses are described as 50, 100 and 200mg. Prior dosing and tolerance of an ACEi/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 49/51mg dose if tolerating the equivalent of enalapril 10mg twice daily or valsartan 160mg twice daily. Patients who are RAS-blocker naïve, tolerating less than this dose, or who severe renal dysfunction or moderate hepatic dysfunction should start with the 24/26mg dose (Online ref 37).

TITRATION assessed strategies for up-titrating and optimizing the dose of sacubitril/valsartan and 498 patients were randomized 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) (Online ref 38). Rates of hypotension, renal dysfunction, and hyperkalemia at 12 weeks were similar in the two treatment groups. Overall, attainment of the target dose of 97/103 mg twice daily was similar between arms and three-quarters of patients were successfully maintained on this dose. However, among patients on lower pre-initiation doses of ACEi/ARB, the conservative uptitration regimen resulted in greater attainment of target dosing compared with the condensed regimen (Online ref 38). In clinical practice, dose increases towards the target dose of 97/103mg may be made every 2-4 weeks,

depending on tolerability assessed by symptoms of hypotension, blood pressure, renal function, and potassium. Sacubitril/valsartan seems to be “diuretic-sparing” and loop diuretic dose may need to be reduced during or after uptitration (Online 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 have 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, as well as reducing 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 compared with valsartan, 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 indication of treatment of HFpEF is currently underway. Ongoing trials are evaluating the clinical utility of sacubitril/valsartan among patients with HFpEF (PARALLAX) and acute MI (PARADISE-MI) (**Supplementary 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.

References

1. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N. Engl. J. Med. 2014;371:993–1004.

2. Packer M, McMurray JJV, Desai AS, et al. Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure. Circulation 2015;131:54–61.

3. Myhre PL, Vaduganathan M, Claggett B, et al. B-Type Natriuretic Peptide During Treatment With Sacubitril/Valsartan: The PARADIGM-HF Trial. J. Am. Coll. Cardiol. 2019;73:1264–1272.

4. Zile MR, Claggett BL, Prescott MF, et al. Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure. J. Am. Coll. Cardiol. 2016;68:2425–2436.

5. Januzzi JL, Prescott MF, Butler J, et al. Association of change in n-terminal pro-b-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA 2019;322:1085–1095.

6. Desai AS, Solomon SD, Shah AM, et al. Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction. JAMA 2019;322:1077–1084.

7. Claggett B, Packer M, McMurray JJV, et al. Estimating the Long-Term Treatment Benefits of Sacubitril–Valsartan. N. Engl. J. Med. 2015;373:2289–2290.

8. Srivastava PK, Claggett BL, Solomon SD, et al. Estimated 5-Year Number Needed to Treat to Prevent Cardiovascular Death or Heart Failure Hospitalization with Angiotensin Receptor-Neprilysin Inhibition vs Standard Therapy for Patients with Heart Failure with Reduced Ejection Fraction. JAMA Cardiol. 2018;3:1226–1231.

9. Mogensen UM, Gong J, Jhund PS, et al. Effect of sacubitril/valsartan on recurrent events

in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Eur. J. Heart Fail. 2018;20:760–768.

10. Desai AS, Claggett BL, Packer M, et al. Influence of Sacubitril/Valsartan (LCZ696) on 30-Day Readmission After Heart Failure Hospitalization. J. Am. Coll. Cardiol. 2016;68:241–8.

11. Desai AS, McMurray JJ V, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur. Heart J. 2015;36:1990–7.

12. Lewis EF, Claggett BL, McMurray JJ V., et al. Health-Related Quality of Life Outcomes in PARADIGM-HF. Circ. Heart Fail. 2017;10:e003430.

13. Chandra A, Lewis EF, Claggett BL, et al. Effects of sacubitril/valsartan on physical and social activity limitations in patients with heart failure, A secondary analysis of the PARADIGM-HF trial. JAMA Cardiol. 2018;3:498–505.

14. Damman K, Gori M, Claggett B, et al. Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure. JACC Hear. Fail. 2018;6:489–498.

15. Desai AS, Vardeny O, Claggett B, et al. Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril. JAMA Cardiol. 2017;2:79.

16. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet 2020.

17. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure. N. Engl. J. Med. 2019;380:539–548.

18. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin–Neprilysin Inhibition in Heart

480 Failure with Preserved Ejection Fraction. N. Engl. J. Med. 2019;381:1609–1620.

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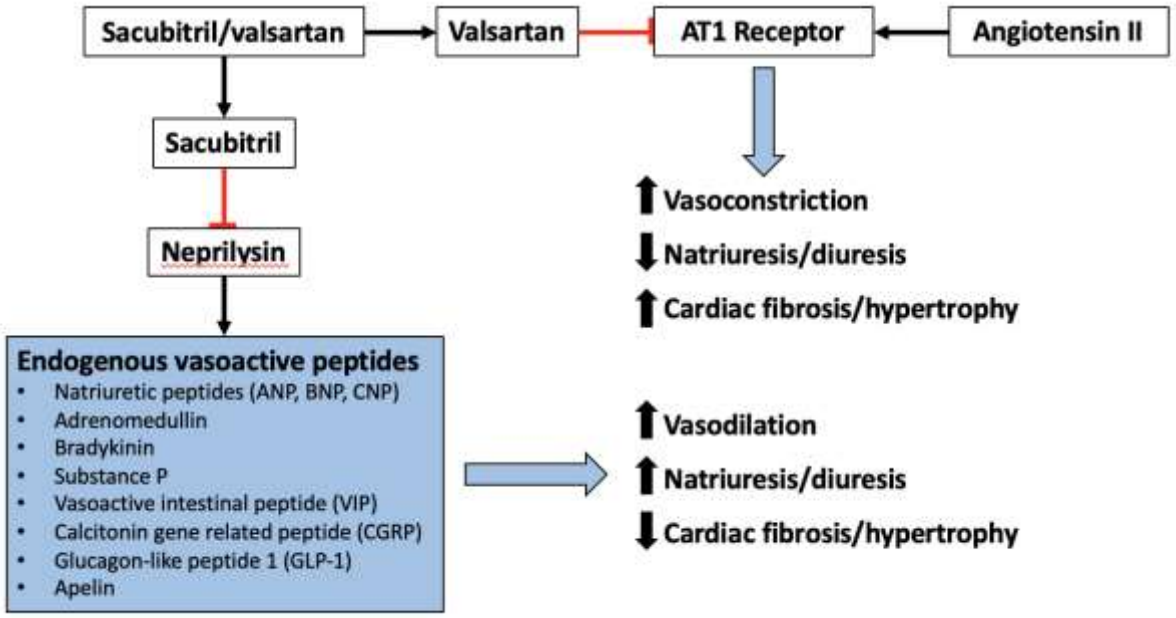
FIGURE 1: Mechanism of action of sacubitril/valsartan **(CENTRAL ILLUSTRATION)**



Red lines denote inhibitory actions.

Abbreviations: ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide.

FIGURE 2: Estimation of extension of life expectancy with sacubitril/valsartan versus enalapril based on projections from PARADIGM-HF trial

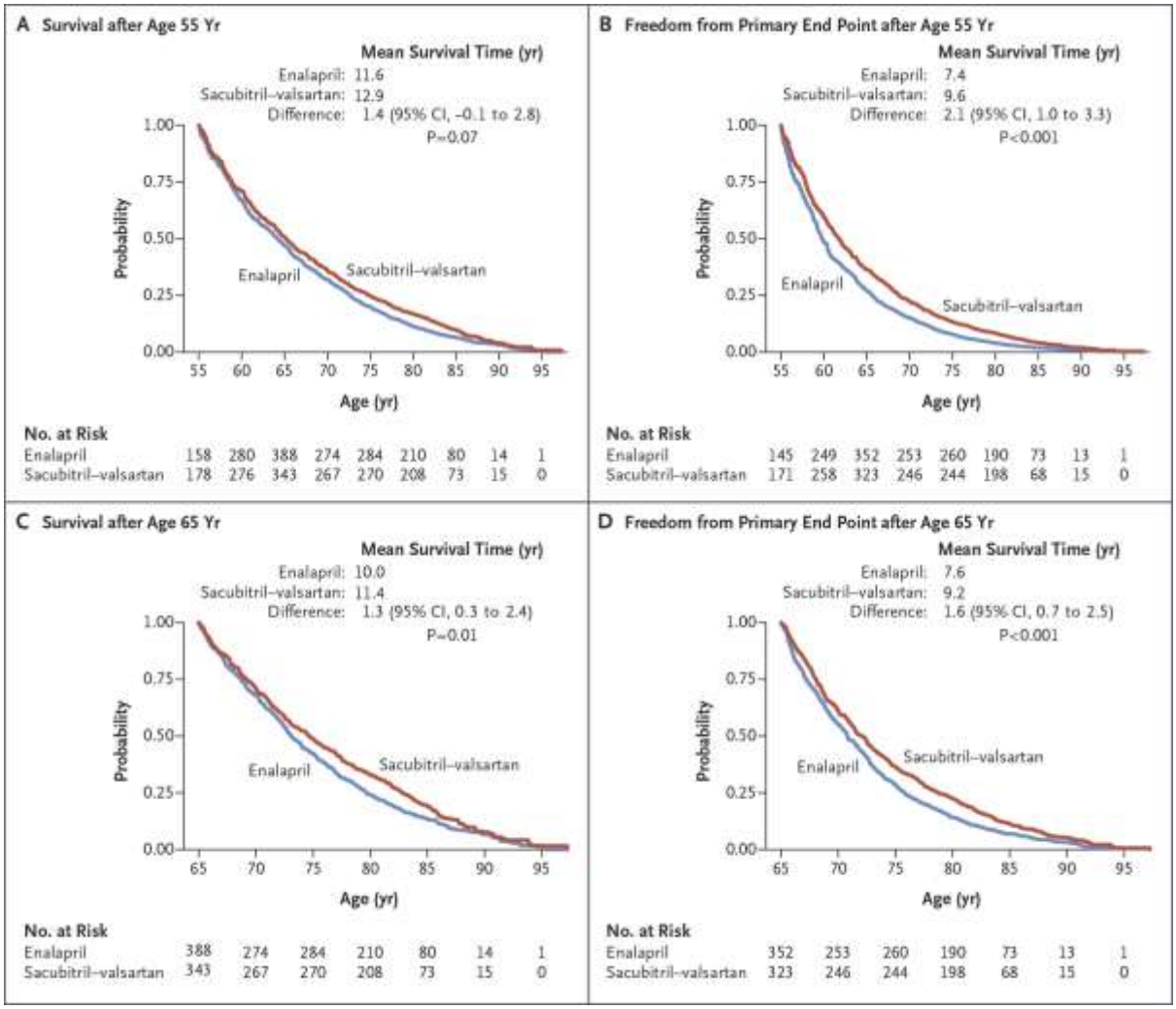


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FIGURE 3: Estimated 5-year Number Needed to Treat for All-Cause Mortality

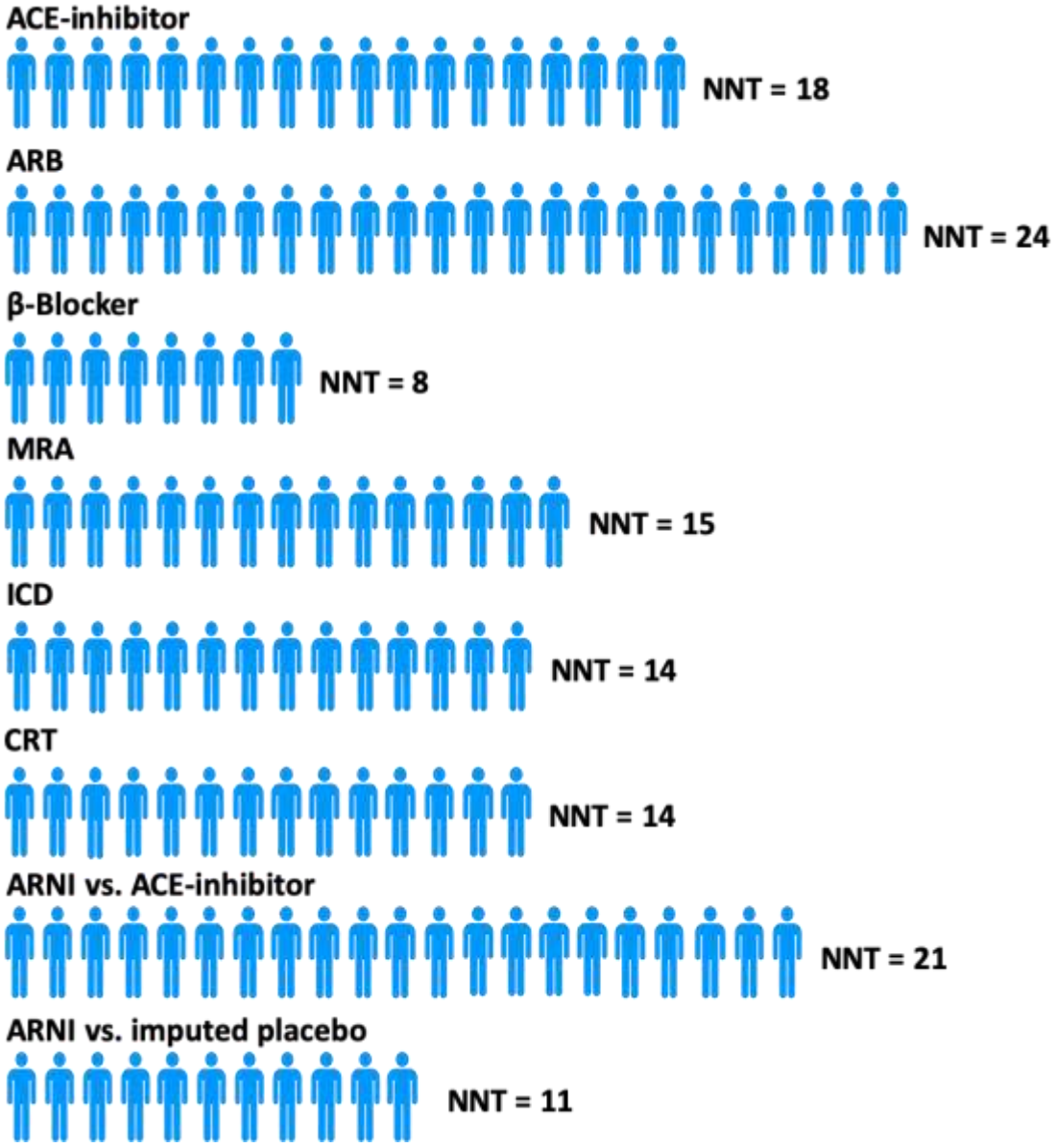

Figure adapted from data from Srivastava PK et al. JAMA Cardiol. 2018;3:1226–1231.(8)
Abbreviations: ACE, angiotensin converting enzyme; NNT, number needed to treat; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; ARNI, angiotensin receptor-neprilysin inhibitor.