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REVIEW ARTICLE

Neprilysin Inhibitors: Filling a Gap in Heart Failure Management, Albeit Amidst Controversy and at a Significant Cost

Antonis S. Manolis[1] · Theodora A. Manolis[2] · Antonis A. Manolis[3] · Helen Melita[4]

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Abstract

Dual angiotensin and neprilysin inhibition using the combination drug sacubitril–valsartan has ushered in a new era in the treatment of heart failure (HF). The randomized controlled PARADIGM-HF trial, which randomized 8399 patients with HF to enalapril or sacubitril–valsartan, showed a 20% reduction in mortality and HF hospitalization with the new drug. This has been heralded as a step toward filling a crucial gap in HF management by providing strong evidence that combined inhibition of the angiotensin receptor and neprilysin is superior to inhibition of the renin–angiotensin system alone in stable patients with chronic HF as it negates the deleterious effects of angiotensin while concomitantly augmenting the beneficial effects of the endogenous natriuretic peptide system. This new therapy is costly, and other confirmatory studies have been lacking for over 2 years since its approval by major regulatory authorities. As such, controversy and heated discussions have amassed, as has detailed information from a plethora of secondary analyses of this pivotal trial about the pros and cons of this promising new therapeutic strategy in HF management. The aim of this review was to provide a critical assessment of all these aspects.

Key Points

The new fixed-combination drug, sacubitril–valsartan, with a dual cardioprotective action conferred via blocking of the deleterious consequences of angiotensin and enhancing the endogenous beneficial effects of natriuretic peptides with no apparent increase in the risk of angioedema, has proven efficacious in ameliorating symptoms and reducing mortality in patients with heart failure, thus filling a gap in heart failure management.

The beneficial effects of this new heart failure therapy have thus far been shown only by one major randomized trial (PARADIGM-HF). Thus, we are in dire need of additional large-scale clinical trials in broader patient groups and of real-world data from post-marketing clinical practice to reproduce and confirm these benefits before this costly therapy can replace conventional heart failure treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Future studies also need to address issues such as long-term drug side effects and risks, cost effectiveness, and patient eligibility for this new therapy.

✉ Antonis S. Manolis
asm@otenet.gr

[1] Third Department of Cardiology, Athens University School of Medicine, Vas. Sofias 114, 115 27 Athens, Greece

[2] Zakynthos Hospital, Zakynthos, Greece

[3] Patras University School of Medicine, Patras, Greece

[4] Onassis Cardiac Surgery Center, Athens, Greece

1 Introduction

Neurohormonal activation is a crucial mechanism in the pathophysiology of heart failure (HF), and its inhibition constitutes a cardinal step in the treatment of this common disease [1–3]. The principal systems involved in the pathophysiology and aggravation of the HF syndrome include the sympathetic nervous system, the renin-angiotensin-aldosterone system (RAAS) and the arginine-vasopressin system. The RAAS is blocked with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs or sartans). Another strategy for the management of HF is to enhance beneficial counter-regulatory systems such as natriuretic peptides (NPs). However, neprilysin, a ubiquitous enzyme (neutral endopeptidase) expressed in several tissues but most commonly in the kidney, is responsible for the breakdown of a number of vasoactive peptides. In addition to degrading the deleterious neurohormone angiotensin II, it also degrades the counter-regulatory NPs, thus depriving the system of their beneficial effects [4]. On the other hand, neprilysin inhibitors have been shown to have a favorable effect in HF. Combining both RAAS and neprilysin inhibitors appears to be synergistic and represents a new paradigm in HF management by expanding pharmacological neuromodulation [5–7].

Inhibition of neprilysin raises levels of several endogenous vasoactive peptides, including NPs, bradykinin, and adrenomedullin, thus countering the neurohormonal overactivation of RAAS that leads to vasoconstriction, sodium retention, and maladaptive remodeling (Fig. 1). Therapy combining a neprilysin inhibitor plus an ARB may constitute an effective alternative to ACEI or ARB therapy [8, 9]. Initial use of a combined ACEI and neprilysin inhibitor (omapatrilat: sacubitril–enalapril) failed to produce desirable effects and was associated with an increased incidence of angioedema [10]. Thus, the ACEI was replaced by an ARB in the combination (sacubitril–valsartan); this does not inhibit the degradation of bradykinin and therefore reduces the risk of angioedema [11].

A recent study measured blood levels of circulating NPs and neprilysin in two patients undergoing replacement of the failing ventricles with a total artificial heart [12]. It indicated that removal of the ventricles was associated with an immediate drop in circulating NPs and a marked decrease in circulating soluble neprilysin. The authors concluded that the heart plays a pivotal role as a regulator of the endocrine response in systolic dysfunction by not only directly releasing NPs but also contributing to circulating neprilysin, which in turn determines the bioavailability of several other vasoactive peptides [12]. Therefore, inhibition of neprilysin's action serves as an added step in neurohormonal deactivation, filling a gap in HF management. It is currently employed in a fixed combination with an ARB for the treatment of HF.

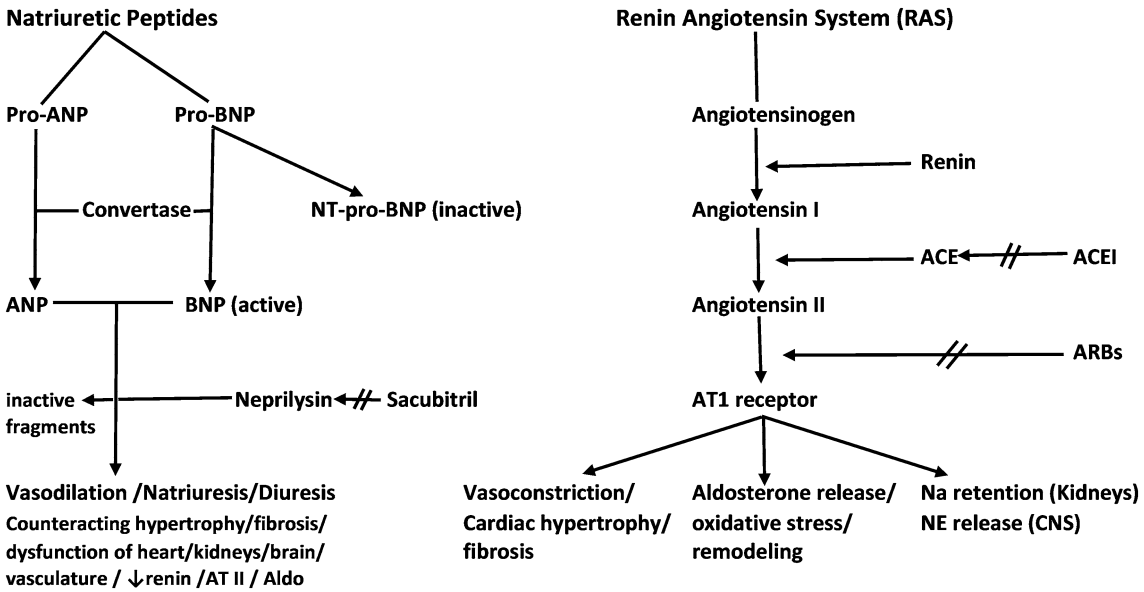

Fig. 1 The two antagonizing neurohormonal systems pivotal to the pathophysiology and treatment of heart failure, the natriuretic peptides (including the two main ones, the ANP and BNP) and the renin angiotensin system, illustrating the metabolism and the key points of intervention in each system with the angiotensin neprilysin inhibitors. *ACE* angiotensin converting enzyme, *ACEI* ACE inhibitor, *Aldo* aldosterone, *ANP* atrial natriuretic peptide, *ARBs* angiotensin receptor blockers, *AT* angiotensin, *BNP* brain natriuretic peptide, *CNS* central nervous system, *NE* norepinephrine, *NT-proBNP* N-terminal pro b-type NP

Sacubitril–valsartan (LCZ696; Entresto®), a supramolecular sodium salt complex of the neprilysin inhibitor prodrug sacubitril and the ARB valsartan, has been approved in the EU (November 2015) and the USA (July 2015) for the treatment of chronic HF with reduced ejection fraction (HFrEF) (New York Heart Association [NYHA] class II–IV).

2 Natriuretic Peptides

Compensatory increases in NP levels are seen in HF. Measurement of NPs may serve as important surrogates for patient clinical status and pathophysiology. NPs are now useful tools in the diagnosis of HF, helpful prognosticators, and can even help with guiding therapy [13].

Atrial NP (ANP) is predominantly produced in the atria and to a lesser extent in the ventricles and extracardiac tissues, such as the kidney. Brain NP (BNP) is synthesized by cardiac ventricular myocytes in response to mechanical stretch. C-type NP (CNP) is produced by the endothelium and kidney, but recent evidence suggests it may also be expressed in the myocardium, as detailed in a following paragraph. NPs have actions that tend to reduce cardiac preload and afterload in an attempt to counteract the deleterious effects of pressure and volume overload encountered in HF. This process includes vasodilation, diuresis, natriuresis, and inhibition of the RAAS [13]. However, this natural increase in NPs remains ineffective at alleviating fluid overload.

One way to circumvent this is the exogenous administration of nesiritide, a synthetic BNP drug. This is only available as an intravenous drug, but—more importantly—despite offering symptom alleviation, nesiritide is associated with significant hypotension, and studies have failed to demonstrate any benefit in patient survival [14] or have even raised concern about its safety in patients with HF [15].

Another, apparently more effective and safe alternative strategy to take advantage of the favorable effect of NPs in HF is neprilysin inhibition via sacubitril–valsartan, which prevents the breakdown of endogenous NPs (Fig. 1). Although the favorable response to neprilysin inhibition may not be simply ascribed to augmentation of endogenous NPs alone, and mechanisms beyond NPs may be playing a role [16], the benefit of such an approach has now been confirmed by a few studies conducted in patients with hypertension, HF with preserved ejection fraction (HFpEF) and HFrEF [17, 18].

Some additional information concerning CNP, the newest of the NP members, is herein provided. CNP, isolated from porcine brain in 1990 [19], is considered a neurotransmitter in the central nervous system, but it is also widely expressed throughout the vasculature and found in particularly high concentrations in the endothelium, where it plays a role in the local regulation of vascular tone [20]. It is stored in endothelial cells and can induce vasorelaxation. Thus, CNP is traditionally viewed as an endothelial peptide. However, newer data suggest that CNP and its NPR-B receptor can play a very important role in regulating cardiac hypertrophy and remodeling. While ANP and BNP were immediately considered cardiac hormones and their role well-characterized and defined in predicting risk in cardiovascular disease (CVD), as biomarkers of acute HF, evidence indicating the role of CNP in cardiovascular regulation has been slow to emerge. In addition to its expression in the endothelium of the vasculature, CNP appears to be also present in cardiac tissue, suggesting a possible synergistic effect with the other natriuretic cardiac peptides, ANP and BNP. Studies indicate that CNP is produced in the heart during HF according to the severity of the disease and may elicit important compensatory physiological consequences in ventricular remodeling, similar to those produced by ANP and BNP. Some have suggested that CNP may be a marker for outcome in patients with HFpEF but not in those with HFrEF [21]; others have associated it with myocardial infarction (MI) [22]. All three NPs can be rapidly degraded by neprilysin, and all NPs have cardiorenal-protective properties, although CNP has the most antifibrotic and least renal effects [23].

3 Heart Failure with Preserved Ejection Fraction (HFpEF)/PARAMOUNT Trial

The efficacy and safety of sacubitril–valsartan was assessed in patients with HFpEF in the PARAMOUNT trial, a phase II, randomized, double-blind multicenter trial comprising patients with NYHA class II–III HF, left ventricular ejection fraction (LVEF) $\geq 45\%$, and N-terminal pro b-type NP (NT-proBNP) > 400 pg/ml [24]. Patients were randomly assigned (1:1) to sacubitril–valsartan ($n = 149$) titrated to 200 mg twice daily (bid) or valsartan ($n = 152$) titrated to 160 mg bid and treated for 36 weeks. NT-proBNP levels were assessed at 12 weeks in 134 patients in the sacubitril–valsartan group and 132 in the valsartan group and were significantly reduced in the sacubitril–valsartan group compared with the valsartan group (from 783 to 605 pg/ml in the sacubitril–valsartan group; from 862 to 835 in the valsartan group; ratio 0.77; $p = 0.005$). Sacubitril–valsartan was well tolerated, and adverse effects were similar to those experienced with valsartan (15 vs. 20%).

An ongoing trial (PARAGON-HF) is further examining the efficacy and safety of sacubitril–valsartan compared with valsartan in 4600 patients with HFpEF (aged ≥ 50 years) [25].

4 Heart Failure with Reduced Ejection fraction (HFrEF)/PARADIGM-HF Trial

Sacubitril–valsartan was successfully studied in the PARADIGM-HF trial [5], a phase III trial in HFrEF that randomized 8399 patients with class II–IV HF and an LVEF of ≤ 40% to receive either sacubitril–valsartan 200 mg bid or enalapril 10 mg bid in addition to standard therapy. The trial was stopped early, after a median follow-up of 27 months, because the boundary for an apparent benefit with sacubitril–valsartan had been crossed. Analysis showed that the primary outcome (death from cardiovascular causes or hospitalization for HF) had occurred in 914 patients (21.8%) in the new drug group and 1117 patients (26.5%) in the enalapril group [hazard ratio (HR) 0.80; $p < 0.001$]. A total of 711 patients (17%) receiving the new drug and 835 patients (19.8%) receiving enalapril died (HR for death from any cause 0.84; $p < 0.001$); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (HR 0.80; $p < 0.001$). As compared with enalapril, sacubitril–valsartan also reduced the risk of hospitalization for HF by 21% ($p < 0.001$) and decreased the symptoms and physical limitations of HF ($p = 0.001$). During the trial, the number needed to treat (NNT) to prevent one primary event was 21 and the NNT to prevent one death from cardiovascular causes was 32. Sacubitril–valsartan resulted in better quality-of-life scores than did enalapril ($p = 0.004$). The sacubitril–valsartan group had higher proportions of patients with hypotension and non-serious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group. The authors concluded that sacubitril–valsartan was superior to enalapril in reducing the risks of death and of hospitalization for HF.

A separate assessment of the risk of re-hospitalization in the PARADIGM-HF trial indicated that, compared with enalapril, treatment with sacubitril–valsartan reduced 30-day readmissions for any cause following discharge from HF hospitalization [26].

Desai et al. [27] further analyzed the mode of death in the trial and showed that sacubitril–valsartan was superior to enalapril in reducing both sudden cardiac deaths and deaths from worsening HF, whereas deaths attributed to other cardiovascular causes, including MI and stroke, and non-cardiovascular deaths were infrequent and equally distributed between treatment groups. More specifically, the majority of deaths were cardiovascular (80.9%), and the risk of cardiovascular death was significantly reduced with sacubitril–valsartan (HR 0.80, $p < 0.001$). Among cardiovascular deaths, both sudden cardiac death (HR 0.80, $p = 0.008$) and death due to worsening HF (HR 0.79, $p = 0.034$) were reduced by treatment with sacubitril–valsartan compared with enalapril.

The PARADIGM-HF investigators also separately reported that sacubitril–valsartan was associated with further evidence of clinical benefit in comparison with enalapril, including fewer visits to an emergency department for HF (HR 0.66, $p = 0.001$) and fewer hospitalizations (HR 0.77, $p < 0.001$), a reduced need for HF treatment intensification (520 vs. 604 patients; HR 0.84, $p = 0.003$), and a lower requirement for intensive care (HR 0.82, $p = 0.005$) or need for inotropic agents (HR 0.69, $p < 0.001$), an HF device or cardiac transplantation (22% risk reduction, $p = 0.07$) [28]. The reduction in HF hospitalization with sacubitril–valsartan was evident within the first 30 days after randomization. Worsening of symptom scores in surviving patients was consistently more common in the enalapril group. Sacubitril–valsartan led to an early and sustained reduction in biomarkers of myocardial wall stress and injury (NT-proBNP and troponin).

Additional secondary analyses of the PARADIGM-HF trial results have followed. In one, the investigators used the treatment arm of the SOLVED-T as the reference trial to investigate an ACEI compared with placebo and the CHARM-Alternative as the reference trial to investigate an ARB compared with placebo [29]. In these indirect comparisons of sacubitril–valsartan with a putative placebo, they showed that the strategy of combined angiotensin receptor blockade and neprilysin inhibition led to striking reductions in cardiovascular and all-cause mortality, as well as in HF hospitalization. These benefits were obtained even though sacubitril–valsartan was added to comprehensive background beta-blocker and mineralocorticoid receptor antagonist therapy. Another analysis showed that, although most patients in PARADIGM-HF had mild symptoms, many were at high risk for adverse outcomes and obtained a large absolute benefit from sacubitril–valsartan, compared with enalapril, over a relatively short treatment period, with a consistent benefit across the spectrum of risk [30]. With regards to patient age influencing the results, a relevant analysis showed that sacubitril–valsartan was more beneficial than enalapril across the spectrum of age, with a favorable benefit–risk profile in all age groups [31]. The pre-specified safety outcomes of hypotension, renal impairment, and hyperkalemia increased with age in both treatment groups; the differences between treatment, with more hypotension but less renal impairment and hyperkalemia with sacubitril–valsartan, were consistent across age categories. In general, a large number of post-hoc analyses of the PARADIGM-HF trial indicated that the benefit of sacubitril–valsartan over enalapril for the primary endpoint in the PARADIGM-HF trial was maintained throughout all these secondary analyses based on HF severity (i.e., LVEF or HF risk scores), impact on alternate outcomes, influence of additional therapies,

tolerability in patients with comorbidities (i.e. diabetes mellitus), long-term benefits, and cost effectiveness [32].

The effects of sacubitril–valsartan on coronary outcomes in PARADIGM-HF were recently examined [33]. At baseline, 3634 (43.3%) of 8399 patients had a prior MI and 4796 (57.1%) had a history of any coronary artery disease. Among all patients, compared with enalapril, sacubitril–valsartan reduced the risk of the primary outcome of cardiovascular death or HF hospitalization (HR 0.80, $p < 0.001$), the broader composite including, in addition, MI, stroke, and resuscitated sudden death (HR 0.83, $p < 0.001$), and the coronary composite of cardiovascular death, non-fatal MI, angina hospitalization, or coronary revascularization (HR 0.83, $p < 0.001$). Although each of the components of the coronary composite occurred less frequently in the sacubitril–valsartan group, compared with the enalapril group, only cardiovascular death was reduced significantly.

Using actuarial estimates from the PARADIGM-HF trial and an extrapolation from the available short-term follow-up, treatment with sacubitril–valsartan was projected to result in 1- to 2-year prolongation of life expectancy and survival free from HF for patients like those in the PARADIGM-HF trial [34]. For example, a 55-year-old patient would have a projected life expectancy of 11.6 additional years while receiving enalapril versus 12.9 years with sacubitril–valsartan (mean benefit of 1.4 years). The same patient would have a respective mean benefit of 2.1 years for freedom from the primary endpoint of death from cardiovascular causes or HF hospitalization. The respective numbers for 65-year-old patients would be 11.4-year life expectancy conferred by sacubitril–valsartan versus 10 years by enalapril, for similar estimated mean long-term benefit of 1.3 vs. 1.6 years for freedom from the primary endpoint.

4.1 Patients with Diabetes Mellitus

Patients with and without diabetes mellitus (DM) benefit equally from therapy with sacubitril–valsartan. Furthermore, the benefit of sacubitril–valsartan compared with enalapril was consistent across all ranges of glycated hemoglobin (HbA_{1c}) in the PARADIGM-HF trial (< 6%; 6–6.4% pre-DM and ≥ 6.5% DM) [35]. Patients with a history of DM [$n = 2907$ (35%)] had a higher risk of the primary composite outcome of HF hospitalization or cardiovascular mortality than did those without a history of DM (adjusted HR 1.38; $p < 0.001$) as did patients with pre-DM (HR 1.27; $p < 0.001$) compared with those without DM ($HbA_{1c} < 6\%$).

Although the rates of new-onset DM were not changed by treatment with sacubitril–valsartan versus enalapril, glycemic control was better in patients treated with sacubitril–valsartan than in those receiving enalapril. Indeed, insulin use in patients with DM in the PARADIGM-HF trial was reduced by 30% [36]. Furthermore, HbA_{1c} levels were actually lower. A possible explanation might relate to the fact that, by inhibiting the action of neprilysin, the ensuing enhanced activity of the NP system may actually play a role in glycemic control. Interestingly, glucagon-like peptide (GLP)-1 is a substrate for neprilysin. Thus, a neprilysin inhibitor may increase the endogenous effect of this peptide, possibly enhancing an antihyperglycemic effect.

A secondary analysis of PARADIGM-HF assessed the change in estimated glomerular filtration rate (eGFR) over a 44-month follow-up period in patients with ($n = 3784$) and without ($n = 4615$) DM [37]. eGFR decreased by 1.1 ml/min per 1.73 m^2 per year in patients without DM and by 2.0 ml/min per 1.73 m^2 per year in those with DM ($p < 0.0001$). Compared with patients treated with enalapril, those treated with sacubitril–valsartan had a slower rate of decline in eGFR (− 1.3 vs. − 1.8 ml/min per 1.73 m^2 per year; $p < 0.0001$), and the magnitude of the benefit was larger in patients with than in those without DM. The authors concluded that in patients in whom the renin-angiotensin system is already maximally blocked, the addition of neprilysin inhibition attenuates the effect of DM to accelerate the deterioration of renal function that occurs in patients with chronic HF.

Finally, concern has been raised about unpredictable drug–drug interactions between the neprilysin inhibitor and the newer classes of antihyperglycemic agents, the GLP-1 receptor agonists and the dipeptidyl peptidase (DPP)-4 inhibitors, as the endogenously produced GLP-1 is degraded rapidly by neprilysin in addition to its degradation by the DPP-4 enzyme [38].

4.2 Post-Myocardial Infarction

In the PARADIGM-HF trial, 3634 (43.3%) of the total 8399 patients randomized had a history of MI. Data from this group have not been analyzed separately. However, these patients were grouped with 4796 (57.1%) who had angiographic evidence of coronary artery disease or a history of MI or angina (stable or unstable), or who had undergone coronary revascularization [33]. As already described, in addition to reducing the risk of cardiovascular death or HF hospitalization, sacubitril–valsartan also reduced the risk of the coronary composite of cardiovascular death, non-fatal MI, angina hospitalization, or coronary revascularization (HR 0.83, $p < 0.001$); however, individually, only cardiovascular death was reduced significantly.

Although data from prior trials support the use of ACEIs early in the treatment of acute MI, either in a wide range of patients or selectively in patients with anterior MI and in those at increased risk of death, no such data are yet available concerning the utility of sacubitril–valsartan in the post-MI patient group. Relevant data are expected from the ongoing PARADISE-MI (Prospective ARNI vs. ACE

Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI) trial (NCT02924727) [39]. This trial will evaluate the efficacy and safety of sacubitril–valsartan titrated to a target dose of 200 mg bid compared with ramipril titrated to a target dose of 5 mg bid, in addition to conventional post-MI treatment, in reducing the occurrence of the composite endpoint of cardiovascular death, HF hospitalization, and outpatient HF in over 4500 post-MI patients with evidence of LV systolic dysfunction and/or pulmonary congestion, with no known prior history of chronic HF.

Survival after acute MI may be improved by sacubitril–valsartan as suggested by an experimental animal study [40]. When the drug was administered in mice, it protected against cardiac rupture and improved the survival rate after MI, probably due to the suppression of pro-inflammatory cytokines and extracellular matrix degradation in macrophages, by dual regulation of RAAS and NP systems.

As suggested, sacubitril–valsartan might ameliorate myocardial ischemia via hemodynamic mechanisms, e.g., reduction in LV wall stress, and may also improve coronary circulation by inhibiting the degradation of CNP locally and through increases in intracellular cyclic guanosine monophosphate (cGMP) concentrations due to the action of circulating ANP and BNP [33]. CNP, which is also a substrate for neprilysin, is involved in the regulation of coronary arterial tone and blood flow and has been shown to be cardio-protective and anti-atherogenic in experimental models. Other sophisticated research using a systems biology approach has indicated that sacubitril–valsartan modulates cardiac remodeling, acting upon hypertrophic processes via valsartan, and limiting myocardial cell death via sacubitril [41].

In a mainly ischemic HFrEF population of 120 patients with an implantable cardioverter defibrillator (ICD) under remote monitor, sacubitril–valsartan decreased ventricular arrhythmias, leading to a reduction of appropriate ICD shocks compared with angiotensin inhibition with ramipril or valsartan [42].

5 Real-World Data

Real-world data on the use of sacubitril–valsartan remain scarce [42–46] despite the drug's approval for use by major regulatory authorities over 2.5 years ago; the drug was approved by the US FDA in July 2015 and by the European Medicines Agency in November 2015. These limited data do indicate symptom improvement and a reduction in hospitalizations. However, they also indicate that the target dose of 200 mg bid is not achievable for a large proportion of patients.

According to a study empirically estimating the potential benefits that could be gained from further implementation of angiotensin receptor–neprilysin inhibitor (ARNI) therapy at the population level, of 2,736,000 patients with HFrEF in the USA, 2,287,296 (84%) were projected to be candidates for ARNI therapy [47]. According to the authors, such an implementation would theoretically prevent 28,484 deaths a year.

However, according to another US study 1 year after FDA approval, only 2.3% of patients with HFrEF without documented contraindications were prescribed ARNI therapy at hospital discharge [48]. The authors ascribed this low rate of penetration and adoption of this new therapy to several obstacles, including formulary approval, prior authorization requirements, and the high drug cost. In addition, questions regarding real-world tolerability, optimal timing for initiation, and potential concerns regarding an increased risk for macular degeneration and dementia might be contributory factors. Nevertheless, it should be noted that this study included only patients discharged after acute HF hospitalization, unlike the PARADIGM-HF trial, which studied only outpatients who were receiving optimal medical therapy and were in a stable chronic HF condition [49].

Further data from clinical practice about the eligibility of patients with HF for the new therapy are available from a British study of 553 patients seen in nurse-led HF clinics over a 6-month period, wherein more than two-thirds (69%) of patients were unsuitable [50]. Unsuitability was related to the fact that most had an LVEF > 35%. Other reasons included hypotension, NYHA class I, renal dysfunction, intolerance of ACEI/ARB and concerns about compliance and significant upfront cost. Another UK study indicated that, among 1396 patients (of 6131 referred to an HF clinic) with HFrEF (LVEF ≤ 40%), only 21% fulfilled the PARADIGM-HF randomization criteria, on which the European Society of Cardiology (ESC) guidelines are based; this proportion rises to 60% if background medication is ignored [51]. Lack of symptoms (32%) and NT-proBNP < 600 ng/l (49%) were common reasons for not fulfilling the criteria.

6 Guideline Recommendations

Pharmacotherapy with neprilysin inhibition with sacubitril–valsartan is currently recommended by both the European and the US guidelines for patients with chronic HF, based on the PARADIGM-HF trial results (Table 1) [5, 8, 9].

Specifically, the ESC guidelines [8] indicate that "sacubitril–valsartan is recommended as a replacement for an ACE inhibitor to further reduce the risk of HF hospitalization and death in *ambulatory patients with HFrEF* who remain symptomatic despite optimal treatment with an ACE inhibitor, a beta-blocker and an MRA [mineralocorticoid receptor antagonist]" (class I, level of evidence [LOE] B). A footnote states that "patient should have elevated NPs (plasma BNP ≥ 150 pg/ml or plasma NT-proBNP ≥ 600 pg/ml, or

Table 1 Current guidelines for use of angiotensin receptor-neprilysin inhibitors in patients with heart failure

	ESC [8]	ACC/AHA [9]	NICE [99]	CCS [52]
Class I	As a replacement for an ACEI to further reduce the risk of HF hospitalization and death in *ambulatory patients with HFrEF* who remain symptomatic despite optimal treatment with an ACEI, a beta-blocker and an MRA (LOE B)	As a replacement to further reduce morbidity and mortality in patients with *chronic symptomatic HFrEF NYHA class II or III* who tolerate an ACEI or ARB (LOE B-R)	As an option for treating symptomatic chronic HF with reduced LVEF, only in people: with NYHA class II–IV symptoms and; with a LVEF of ≤ 35% and; who are already taking a stable dose of ACEI or ARB	To be used in place of an ACEI or ARB, in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT to decrease CV death, HF hospitalizations, and symptoms (high-quality evidence)
Notes	Patient should have elevated NPs (plasma BNP ≥ 150 pg/ml or NT-proBNP ≥ 600 pg/ml, or if HF hospitalization within the last 12 months, BNP ≥ 100 pg/ml or NT-proBNP ≥ 400 pg/ml) and able to tolerate enalapril 10 mg bid	ARNI should not be administered concomitantly with ACEI or within 36 h of the last ACEI dose ARNIs should not be administered to patients with a history of angioedema	Treatment with sacubitril–valsartan should be started by an HF specialist with access to a multidisciplinary HF team Dose titration and monitoring should be performed by the most appropriate team member	Drug tolerability, side effects, and laboratory monitoring with use of ARNIs is similar to that of ACEIs or ARBs noted previously The PARADIGM-HF trial excluded patients with a serum potassium > 5.2 mmol/l, an eGFR < 30 ml/min, and symptomatic hypotension (< 100 mmHg) When switching between an ARNI and an ACEI, a washout period of at least 36 h is required to decrease risk of angioedema. No washout period is required for conversion between ARNIs and ARBs ARNIs should not be used in anyone with history of angioedema Initial dosing and rate of titration is dependent on pre-existing treatment and comorbidities and should be individualized

ACC American College of Cardiology, *ACEI* angiotensin converting enzyme inhibitor, *AHA* American Heart Association, *ARB* angiotensin receptor blocker, *ARNI* angiotensin receptor neprilysin inhibitor, *bid* twice daily, *BNP* brain natriuretic peptide, *CCS* Canadian Cardiovascular Society, *CV* cardiovascular, *eGFR* estimated glomerular filtration rate, *ESC* European Society of Cardiology, *GDMT* guideline-directed medical therapy, *HF* heart failure, *HFrEF* heart with reduced ejection fraction, *LOE* level of evidence, *LVEF* left ventricular ejection fraction, *MRA* mineralocorticoid receptor antagonist, *NICE* National Institute for Health and Care Excellence, *NPs* natriuretic peptides, *NT-proBNP* N-terminal pro b-type NP, *NYHA* New York Heart Association

if HF hospitalization within the last 12 months, plasma BNP ≥ 100 pg/ml or plasma NT-proBNP ≥ 400 pg/ml) and able to tolerate enalapril 10 mg bid."

The American guidelines [9] state "In patients with *chronic symptomatic HFrEF NYHA class II or III* who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality" (class I, LOE B-R). They also state that "ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor" and "ARNI should not be administered to patients with a history of angioedema."

British guidelines recommend sacubitril–valsartan as an option for treating symptomatic chronic HF with reduced LVEF, only in people with NYHA class II–IV symptoms and with an LVEF of ≤ 35% and who are already taking a stable dose of ACE inhibitors or ARBs [99].

Canadian guidelines [52] recommend that an ARNI be used in place of an ACEI or ARB in patients with HFrEF who remain symptomatic despite treatment with appropriate doses of guideline-directed medical therapy (GDMT) to decrease cardiovascular death, HF hospitalizations, and symptoms (strong recommendation; high-quality evidence). They also provide several useful and practical tips. They indicate that drug tolerability, side effects, and laboratory monitoring with ARNIs is similar to that with ACEIs or ARBs. They point out that patients with a serum potassium > 5.2 mmol/l, an eGFR < 30 ml/min, and symptomatic hypotension with a systolic blood pressure (SBP) of < 100 mm Hg had been excluded from the PARADIGM-HF trial. Like the US guidelines, they also recommend a washout period of at least 36 h when switching between an ARNI and an ACEI to decrease the risk of angioedema. No washout period is required for conversion between ARNIs and ARBs. They emphasize that ARNIs should not be used in anyone with a history of angioedema. Finally, they advise that initial dosing and rate of titration should be dependent on pre-existing treatment and comorbidities and should be individualized.

The drug has not been adequately studied in patients who have been recently hospitalized for HF [48]. A subanalysis of the PARADIGM-HF trial compared outcomes among patients who had prior recent hospitalization and found an increased risk associated with more recent hospitalization [53]: within 3 months of screening (HR 1.46), within 3–6 months (HR 1.46), within 6–12 months (HR 1.29), and > 12 months (HR 1.26) compared with those who had never been hospitalized ($p < 0.001$ for trend). A total of 20% of patients without prior HF hospitalization experienced a primary endpoint of cardiovascular death or HF hospitalization, and 17% died during the course of the trial. In the least stable patients–those with an HF hospitalization within 3 months of screening—29% had a primary event and 19% died during the course of the trial. Ongoing clinical trials, such as TRANSITION (Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event; NCT02661217) and PIONEER-HF (Comparison Of Sacubitril–valsartan Versus Enalapril on Effect on NTpro-BNP in Patients Stabilized From an Acute Heart Failure Episode; NCT02554890) are further studying this particular population [54, 55].

Another group of patients with HF that has not been adequately studied are those with NYHA class IV HF symptoms, as only 60 patients with NYHA class IV symptoms were randomized in the PARADIGM-HF trial, of whom 33 (0.8%) received sacubitril–valsartan and 27 (0.6%) received enalapril [5]. This patient group will be studied in the LIFE study (NCT02816736), a randomized, double-blind, active-controlled trial designed to assess the efficacy, safety, and tolerability of sacubitril–valsartan versus valsartan in 400 patients with class IV HFrEF (LVEF ≤ 35%). The study will assess a change from baseline in NT-proBNP levels at weeks 4, 8, 12, and 24 [56].

Finally, there are no data for a benefit of sacubitril–valsartan in pediatric patients with HF. The PANORAMA-HF study will determine whether sacubitril–valsartan is superior to enalapril for treatment of pediatric patients with HFrEF [57].

7 Hypertension

In the PARADIGM-HF trial, the effect of sacubitril–valsartan was consistently beneficial across all prespecified subgroups, including the large (~ 70%) subgroup of patients with a history of hypertension [5, 58]. Although the combined drug appears to have a potent hypotensive effect (14% of the PARADIGM-HF patients receiving the drug had symptomatic hypotension vs. 9% in the enalapril group; $p < 0.001$) [5, 59], relatively few data are available for its efficacy in the treatment of hypertension alone [60]. In a phase II study, 1328 patients aged 18–75 years with mild-to-moderate hypertension were randomly assigned (double-blind) to 8 weeks' treatment with different doses of sacubitril–valsartan, valsartan, or placebo, and 1215 patients completed the 8-week treatment period [61]. Sacubitril–valsartan showed significantly greater reductions in mean sitting diastolic blood pressure (DBP) (mean reduction − 2.17 mmHg; $p < 0.0001$), except for the lowest dose of sacubitril–valsartan. The drug was well tolerated, and no cases of angioedema were reported. The authors concluded that the drug holds promise for the treatment of hypertension and cardiovascular disease.

Another recent randomized, double-blind phase III trial assessed the superiority of sacubitril–valsartan 200 mg over continued olmesartan 20 mg in reducing ambulatory SBP

after 8 weeks of treatment in 376 patients with mild to moderate essential hypertension uncontrolled with olmesartan 20 mg alone [62]. Significant reductions were observed in the sacubitril–valsartan group versus the olmesartan group in 24-h mean ambulatory SBP (−4.3 vs. −1.1 mmHg; $p<0.001$), and in 24-h mean ambulatory DBP and pulse pressure and office SBP and DBP ($p<0.014$). The overall incidence of adverse events was comparable between the groups. Similar results were obtained in another randomized, double-blind, 14-week study, where 588 Asian hypertensive patients received uptitrated doses of sacubitril–valsartan versus olmesartan [63]. At weeks 10 and 14, sacubitril–valsartan provided superior mean sitting SBP (22.71 vs. 16.11 mmHg, respectively; $p<0.001$) and other BP and pulse pressure reductions versus olmesartan. Both treatments were generally well-tolerated. However, when the study extended to 52 weeks, the incidence of adverse events increased to 64%, with serious adverse events observed in ~4%; no deaths were reported [64]. The most frequent adverse events were nasopharyngitis (18.2%) and dizziness (8.8%). Hypotensive episodes were infrequent. The PARAMETER study also demonstrated superiority of sacubitril–valsartan versus olmesartan in reducing clinic and ambulatory central aortic and brachial pressures in 454 elderly patients with systolic hypertension and stiff arteries [65].

Finally, a meta-analysis of 12 studies involving 3816 patients (seven studies comparing sacubitril–valsartan with valsartan and five studies comparing sacubitril–valsartan with olmesartan) showed that sacubitril–valsartan conferred a greater reduction in SBP (mean difference [MD] −5.43 mmHg), DBP (MD −2.34 mmHg), 24-h ambulatory SBP (MD −3.57 mmHg), and 24-h ambulatory DBP (MD −1.32 mmHg) from the baseline than ARBs (all $p<0.001$), with no difference in the incidence of adverse events [60]. However, only short- and medium-term results are available [60, 66]; long-term data in hypertensive patients are currently scarce and direly needed as they will be very important, especially in view of concerns about possible late side effects from the brain (see discussion below) [67, 68].

8 Sacubitril–Valsartan Dosing

The tolerability of initiating/uptitrating sacubitril–valsartan from 50 to 200 mg bid (target dose) over 3 and 6 weeks was assessed in patients with HF with an LVEF ≤ 35% (TITRATION trial) [69]. A 5-day open-label run-in (sacubitril–valsartan 50 mg bid) preceded an 11-week, double-blind, randomization period (100 mg bid for 2 weeks followed by 200 mg bid ["condensed" regimen] vs. 50 mg bid for 2 weeks, 100 mg bid for 3 weeks, followed by 200 mg bid ["conservative" regimen]). Pre-defined tolerability criteria of hypotension, renal dysfunction, hyperkalemia, and adjudicated angioedema occurred in 9.7 vs. 8.4% (condensed vs. conservative), 7.3 vs. 7.6%, 7.7 vs. 4.4%, and 0 vs. 0.8% of patients, respectively (p-value not significant). In total, 378 (76%) patients achieved and maintained sacubitril–valsartan 200 mg bid without dose interruption/downtitration over 12 weeks (77.8 vs. 84.3% for condensed vs. conservative; $p=0.078$). The authors concluded that initiation/uptitration of sacubitril–valsartan from 50 to 200 mg bid over 3 or 6 weeks had a tolerability profile in line with other HF treatments. More gradual initiation/uptitration maximized attainment of target dose in the low-dose (enalapril ≤ 10 mg daily or equivalent) ACEI/ARB group.

The drug is currently available in three doses: 50 mg (sacubitril–valsartan: 24 mg/26 mg), 100 mg (49 mg/51 mg), and 200 mg (97 mg/103 mg) prescribed on a bid schedule [70]. The recommended starting dosage is 100 mg bid; the dose may be doubled at 2–4 weeks as tolerated to reach the target maintenance dosage of 200 mg bid. ACEI therapy should be discontinued for 36 h before initiating treatment with sacubitril–valsartan. Patients who are ACEI or ARB naive or those receiving an ACEI or ARB equivalent of enalapril < 10 mg daily, those with severe chronic kidney disease (eGFR < 30 ml/min/1.73 m^2), patients with moderate hepatic insufficiency (contraindicated in severe liver disease), and patients with low BP should be started on the lower dose (50 mg bid) and carefully monitored; dosage may be doubled every 2–4 weeks as tolerated to reach the maximal dose of 200 mg bid. Note that the valsartan salt in sacubitril–valsartan is different from the salt in other regular preparations of valsartan, with the 103-mg dose corresponding to 160 mg of regular valsartan.

9 Side Effects

The most common reason for medication discontinuation is hypotension [5], especially when the drug is started in patients who are hospitalized, a patient population that differs from those studied in the PARADIGM-HF trial [49]. A total of 851 cases of hypotension have been reported in post-marketing surveillance by patients taking sacubitril combined with valsartan and other drugs for hypertension and HF [71]. Additional reasons for drug discontinuation include renal dysfunction and hyperkalemia [5]. In a secondary analysis of the PARADIGM-HF trial, the incidence of severe hyperkalemia (> 6 mEq/l) among those taking an MRA was more common in patients receiving enalapril than in those receiving sacubitril–valsartan (HR 1.37; $p=0.02$) [72].

Dose reduction was also required for emerging side effects during the PARADIGM-HF trial [73]. Reasons reported for dose reductions included hypotension, responsible for more

dose reductions among those taking sacubitril–valsartan than among those receiving enalapril, and cough, which was more common in those randomized to enalapril. A total of 43% of patients in the enalapril arm and 42% of patients in the sacubitril–valsartan arm reduced their dose at any time after randomization (p value not significant). Of those with a dose reduction, 37.5% subsequently returned to target study medication doses, and this occurred more frequently in patients randomized to sacubitril–valsartan than in those receiving enalapril (39.8 vs. 35.3%; $p = 0.005$). However, although dose reductions of study medications were frequent in patients with HF who were unable to tolerate target doses of the study drugs, the efficacy of sacubitril–valsartan relative to enalapril was maintained, even among participants taking lower doses. According to the investigators, these data suggest that patients taking less than target doses of these drugs would still derive greater benefit from sacubitril–valsartan than from enalapril.

Angioedema remains a risk with sacubitril–valsartan [74]. In the PARADIGM-HF trial, the risk of angioedema was comparable to that with enalapril, primarily in the Black population [75]. Thus, the addition of a neprilysin inhibitor to an ARB increases the risk of angioedema, which is historically lower with an ARB than with an ACEI, which is the reason for using an ARB rather than an ACEI as the RAAS blocker in ARNIs to circumvent the issue of bradykinin accumulation. The guidelines recommend avoiding sacubitril–valsartan concurrently or within 36 h of the last dose of an ACEI or in patients with a history of angioedema to minimize the risk of angioedema.

Studies have also raised the issue that inhibition of neprilysin metabolism of amyloid-β peptides might have an effect on Alzheimer disease (AD), age-related macular degeneration, and cerebral amyloid angiopathy [76]. Thus, there is concern about the potential effect of neprilysin inhibition in the development or progression of AD, as there is considerable overlap between the populations with HF and AD, and in the emergence of visual dysfunction in the form of early macular degeneration [68, 77]. Hence, such possible consequences of chronic neprilysin inhibition indicate a need for vigilance in the use of ARNIs. A secondary analysis of the data from the PARADIGM-HF trial regarding AD was reassuring: no evidence was found that sacubitril–valsartan, compared with enalapril, increased dementia [78]. However, the duration of follow-up was very short, at a median of 2.25 years (up to 4.3 years). During this period, a similar number of total dementia-related adverse effects (97 [2.30%] and 104 [2.48%]) were identified in the two treatment arms.

Regarding renal dysfunction, a meta-analysis was conducted of four randomized controlled trials (RCTs) ($n = 15{,}043$) of either neprilysin–ACEI or ARNI reporting on renal function to determine the renal effects of neprilysin–RAAS inhibition [79]. Overall, compared with ACEI or ARB alone, combined neprilysin–RAAS inhibition resulted in a 32% reduction in risk of decline in renal function (risk ratio 0.68; $p = 0.01$).

Another meta-analysis of six RCTs [80] that used sacubitril–valsartan in patients with HF and hypertension ($n = 11{,}821$) indicated that sacubitril–valsartan increased the risk of angioedema and dizziness but decreased the risk of renal dysfunction and bronchitis. There was no difference for hypotension, hyperkalemia, cough, upper respiratory tract inflammation, diarrhea, back pain, nasopharyngitis, headache, and influenza between the sacubitril–valsartan group and the ACEI/ARB group.

10 Natriuretic Peptide Levels/Biomarkers

Inhibition of neprilysin results in increased levels of BNP, hence it is no longer going to be as good a biomarker of the severity of HF. In this case, one can instead determine the levels of NT- (or N-terminal) proBNP, as NT-proBNP is not a substrate for neprilysin and thus remains a reliable marker of the severity of HF, even in the setting of neprilysin inhibition [81].

In PARADIGM-HF, baseline NT-proBNP was assessed in 2080 patients; 1292 had baseline values > 1000 pg/ml and were remeasured at 1 and 8 months; NT-proBNP change was related to outcomes [82]. At 1 month after randomization, 24% of the baseline NT-proBNP levels > 1000 pg/ml had dropped to ≤ 1000 pg/ml. Risk of HF hospitalization and cardiovascular mortality was 59% lower in patients with a decrease in NT-proBNP to ≤ 1000 pg/ml than in those without such a change. In patients receiving sacubitril–valsartan, median NT-proBNP was significantly lower 1 month after randomization than in enalapril-treated patients, and it fell to ≤ 1000 pg/ml in 31 vs. 17% of patients treated with sacubitril–valsartan and enalapril, respectively. The authors concluded that patients who achieved a significant reduction in NT-proBNP had a lower subsequent rate of cardiovascular death or HF hospitalization, independent of the treatment group. Treatment with sacubitril–valsartan was nearly twice as likely as enalapril to reduce NT-proBNP to values ≤ 1000 pg/ml.

A study in 1021 ambulatory patients with HF evaluated the association between the soluble form of neprilysin (sNEP) levels, as an emerging biomarker, and long-term all-cause, cardiovascular, and acute HF recurrent admissions [83]. Over a median of 3.4 years, the adjusted incidence rate ratios for the top (> 1.22 ng/ml) versus the bottom (≤ 0.39 ng/ml) quartiles of sNEP were 1.37 ($p = 0.032$), 1.51 ($p = 0.010$), and 1.51 ($p = 0.026$) for all-cause, cardiovascular, and acute HF admissions, respectively. The authors concluded that elevated sNEP levels predicted an increased risk of recurrent all-cause, cardiovascular, and acute HF

admissions in ambulatory patients with HF. They speculated that measuring neprilysin activity may be useful for not only identifying patients who will benefit the most from sacubitril–valsartan but also tailoring the intensity of treatment. However, high neprilysin levels lose their predictive role in patients with chronic kidney disease [84].

The effects of treatment on serum levels of soluble ST2 (sST2), a biomarker associated with cardiac remodeling and fibrosis, were assessed in PARADIGM-HF [85]. Sacubitril–valsartan led to more reductions and fewer increases in sST2 levels compared with enalapril. After adjusting for other predictors, including NT-proBNP and high-sensitivity troponin T (hs-TnT), baseline sST2 remained an independent predictor of outcomes. Associations between baseline sST2 and outcomes were linear. sST2 increases at 1 month were associated with worse subsequent outcomes and decreased with better outcomes.

The effect of sacubitril–valsartan on serum uric acid levels and their association with outcomes was examined in a secondary analysis of PARADIGM-HF [86]. Higher serum uric acid levels were associated with a higher risk of the primary outcome of cardiovascular death or HF hospitalization, its components, and all-cause mortality ($p = 0.001$). Compared with enalapril, sacubitril–valsartan reduced uric acid levels by 0.24 mg/dl over 12 months ($p < 0.0001$). Sacubitril–valsartan improved outcomes, irrespective of serum uric acid concentration.

A new study (PROVE-HF) will assess changes from baseline to 1 year in biomarkers linked to ventricular remodeling, myocardial injury, and fibrosis in ~ 830 patients with HFrEF receiving sacubitril–valsartan [87].

11 Cost and Cost Effectiveness

Currently, all parties involved (drug manufacturer, physicians, and patients) admittedly consider this new therapy very costly, reaching $US4560 annually in the USA [88]. Cost-effectiveness analyses have been few, but it should be noted that the results always depend on the societal willingness-to-pay thresholds. A US study using data from the PARADIGM-HF trial indicated that the ACEI arm had averages of 5.56 quality-adjusted life-years (QALYs) and total costs of $US123,578 [88]. The sacubitril–valsartan arm produced an additional 0.57 QALYs at the additional expense of $US29,138, resulting in an incremental cost-effectiveness ratio (ICER) of $US50,915, which is apparently borderline affordable by the US healthcare system. However, the ICER would exceed $US100,000 per QALY if the benefits of sacubitril–valsartan over enalapril lasted for < 3.3 years.

According to another US study analyzing patients who were aged 60 years at model entry and modeled over a lifetime (40 years) and deriving clinical probabilities mostly from PARADIGM-HF, sacubitril–valsartan, compared with enalapril, was much more expensive ($US60,391 vs. 21,758) but more effective (6.49 vs. 5.74 QALYs) over a lifetime [89]. The ICER of sacubitril–valsartan was highly dependent on duration of treatment, ranging from the exorbitant cost of $US249,411 per QALY at 3 years to $US50,959 per QALY gained over a lifetime. Apparently, such ICER values are prohibitive for all countries when limited to 3-year estimates and for low- and moderate-income countries when estimated over a lifetime. Another analysis provided similar results with incremental costs and QALYs gained with sacubitril–valsartan treatment estimated at $US35,512 and 0.78, respectively, compared with enalapril, equating to an ICER of $US45,017 per QALY, which could range from $US35,357 to 75,301 per QALY according with sensitivity analyses [90]. Likewise, one more US analysis determined the overall cost per QALY gained at $US47,053, at $US44,531 for patients with NYHA class II HF and at $US58,194 for those with class III or IV HF [91]. Again, the cost per QALY gained climbs to $US120,623 if the duration is limited to the length of the trial (median 27 months).

A Swiss cost-effectiveness analysis [92] in a patient population that was the same as that enrolled in the PARADIGM-HF trial indicated that the sacubitril–valsartan strategy decreased the number of hospitalizations (6% per year absolute reduction) and lifetime hospital costs by 8% (discounted) when compared with enalapril and was predicted to improve overall and quality-adjusted survival by 0.50 years and 0.42 QALYs, respectively. Additional net total costs were Swiss franc (CHF)10,926. This led to an ICER of CHF25,684 which was considered affordable for Switzerland.

A UK study indicated that, in the UK, the cost per QALY gained for sacubitril–valsartan (using cardiovascular mortality) was £17,100 (€20,400) versus enalapril. In Denmark, the ICER for sacubitril–valsartan was Danish Krone (Kr)174,000 (€22,600) [93]. In Colombia, the ICER was Colombian peso (COP$) 39.5 million (€11,200) per QALY gained. Results were most sensitive to the extrapolation of mortality, duration of treatment effect, and time horizon. The authors considered that the ICERs were below the willingness-to-pay threshold for all three country settings. A Dutch cost-effectiveness analysis also found a cost-effective ICER for this therapy, estimated at €17,600 per QALY gained [94].

The US Institute for Clinical and Economic Review [100] announced in September 2015 that, at the price of $US4560 per year, sacubitril–valsartan "does not save money over the long term but its added costs are well-aligned with the degree of benefit it brings to patients, meaning that it can be judged "cost effective" in the long-term according to commonly accepted cost-effectiveness thresholds. However, our analysis predicts that nearly 2 million patients could be prescribed the drug over the first five years, creating a total

budget impact so high that excessive cost burdens would be placed on the overall health care system." For this reason, the Institute called for a 17% discount off the list price.

In conclusion, at current prices, the new drug is very costly and borderline cost effective for high-income countries, whereas the ICER is prohibitive for all countries when considering its effect over a 3-year period (the duration of follow-up offered by PARADIGM-HF) and possibly acceptable for high-income countries when considered long-term or over a lifetime.

12 Critique and Controversies

Since its publication, several limitations of the PARADIGM-HF trial have been highlighted, relating to the design, exclusions, under-represented patient categories in the study, and potential long-term side effects of the neprilysin inhibitor [95].

The majority (~72%) of patients with HF participating in the PARADIGM-HF trial were stable NYHA class II patients; only 23% had NYHA class III symptoms, 4% NYHA class I, and < 1% NYHA class IV [5]. Patient stability is also reflected by a mean SBP of 122 mmHg; in most clinical practices, patients with HF who are already receiving triple therapy, usually have much lower BP so it remains doubtful whether they may be able to tolerate the new drug. Indeed, a secondary analysis of the PARADIGM-HF trial indicated that symptomatic hypotension, study drug dose reduction and discontinuation were more frequent in patients with a lower SBP [58]. The study also lacked patients with devices, as only 15% had an ICD and 7% a cardiac resynchronization therapy (CRT) device [5]. With regards to race, 66% were White patients, 5% were Black, and 18% were Asian. The percentage of post-MI patients included in the study was 43%. Hence, the critique relates to the fact that this was mainly a study of White patients with stable NYHA class II HF, and results may not be necessarily extrapolated to other patient categories. Thus, a study of higher disease severity including more patient categories is needed to provide information about the effect of the drug in a broader HF patient group [77]. Finally, it should also be noted that the PARADIGM-HF trial excluded patients with severe renal insufficiency (eGFR ≤ 30 ml/min/1.73 m^2), low (≤ 100 mmHg) BP at rest, and mildly elevated (≥ 5.2 mmol/l) baseline serum potassium levels, and patients not currently receiving an ACEI or equivalent at a specified dose (enalapril 10 mg/day).

Following publication of PARADIGM-HF in the *New England Journal of Medicine* (NEJM), NEJM Journal Watch published a critique [101] that generated a lot of heated discussion by readers and the investigators [102]. Briefly, the critique related to three caveats that could potentially have accounted for the difference between the two therapies: the ("unfair") lower dosing of enalapril in the trial (10 mg bid instead of 20 mg bid) versus the maximal dosing of valsartan (320 mg); the "problematic" use [96] of a run-in period in the trial, which may overestimate the benefits and underestimate the risks of treatment; and having patients stop their current ACEI or ARB therapy that was already working in order to enter the trial. The discussion raised critique about the drug effect on BP (being larger by sacubitril–valsartan) as a determinant of outcome; defended the non-use of a higher dose of enalapril as potentially non-tolerable, and the use of the run-in period as supported by the FDA; insisted on dose differences as favoring the new drug, indicating that no trial has compared valsartan 320 mg versus enalapril 20 mg; and proposed that the ACEI arm of the trial should have had valsartan as the comparator, or—even better—sacubitril should have been tested on its own merit and not in a combination. Additional issues included the high cost of the new therapy; the imbalance in the length of the drug run-in period, which was twice as long for valsartan–sacubitril than for enalapril (median 29 vs. 15 days), providing an advantage for the study drug; the notion that the best trial would have been an RCT of sacubitril versus placebo among patients already receiving an ARB, countering the notion of testing the addition of sacubitril to a patient's usual ARB therapy since the standard and first-line therapy is an ACEI; also countering the suggestion of a higher enalapril dose, as the maximum enalapril dose ever achieved in any prior study did not exceed a daily average of 19–20 mg. The discussion repeatedly pointed out that sacubitril should have been tested alone and thus there is currently no information about its isolated benefits or harms. Other readers considered the design of the study flawed in that two drugs (sacubitril and valsartan) were compared with one, and others were convinced about the benefits of the new therapy and consider it unethical not to offer this therapy to patients with HFrEF. Finally, the fact that the trial was stopped early might have its own problems in detecting long-term safety issues while overestimating treatment effects.

Critique has also been voiced with regards to the following FDA labeling of the indications for the new drug: "patients with chronic HF (NYHA Class II–IV) and reduced ejection fraction, … usually administered in conjunction with other HF therapies, in place of an ACE inhibitor or other ARB" [103]. The critique relates to the discrepancy between the patient population represented in PARADIGM-HF and the significantly broader population who have FDA approval for therapy with sacubitril–valsartan [97]. Specifically, in this report from the Cleveland Clinic, of 210 patients with post-discharge follow-up, 149 were eligible for sacubitril–valsartan therapy on the basis of the FDA criteria, and only 54 (37%) met PARADIGM-HF criteria. Patients who did not meet these criteria ($n = 95$) had a higher NYHA

functional class, lower SBP, higher NT-proBNP levels, and lower eGFR. In addition, fewer ineligible patients were taking beta-blockers, ACEIs, or ARBs, and MRA. The principal reasons for ineligibility included SBP ≤ 100 mmHg (39%); eGFR ≤ 30 ml/min/1.73 m^2 (20%); not taking an ACEI or ARB (54%); not taking a beta-blocker (38%); and serum potassium ≥ 5.2 mmol/l (9.4%).

13 Conclusion

Sacubitril–valsartan, a combination drug of a new class of dual-acting ARNI offering cardioprotection via blocking the deleterious effects of angiotensin and concomitantly enhancing the endogenous beneficial action of NPs without increased risk of angioedema, has been successful in improving symptoms in patients with HFpEF and HFrEF and in reducing mortality in patients with HFrEF. However, we are in dire need of additional large-scale clinical trials in a broader patient group and real-world data from post-marketing clinical practice that would reproduce and confirm these benefits before ARNIs would replace ACEIs and ARBs in the treatment of HFrEF. Furthermore, future studies need to address issues such as drug side effects and risks (particularly with chronic use), cost effectiveness, and patient eligibility.

14 Perspective

As this new therapy is only supported by a single RCT, and considerable time has elapsed without any other studies—RCTs or real-world observational studies—being conducted using this novel approach, critique is mounting with regards to the reproducibility and practical applicability of this strategy. An RCT similar to, albeit smaller than, PARADIGM-HF is being planned, the PARALLEL-HF study, which is aligned with the PARADIGM-HF study and aims to assess the efficacy and safety of sacubitril–valsartan in 220 Japanese patients with HFrEF [98]. The drug manufacturer has launched a global program with a plethora of studies involving different patient groups. Obviously, the company has an invested interest to do this, but the scientific community needs to react and make its own proposals and design appropriate and uninfluenced studies seeking further data on this promising avenue of augmenting the benefits of current established HF therapies via the enhanced activity of the endogenous NPs offered by the pathway of neprilysin inhibition.

Despite the criticism and skepticism that the PARADIGM-HF trial has stirred, the fact remains that, after many years of stagnancy in the development of effective new drugs for HF, hope is renewed that a new agent, even in a fixed combination, can save lives in this very large patient population. This behooves us to find ways to refine its indications with optimal patient selection, while being vigilant for long-term safety issues, and at the same time pressing for price reductions and discounts so that more suitable patients avail themselves of this new therapy without overburdening healthcare systems.

Compliance with ethical standards

Conflict of interest ASM, TAM, AAM, and HM have no conflicts of interest that might be relevant to the contents of this manuscript.

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References

1. Manolis AS, Varriale P, Nobile J. Short-term hemodynamic effects of intravenous methyldopa in patients with congestive heart failure. Pharmacotherapy. 1987;7:216–22.
2. van Bilsen M, Patel HC, Bauersachs J, et al. The autonomic nervous system as a therapeutic target in heart failure: a scientific position statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2017;19:1361–78.
3. von Lueder TG, Kotecha D, Atar D, Hopper I. Neurohormonal Blockade in Heart Failure. Card Fail Rev. 2017;3:19–24.
4. von Lueder TG, Sangaralingham SJ, Wang BH, et al. Renin-angiotensin blockade combined with natriuretic peptide system augmentation: novel therapeutic concepts to combat heart failure. Circ Heart Fail. 2013;6:594–605.
5. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.
6. Chrysant SG. Pharmacokinetic, pharmacodynamic, and antihypertensive effects of the neprilysin inhibitor LCZ-696: sacubitril/valsartan. J Am Soc Hypertens. 2017;11:461–8.
7. Tajik AA, Dickstein K. What constitutes optimal neurohumoral antagonism in chronic heart failure? Heart. 2016;102:1922–32.
8. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129–200.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol. 2017;70:776–803.
10. Singh JS, Lang CC. Angiotensin receptor-neprilysin inhibitors: clinical potential in heart failure and beyond. Vasc Health Risk Manag. 2015;11:283–95.
11. Volterrani M, Iellamo F, Senni M, Piepoli MF. Therapeutic options of Angiotensin Receptor Neprilysin inhibitors (ARNis) in chronic heart failure with reduced ejection fraction: Beyond RAAS and sympathetic nervous system inhibition. Int J Cardiol. 2017;226:132–5.

12. Arrigo M, Vodovar N, Nougue H, et al. The heart regulates the endocrine response to heart failure: cardiac contribution to circulating neprilysin. Eur Heart J. 2018;39:1794–8.
13. Maisel AS, Duran JM, Wettersten N. Natriuretic peptides in heart failure: Atrial and B-type natriuretic peptides. Heart Fail Clin. 2018;14:13–25.
14. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med. 2011;365:32–43.
15. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. JAMA. 2005;293:1900–5.
16. Singh JSS, Burrell LM, Cherif M, Squire IB, Clark AL, Lang CC. Sacubitril/valsartan: beyond natriuretic peptides. Heart. 2017;103:1569–77.
17. Vardeny O, Miller R, Solomon SD. Combined neprilysin and renin-angiotensin system inhibition for the treatment of heart failure. JACC Heart Fail. 2014;2:663–70.
18. Gori M, Volterrani M, Piepoli M, Senni M. Angiotensin receptor-neprilysin inhibitor (ARNi): clinical studies on a new class of drugs. Int J Cardiol. 2017;226:136–40.
19. Sudoh T, Minamino N, Kangawa K, Matsuo H. C-type natriuretic peptide (CNP): a new member of natriuretic peptide family identified in porcine brain. Biochem Biophys Res Commun. 1990;168:863–70.
20. Del Ry S. C-type natriuretic peptide: a new cardiac mediator. Peptides. 2013;40:93–8.
21. Lok DJ, Klip IT, Voors AA, et al. Prognostic value of N-terminal pro C-type natriuretic peptide in heart failure patients with preserved and reduced ejection fraction. Eur J Heart Fail. 2014;16:958–66.
22. Sangaralingham SJ, McKie PM, Ichiki T, et al. Circulating C-type natriuretic peptide and its relationship to cardiovascular disease in the general population. Hypertension. 2015;65:1187–94.
23. Wong PC, Guo J, Zhang A. The renal and cardiovascular effects of natriuretic peptides. Adv Physiol Educ. 2017;41:179–85.
24. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380:1387–95.
25. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF Trial. JACC Heart Fail. 2017;5:471–82.
26. 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.
27. Desai AS, McMurray JJ, 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.
28. Packer M, McMurray JJ, 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.
29. McMurray J, Packer M, Desai A, et al. A putative placebo analysis of the effects of LCZ696 on clinical outcomes in heart failure. Eur Heart J. 2015;36:434–9.
30. Simpson J, Jhund PS, Silva Cardoso J, et al. Comparing LCZ696 with enalapril according to baseline risk using the MAGGIC and EMPHASIS-HF risk scores: an analysis of mortality and morbidity in PARADIGM-HF. J Am Coll Cardiol. 2015;66:2059–71.
31. Jhund PS, Fu M, Bayram E, et al. Efficacy and safety of LCZ696 (sacubitril–valsartan) according to age: insights from PARADIGM-HF. Eur Heart J. 2015;36:2576–84.
32. Smith KR, Hsu CC, Berei TJ, et al. PARADIGM-HF Trial: Secondary Analyses Address Unanswered Questions. Pharmacotherapy. 2018;38:284–98.
33. Mogensen UM, Kober L, Kristensen SL, et al. The effects of sacubitril/valsartan on coronary outcomes in PARADIGM-HF. Am Heart J. 2017;188:35–41.
34. Claggett B, Packer M, McMurray JJ, et al. Estimating the long-term treatment benefits of sacubitril–valsartan. N Engl J Med. 2015;373:2289–90.
35. Kristensen SL, Preiss D, Jhund PS, et al. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial. Circ Heart Fail. 2016;9(1):e002560.
36. Seferovic JP, Claggett B, Seidelmann SB, et al. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. Lancet Diabetes Endocrinol. 2017;5:333–40.
37. Packer M, Claggett B, Lefkowitz MP, et al. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. Lancet Diabetes Endocrinol. 2018. https://doi.org/10.1016/S2213-8587(18)30100-1 **(Epub ahead of print)**.
38. Packer M. Does neprilysin inhibition potentiate or minimize the adverse effects of glucagon-like peptide-1 receptor agonists in chronic heart failure? J Card Fail. 2018;24:109–11.
39. Yandrapalli S, Andries G, Biswas M, Khera S. Profile of sacubitril/valsartan in the treatment of heart failure: patient selection and perspectives. Vasc Health Risk Manag. 2017;13:369–82.
40. Ishii M, Kaikita K, Sato K, et al. Cardioprotective effects of LCZ696 (sacubitril/valsartan) after experimental acute myocardial infarction. JACC: Basic to Translational. Science. 2017;2:655–68.
41. Iborra-Egea O, Galvez-Monton C, Roura S, et al. Mechanisms of action of sacubitril/valsartan on cardiac remodeling: a systems biology approach. NPJ Syst Biol Appl. 2017;3:12.
42. de Diego C, Gonzalez-Torres L, Nunez JM, et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhythm. 2018;15:395–402.
43. Kaluzna-Oleksy M, Kolasa J, Migaj J, et al. Initial clinical experience with the first drug (sacubitril/valsartan) in a new class—ARNIs in patients with heart failure with reduced left ventricular ejection fraction in Poland. Kardiol Pol. 2018;76(2):381–7.
44. Ali D, Riley F, Kirkland S, Hyland J, Banerjee P. Sacubitril/valsartan in chronic symptomatic heart failure with reduced ejection fraction: first clinical experience from a large UK tertiary centre. Heart. 2017;103:A1.
45. Crawley R, Guha K, Kalra P, Morton G. Sacubitril/valsartan: real world experience of delivery and tolerability. Heart. 2017;103:A1–2.
46. Antol DD, Casebeer AW, DeClue RW, Stemkowski S, Russo PA. An early view of real-world patient response to sacubitril/valsartan: a retrospective study of patients with heart failure with reduced ejection fraction. Adv Ther. 2018. https://doi.org/10.1007/s12325-018-0710-4 **(Epub ahead of print)**.
47. Fonarow GC, Hernandez AF, Solomon SD, Yancy CW. Potential mortality reduction with optimal implementation of angiotensin receptor neprilysin inhibitor therapy in heart failure. JAMA Cardiol. 2016;1:714–7.
48. Luo N, Fonarow GC, Lippmann SJ, et al. Early adoption of sacubitril/valsartan for patients with heart failure with reduced

ejection fraction: insights from get with the guidelines-heart failure (GWTG-HF). JACC Heart Fail. 2017;5:305–9.
49. Di Tano G, Bettari L. Adoption of sacubitril/valsartan must take into account different heart failure patient types. JACC Heart Fail. 2017;5:688–9.
50. Lodge FM, Phillips J, Groves T, Yousef ZR. Eligibility of patients for sacubitril/valsartan in a secondary care heart failure service. Br J Cardiol. 2016;23:148–50.
51. Pellicori P, Urbinati A, Shah P, et al. What proportion of patients with chronic heart failure are eligible for sacubitril-valsartan? Eur J Heart Fail. 2017;19:768–78.
52. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 comprehensive update of the canadian cardiovascular society guidelines for the management of heart failure. Can J Cardiol. 2017;33:1342–433.
53. Solomon SD, Claggett B, Packer M, et al. Efficacy of sacubitril/valsartan relative to a prior decompensation: the PARADIGM-HF trial. JACC Heart Fail. 2016;4:816–22.
54. Luo N, Mentz RJ, O'Brien EC. Reply: adoption of sacubitril/valsartan must take into account different heart failure patient types. JACC Heart Fail. 2017;5:689.
55. Velazquez EJ, Morrow DA, DeVore AD, et al. Rationale and design of the comParIson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure episode (PIONEER-HF) trial. Am Heart J. 2018;198:145–51.
56. Ambrosy AP, Mentz RJ, Fiuzat M, et al. The role of angiotensin receptor-neprilysin inhibitors in cardiovascular disease-existing evidence, knowledge gaps, and future directions. Eur J Heart Fail. 2018;20:963–72.
57. Shaddy R, Canter C, Halnon N, et al. Design for the sacubitril/valsartan (LCZ696) compared with enalapril study of pediatric patients with heart failure due to systemic left ventricle systolic dysfunction (PANORAMA-HF study). Am Heart J. 2017;193:23–34.
58. Bohm M, Young R, Jhund PS, et al. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. Eur Heart J. 2017;38:1132–43.
59. Vardeny O, Claggett B, Kachadourian J, et al. Incidence, Predictors, and Outcomes Associated With Hypotensive Episodes Among Heart Failure Patients Receiving Sacubitril/Valsartan or Enalapril: The PARADIGM-HF Trial (Prospective Comparison of Angiotensin Receptor Neprilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure). Circ Heart Fail. 2018;11:e004745.
60. Zhao Y, Yu H, Zhao X, Ma R, Li N, Yu J. The effects of LCZ696 in patients with hypertension compared with angiotensin receptor blockers: a meta-analysis of randomized controlled trials. J Cardiovasc Pharmacol Ther. 2017;22:447–57.
61. Ruilope LM, Dukat A, Bohm M, Lacourciere Y, Gong J, Lefkowitz MP. Blood-pressure reduction with LCZ696, a novel dual-acting inhibitor of the angiotensin II receptor and neprilysin: a randomised, double-blind, placebo-controlled, active comparator study. Lancet. 2010;375:1255–66.
62. Cheung DG, Aizenberg D, Gorbunov V, Hafeez K, Chen CW, Zhang J. Efficacy and safety of sacubitril/valsartan in patients with essential hypertension uncontrolled by olmesartan: a randomized, double-blind, 8-week study. J Clin Hypertens (Greenwich). 2018;20:150–8.
63. Supasyndh O, Wang J, Hafeez K, Zhang Y, Zhang J, Rakugi H. Efficacy and safety of sacubitril/valsartan (LCZ696) Compared with olmesartan in elderly Asian patients (>/=65 Years) with systolic hypertension. Am J Hypertens. 2017;30:1163–9.
64. Supasyndh O, Sun N, Kario K, Hafeez K, Zhang J. Long-term (52-week) safety and efficacy of sacubitril/valsartan in Asian patients with hypertension. Hypertens Res. 2017;40:472–6.
65. Williams B, Cockcroft JR, Kario K, et al. Effects of sacubitril/valsartan versus olmesartan on central hemodynamics in the elderly with systolic hypertension: The PARAMETER Study. Hypertension. 2017;69:411–20.
66. Izzo JL Jr, Zappe DH, Jia Y, Hafeez K, Zhang J. Efficacy and safety of crystalline valsartan/sacubitril (LCZ696) compared with placebo and combinations of free valsartan and sacubitril in patients with systolic hypertension: the RATIO Study. J Cardiovasc Pharmacol. 2017;69:374–81.
67. Chrysant SG. Benefits and pitfalls of sacubitril/valsartan treatment in patients with hypertension. J Clin Hypertens (Greenwich). 2018;20:351–5.
68. Patel N, Gluck J. Is Entresto good for the brain? World J Cardiol. 2017;9:594–9.
69. Senni M, McMurray JJ, Wachter R, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. Eur J Heart Fail. 2016;18:1193–202.
70. Sacubitril/valsartan (Entresto) for heart failure. Med Lett Drugs Ther. 2015;57(1474):107–9.
71. Aronow WS, Shamliyan TA. Benefits and harms of sacubitril in adults with heart failure and reduced left ventricular ejection fraction. Am J Cardiol. 2017;120:1166–70.
72. 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: a secondary analysis of the PARADIGM-HF trial. JAMA Cardiol. 2017;2:79–85.
73. Vardeny O, Claggett B, Packer M, et al. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. Eur J Heart Fail. 2016;18:1228–34.
74. Owens RE, Oliphant CS. Angioedema spotlight: a closer examination of sacubitril/valsartan safety results. J Am Board Fam Med. 2017;30:556–7.
75. Shi V, Senni M, Streefkerk H, Modgill V, Zhou W, Kaplan A. Angioedema in heart failure patients treated with sacubitril/valsartan (LCZ696) or enalapril in the PARADIGM-HF study. Int J Cardiol. 2018;264:118–23.
76. Campbell DJ. Long-term neprilysin inhibition—implications for ARNIs. Nat Rev Cardiol. 2017;14:171–86.
77. Feldman AM. Neprilysin Inhibition in the time of precision medicine. JACC Heart Fail. 2016;4:409–14.
78. Cannon JA, Shen L, Jhund PS, et al. Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction. Eur J Heart Fail. 2017;19:129–37.
79. Bodey F, Hopper I, Krum H. Neprilysin inhibitors preserve renal function in heart failure. Int J Cardiol. 2015;179:329–30.
80. Li B, Zhao Y, Yin B, et al. Safety of the neprilysin/renin-angiotensin system inhibitor LCZ696. Oncotarget. 2017;8:83323–33.
81. Richards AM. N-terminal B-type natriuretic peptide in heart failure. Heart Fail Clin. 2018;14:27–39.
82. 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;68:2425–36.
83. Nunez J, Nunez E, Barallat J, et al. Serum neprilysin and recurrent admissions in patients with heart failure. J Am Heart Assoc. 2017;6:e005712.
84. Emrich IE, Vodovar N, Feuer L, et al. Do plasma neprilysin activity and plasma neprilysin concentration predict cardiac events in chronic kidney disease patients? Nephrol Dial Transplant. 2018. https://doi.org/10.1093/ndt/gfy066 **(Epub ahead of print)**.

85. O'Meara E, Prescott MF, Claggett B, et al. Independent Prognostic Value of Serum Soluble ST2 Measurements in Patients With Heart Failure and a Reduced Ejection Fraction in the PARADIGM-HF Trial (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure). Circ Heart Fail. 2018;11:e004446.
86. Mogensen UM, Kober L, Jhund PS, et al. Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF. Eur J Heart Fail. 2018;20:514–22.
87. Januzzi JL, Butler J, Fombu E, et al. Rationale and methods of the prospective study of biomarkers, symptom improvement, and ventricular remodeling during sacubitril/valsartan therapy for heart failure (PROVE-HF). Am Heart J. 2018;199:130–6.
88. Ollendorf DA, Sandhu AT, Pearson SD. Sacubitril–valsartan for the treatment of heart failure: effectiveness and value. JAMA Intern Med. 2016;176:249–50.
89. King JB, Shah RU, Bress AP, Nelson RE, Bellows BK. Cost-effectiveness of sacubitril–valsartan combination therapy compared with enalapril for the treatment of heart failure with reduced ejection fraction. JACC Heart Fail. 2016;4:392–402.
90. Gaziano TA, Fonarow GC, Claggett B, et al. Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure and reduced ejection fraction. JAMA Cardiol. 2016;1:666–72.
91. Sandhu AT, Ollendorf DA, Chapman RH, Pearson SD, Heidenreich PA. Cost-effectiveness of sacubitril–valsartan in patients with heart failure with reduced ejection fraction. Ann Intern Med. 2016;165:681–9.
92. Ademi Z, Pfeil AM, Hancock E, et al. Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction. Swiss Med Wkly. 2017;147:w14533.
93. McMurray JJV, Trueman D, Hancock E, et al. Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. Heart. 2018;104:1006–13.
94. Ramos IC, Versteegh MM, de Boer RA, et al. Cost Effectiveness of the Angiotensin Receptor Neprilysin Inhibitor Sacubitril/Valsartan for Patients with Chronic Heart Failure and Reduced Ejection Fraction in the Netherlands: A Country Adaptation Analysis Under the Former and Current Dutch Pharmacoeconomic Guidelines. Value Health. 2017;20:1260–9.
95. Yandrapalli S, Aronow WS, Mondal P, Chabbott DR. Limitations of sacubitril/valsartan in the management of heart failure. Am J Ther. 2017;24:e234–9.
96. Pablos-Mendez A, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. JAMA. 1998;279:222–5.
97. Perez AL, Kittipibul V, Tang WHW, Starling RC. Patients not meeting PARADIGM-HF enrollment criteria are eligible for sacubitril/valsartan on the basis of FDA approval: the need to close the gap. JACC Heart Fail. 2017;5:460–3.
98. Tsutsui H, Momomura S, Saito Y, et al. Efficacy and safety of sacubitril/valsartan (LCZ696) in Japanese patients with chronic heart failure and reduced ejection fraction: rationale for and design of the randomized, double-blind PARALLEL-HF study. J Cardiol. 2016;70:225–31.
99. National Institute for Health and Care Excellence. Sacubitril valsartan for treating symptomatic chronic hert failure with reduced ejection fraction. Technology appraisal guidance [TA388]. 2016. www.nice.org.uk/guidance/ta388. Accessed 22 Jan 2018.
100. Institute for Clinical and Economic Review. ICER draft report on CardioMEMS and Entresto for management of congestive heart failure posted for public comment [media release]. 2015. https://icer-review.org/announcements/chf-draft-report-posted/. Accessed 22 Jan 2018.
101. Prasad V. Let's take a closer look at PARADIGM-HF [blog post] 1 September 2014. NEJM Journal Watch. 2014. https://blogs.jwatch.org/cardioexchange/2014/09/01/lets-scrutinize-paradigm-hf/. Accessed 22 Jan 2018.
102. CardioExchange Editors, Staff. Perspectives on PARADIGM-HF [blog post]. 5 Septembe 2014. NEJM Journal Watch. 2014. https://blogs.jwatch.org/cardioexchange/2014/09/05/perspectives-on-paradigm-hf/. Accessed 22 Jan 2018.
103. Entresto (sacubitril and valsartan) tablets: US prescribing information. New Jersey: Novartis Pharmaceuticals Corporation, 2017.