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The Role of Angiotensin Receptor-Neprilysin Inhibitors in Cardiovascular Disease

Existing Evidence, Knowledge Gaps, and Future Directions

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ABSTRACT

Although traditional renin-angiotensin system (RAS) antagonists including angiotensin converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have revolutionized the treatment of cardiovascular disease (CVD), the pivotal *PARADIGM-HF* trial demonstrated that sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), was superior to an angiotensin converting-enzyme inhibitor in reducing CV morbidity and mortality in patients with heart failure and a reduced ejection fraction (HFrEF). However, despite international regulatory approval and strong recommendations in the guidelines, uptake of sacubitril/valsartan has been disappointing. Sacubitril/valsartan is now the focus of a large program of clinical trials testing the hypothesis that ARNIs may supplant conventional RAS inhibitors across the spectrum of CVD, including hypertension, secondary prevention after myocardial infarction, and HF with a preserved ejection fraction (HFpEF). This review summarizes the existing evidence, knowledge gaps, and future directions of ARNIs in CVD based on discussions between clinical trialists, industry representatives, and regulatory authorities at the 2016 Global CardioVascular Clinical Trialists Forum in Washington, D.C.

Keywords: heart failure, reduced ejection fraction, angiotensin receptor-neprilysin inhibitor, sacubitril/valsartan

ABBREVIATIONS

CVD = cardiovascular disease

RAS = renin-angiotensin system

ACEI = angiotensin converting-enzyme inhibitor

ARB = angiotensin receptor blocker

ARNI = angiotensin receptor-neprilysin inhibitor

HFrEF = heart failure with a reduced ejection fraction

HFpEF = heart failure with a preserved ejection fraction

MI = myocardial infarction

FDA = Food and Drug Administration

EMA = European Medicines Agency

NYHA = New York Heart Association

BNP = b-type natriuretic peptide

NT-proBNP = amino terminal pro b-type natriuretic peptide

SBP = systolic blood pressure

DBP = diastolic blood pressure

eGFR = estimated glomerular filtration rate

HR = hazard ratio

CI = confidence interval

INTRODUCTION

The prognosis of patients with CVD has been revolutionized by guideline-directed medical therapies (1). Although traditional RAS antagonists, including ACEIs and ARBs, have been the cornerstone of therapy for CVD for several decades (2), the *PARADIGM-HF* trial, demonstrated that substitution of an ACEI (i.e. enalapril) with an ARNI (i.e. sacubitril/valsartan) led to a 20% relative reduction in the risk of CV death or HF hospitalization in patients with chronic, stable HFrEF (3, 4). As a result, the FDA and EMA approved sacubitril/valsartan (**Table 1**) and the ACC/AHA/HFSA and ESC updated their guidelines to reflect these new results (**Table 2**) (5, 6). In addition, Novartis initiated a large clinical trial program to find out whether ARNIs might be superior to ACEIs across the spectrum of CVD. The objective of this review is to critically evaluate the role of sacubitril/valsartan in CVD and to discuss completed, ongoing, and planned clinical trials in HFrEF, HFpEF, post-MI, and hypertension (**Table 3**).

HEART FAILURE WITH A REDUCED EJECTION FRACTION

PARADIGM-HF

Study Overview

The *PARADIGM-HF* trial was designed to test the hypothesis that inhibiting neprilysin, thereby preventing the degradation of natriuretic and many other vasoactive peptides, in addition to blocking angiotensin-II-type-1 receptors, would reduce CV morbidity and mortality in patients with HFrEF compared to an ACEI used in guideline-recommended doses (3). Patients aged $\geq$18 years with chronic HFrEF (EF $\leq$35-40%) and NYHA functional class II-IV symptoms, an elevated BNP or NT-proBNP, an eGFR >30

mL/min/1.73 m^2**,** and a stable dose of a β-blocker and an ACEI/ARB equivalent to at least 10 mg of enalapril daily were eligible for enrollment.

A total of 10,521 patients entered sequential single-blind run-in periods with enalapril 10 mg twice daily for 2 weeks followed by sacubitril/valsartan initially at a dose of 100 mg (i.e. currently marketed as 49/51 mg tablet) twice daily uptitrated to 200 mg (i.e. 97/103 mg tablet) twice daily for 4 to 6 weeks. Following the run-in phase, 8442 patients (80%) who had tolerated both interventions and who were still willing and able to participate were randomized in a 1:1 fashion to double-blind treatment with either enalapril 10 mg twice daily or sacubitril/valsartan 200 mg twice daily (7).

Efficacy of Sacubitril/Valsartan

On March 28, 2014 after the third interim analysis, the data and safety monitoring board notified the principal investigators that the boundary for overwhelming benefit had been crossed and the executive committee voted to stop the trial early (4). At the time the study was terminated, enrollment had been completed and there was a median follow-up duration of 27 months. Patients receiving sacubitril/valsartan (914 events, 21.8%), compared to enalapril (1117 events, 26.5%), were at lower risk for the primary outcome, death due to CV causes or first hospitalization for HF (Hazard Ratio [HR] 0.80, 95% Confidence Interval [CI] 0.73-0.87; p-value <0.001), as well as each of the components of the composite endpoint (**Figure 1**). Treatment with sacubitril/valsartan (711 events, 17.0%) vs. enalapril (835 events, 19.8%) also led to a significant reduction in all-cause mortality (HR 0.84, 95% CI 0.76-0.93; p-value = <0.001). Based on the *PARADIGM-HF* data and actuarial estimates of event rates and life expectancy, it has been projected that

treatment with sacubitril/valsartan would prolong survival an average of 1 to 2 years across a wide range of age groups (8).

Although health-related quality of life, as assessed by the change in the KCCQ clinical summary score from baseline to 8 months, declined in both treatment arms during follow-up, it worsened to a greater extent in the enalapril arm (9). However, when zero values were not imputed for patients who died, the magnitude of the between-group difference (0.95 points, 95% CI 0.31-1.59; p-value = 0.004) was greatly diminished suggesting that the KCCQ analyses were confounded by the competing risk of death. Additional research is required to evaluate the impact of ARNI therapy on health-related quality of life and functional capacity.

Safety and Tolerability of Sacubitril/Valsartan

Patients receiving sacubitril/valsartan experienced higher rates of symptomatic hypotension vs. enalapril (14.0% vs. 9.2%, p-value = <0.001). (**Figure 2**) (10). However, there were no differences between the sacubitril/valsartan and enalapril groups in permanent study drug discontinuation due to hypotension (0.9% vs. 0.7%, p-value = 0.38). The incidence of renal insufficiency (i.e. defined as a serum creatinine $\geq$2.5 mg/dL) and hyperkalemia during follow-up was lower in patients treated with sacubitril/valsartan compared to enalapril. In addition, the occurrence of minor and life-threatening episodes of angioedema was low (<0.5%) and did not differ between treatment groups. Of note, as a condition for approval, the FDA has required Novartis Pharma AG (Basel, Switzerland) to conduct an observational registry to further clarify

the risk of angioedema in black patients treated with sacubitril/valsartan vs. conventional RAS inhibitors (New Drug Application 207620 Approval, accessdata.fda.gov).

Finally, because neprilysin plays a role in removing amyloid-β peptides from the brain, it has been postulated that long-term treatment with an ARNI might affect cognitive function (11). Despite this theoretical concern, neprilysin is only one of more than 20 enzymes involved in amyloid-β clearance. There was no discernible signal of increased risk of dementia with sacubitril/valsartan, compared to enalapril, in the *PARADIGM-HF* trial. However, additional research is required to evaluate the association between treatment with sacubitril/valsartan and mild cognitive impairment in patients with additional risk factors for dementia as well as over a longer duration of follow-up (12). Thus, as part of the FDA approval process, the manufacturer will conduct a multicenter, randomized, double-blind, active-controlled trial to evaluate the effects of sacubitril/valsartan vs. valsartan on cognitive function as assessed by comprehensive neurocognitive testing and brain imaging (New Drug Application 207620 Approval, accessdata.fda.gov).

Real-World Adoption of Sacubitril/Valsartan

Despite receiving FDA approval and strong recommendations in international guidelines, the uptake of sacubitril/valsartan in routine practice has been disappointing. The American Heart Association's GWTG-HF registry found that based on FDA labeling, nearly 70% of patients hospitalized for HFrEF (i.e. EF $\leq$40%) would be eligible for sacubitril/valsartan (13). Similarly, data from the United Kingdom suggest that upwards of 60% of outpatients consecutively referred to a community HF clinic would be

eligible for ARNI therapy (14). In contrast, only 2.3% of patients hospitalized for HFrEF were prescribed sacubitril/valsartan at discharge in the first 12 months following FDA approval (15). Some estimates suggest that optimal implementation of ARNI therapy could prevent more than 28,000 deaths per year (16). Given the relative efficacy and safety profile of sacubitril/valsartan compared to conventional RAS inhibitors, it is important to carefully consider provider reasons for not prescribing, system level barriers to implementation, and patient factors for decision making with respect to this life-prolonging therapy.

Stability on Traditional RAS Inhibitors

There is a clinical inertia among providers and a resistance to change among patients if things seem to be going well and the situation is stable (17). However, the *PARADIGM-HF* trial found that HF is a lethal syndrome, regardless of the severity of symptoms, as evidenced by the high short-term mortality rate seen in a minimally symptomatic patient population. Despite the fact that nearly 40% of patients had no prior hospitalization for HF, one in five of these patients died due to CV causes or were hospitalized for HF during follow-up (18). In addition to improving survival, sacubitril/valsartan, compared to enalapril, reduced the risk of clinical deterioration including hospitalizations (HR 0.79, 95% CI 0.71-0.89; p-value <0.001), emergency department visits (HR 0.66, 95% 0.52-0.58; p-value = 0.001), and/or intensification of medical therapy in the outpatient setting (HR 0.84, 95% 0.74-0.94; p-value = 0.003) for worsening HF (19, 20). Similarly, among patients recently admitted for a primary diagnosis of HF, readmission for any cause (OR 0.74, 95% CI 0.56-0.97; p-value =

0.031) and/or for HF (OR 0.62, 95% CI 0.45-0.87; p-value = 0.006) at 30-days were lower in the sacubitril/valsartan arm (21). Thus, given the dissociation between HF signs and symptoms and prognosis and the overwhelming benefit of sacubitril/valsartan on both fatal and non-fatal endpoints, there is not a clear rationale to wait for clinical progression or deterioration before switching patients from traditional RAS inhibitors to an ARNI.

Validity of the PARADIGM-HF Trial

Another potential reason for clinical aversion to switching patients to sacubitril/valsartan may be reservations regarding the design of the *PARADIGM-HF* trial (22). It has been argued that enalapril and/or the target dose used in the *PARADIGM-HF* trial were not the gold standard comparator. However, this is the only dose of any ACEI that has been shown in a clinical trial to improve long-term survival (23). Although *CONSENSUS* tested a higher target dose of enalapril (i.e. 40 mg daily), less than 25% of patients reached the highest dose and the mean daily dose of enalapril achieved in *PARADIGM-HF* was actually marginally higher (i.e. 18.9 mg vs. 18.6 mg) (24, 25). Thus, any difference between sacubitril/valsartan and enalapril in terms of outcomes is likely to be due to the addition of neprilysin inhibition.

Reproducibility of the PARADIGM-HF Trial

It has also been argued that *PARADIGM-HF* was a single trial and the results need to be replicated before ARNI therapy supplants traditional RAS inhibitors as the standard of care. However, the idea of carrying out a hypothetical *PARADIGM-HF-2*

may be both unethical and unnecessary. If *PARADIGM-HF* was divided at the chronological midpoint into two distinct clinical trials and the results reexamined, despite the loss of statistical power, the outcomes of both smaller trials would be identical to the parent trial (22). The statistical power of *PARADIGM-HF* was equal to or greater than that of four separate clinical trials each showing a reduction in CV mortality with a p-value <0.05. The possibility that the primary results were due to chance is less than one in one million (26). This assertion is further substantiated by a meta-analysis of pooled data from three clinical trials in HFrEF (i.e. *IMPRESS*, *OVERTURE*, and *PARADIGM-HF*) which found that combined neprilysin-RAS inhibition (i.e. omapatrilat or sacubitril/valsartan) compared to traditional RAS inhibition improved survival (27).

Cost Considerations with Sacubitril/Valsartan

Another patient and system level barrier to implementation and widespread adoption of sacubitril/valsartan is cost (28). The estimated wholesale price of twice-daily dosing of sacubitril/valsartan in the United States is $12.50 per day costing upwards of $4500 annually (29). However, it is difficult to estimate true out-of-pocket expenses as there is tremendous variation based on insurance status and level of reimbursement. In addition, obtaining approval for even partial reimbursement may require clear documentation in the medical record and paperwork for prior authorization, placing an additional burden on prescribers.

In contrast, although the cost of the therapy may be substantial for patients and healthcare payers, it should be pointed out that several analyses have found sacubitril/valsartan to be cost-effective compared to conventional RAS inhibitors (i.e.

traditionally defined as less than $50,000 per quality-adjusted life year) in HFrEF patients with NYHA functional class II-IV symptoms (30-32).

The Use of Sacubitril/Valsartan in Primary Care

Although the 2016 ACC/AHA/HFSA focused update recommends ARNI therapy as a first-line alternative to traditional RAS inhibitors in patients with HFrEF who remain symptomatic despite optimal medical therapy (5, 6), the American Academy of Family Physicians has not yet endorsed this guideline because of concerns about its methodology and insufficient evaluation of harm (33). Due to their advanced age and multiple comorbidities, it is not uncommon for HFrEF patients to receive regular care from general practitioners and multiple specialists and subspecialists. Many primary care physicians may treat a significant number of patients with HFrEF and some may be the primary provider for HF-related care in addition to general medical conditions. It is confusing and counterproductive to general practitioners when a discrepancy exists between the guideline recommendations published by cardiologists and HF specialists and the public statements issued by their own professional societies. As a result, increasing the uptake of sacubitril/valsartan in the outpatient setting may require providing continuing medical education focused on the specific needs and concerns of primary care physicians. The experience with sacubitril/valsartan is a learning opportunity and moving forward guideline committees addressing topics in cardiology and HF should include physicians with training in internal and/or family medicine who are currently practicing and selected to represent the viewpoint and serve as a liaison for their respective professional organizations.

LIFE

Although sacubitril/valsartan was broadly approved by the FDA for the management of patients with HFrEF (i.e. defined as EF ≤40%) and NYHA functional class II-IV symptoms, it is noteworthy that only 33 patients (0.8%) with NYHA functional class IV symptoms were randomized to sacubitril/valsartan. Thus, the *LIFE* study (**ClinicalTrials.gov Identifier**: NCT02816736) is a randomized, double-blind, active-controlled trial designed to assess the efficacy, safety, and tolerability of sacubitril/valsartan in a planned 400 patients with HFrEF and severe symptoms. Patients are eligible for enrollment if they have advanced HFrEF defined as an EF ≤35% and NYHA functional class IV symptoms (i.e. chronic dyspnea or fatigue at rest or with minimal exertion) or requiring chronic inotropic therapy, an elevated BNP or NT-proBNP, and one or more enrichment criteria. Patients are randomized to sacubitril/valsartan vs. valsartan titrated to the maximally-tolerated dose and followed for 24 weeks. The primary endpoint is the proportional change from baseline in the area under the curve for NT-proBNP levels at weeks 4, 8, 12, and 24.

Although it is difficult to define advanced HF, the *LIFE* trial requires one or more enrichment criteria as objective evidence of advanced HF including need for inotropic support, repeat hospitalizations, and assessments of functional capacity. In addition, both treatment arms in the *LIFE* trial differ in clinically important ways compared to *PARADIGM-HF*. First, the *LIFE* trial will make use of a lower dose of sacubitril/valsartan (i.e. 24/26 mg tablet by mouth twice daily), which was not used in *PARADIGM-HF*. This will allow a better assessment of the safety and tolerability of this

lower dose, particularly with respect to symptomatic hypotension. Second, the comparator arm is valsartan, an ARB, as opposed to enalapril, the gold standard ACEI. This will potentially allow a more direct interpretation of the effects of neprilysin inhibition in isolation. However, it should be noted that the selection of valsartan for the control arm has been criticized given the limited experience with ARBs in HFrEF patients with NYHA functional class IV symptoms compared to ACEIs. Despite these strengths, the primary endpoint of the *LIFE* trial will assess time-averaged change in a surrogate biomarker (i.e. NT-proBNP). While natriuretic peptide levels are strongly correlated with adverse events (34), the trial will be underpowered to draw definitive conclusions on hard clinical outcomes. In addition, recruitment may be challenging given that one of the first harbingers of advanced HF is an inability to tolerate guideline-directed medical therapies.

PIONEER-HF

The *PIONEER-HF* study (**ClinicalTrials.gov Identifier**: NCT02554890) is a multicenter trial designed to assess the role of sacubitril/valsartan in patients with HFrEF stabilized during hospitalization for worsening HF. Patients are eligible for enrollment no earlier than 24 hours and up to 10 days from initial presentation for a primary diagnosis of HF if they have an EF $\leq$40%, an elevated BNP or NT-proBNP, and are clinically stable (i.e. defined as an SBP $\geq$100 mmHg and no recent intensification in IV therapies). Patients are randomized 1:1 to in-hospital initiation of sacubitril/valsartan vs. enalapril titrated to target dose over 8 weeks of double-blind treatment and 4 weeks of open-label sacubitril/valsartan using an algorithm based on SBP. The primary endpoint of

PIONEER-HF is the time-average proportional change in NT-proBNP from baseline through weeks 4 and 8. Secondary and exploratory endpoints include urgent and emergent episodes of care and serum and urinary biomarkers of myocardial stress, cardiac fibrosis/remodeling, inflammation, and tissue perfusion/injury.

There are several unique aspects of the *PIONEER-HF* study which will further explore the application of sacubitril/valsartan in routine practice. Of note, *PIONEER-HF* was designed to enroll patients hospitalized for worsening HF following stabilization irrespective of duration of diagnosis or background HF therapy and without a preceding run-in period. Thus, this will be the first opportunity to assess the safety and tolerability of in-hospital initiation of sacubitril/valsartan in *de novo* HF and in a treatment naïve patient population. In addition, the secondary endpoints of *PIONEER-HF* move beyond traditional outcome measures by incorporating worsening HF treated in the outpatient setting including unscheduled office, urgent care, and ER visits. The available data suggest that including unscheduled or urgent episodes of care not leading to hospitalization in the composite clinical endpoint may increase the total number of accrued events by upwards of 15% (20). Finally, the biomarker data may provide valuable insights into the mechanism of action of sacubitril/valsartan and the pathophysiology of HF.

HEART FAILURE WITH A PRESERVED EJECTION FRACTION

PARAMOUNT and PARAGON-HF

The *PARAMOUNT* trial was designed to assess the therapeutic value of sacubitril/valsartan in HFpEF (35). Patients were eligible if they had an EF $\geq$45% and a

history of HF with associated signs and symptoms and an elevated NT-proBNP. Following a run-in phase, 301 patients were randomized 1:1 in a double-blind fashion to treatment with valsartan 160 mg twice daily (n = 152) or sacubitril/valsartan 200 mg twice daily (n = 149). The *PARAMOUNT* trial was continued for 36 weeks including the 12-week main study period and a 24-week extension phase. The primary efficacy endpoint was change in NT-proBNP from baseline to week 12.

Treatment with sacubitril/valsartan, compared to valsartan, led to an early and sustained reduction in NT-proBNP through week 12. Although NT-proBNP levels continued to decrease in patients treated with sacubitril/valsartan, the between-group difference was no longer statistically significant at 36 weeks (p-value = 0.20). In addition, after 36 weeks of treatment with sacubitril/valsartan, compared to valsartan, left atrial volume and dimension were both significantly reduced. However, there was no difference in EF, ventricular volumes, or other diastolic parameters. Patients treated with sacubitril/valsartan also experienced an improvement in NYHA functional class at 36 weeks compared to the valsartan arm. *PARAGON-HF* (**ClinicalTrials.gov Identifier**: NCT01920711), a CV outcomes trial of sacubitril/valsartan in HFpEF, has fully enrolled over 4800 patients with a planned follow-up duration of up to 57 months for the composite endpoint of CV mortality and total hospitalizations for worsening HF (36).

Although the results of the *PARAGON-HF* trial are highly anticipated, it is notoriously difficult to make the assessment that dyspnea in a patient with a preserved EF is due to HF and not a comorbid condition (i.e. obesity, COPD, sleep disordered breathing, etc.). The experience with the *TOPCAT* study further highlights the challenges of designing and conducting global clinical trials in HFpEF (37, 38). In short, the

TOPCAT investigators found tremendous geographic variation in patient characteristics, outcomes, and response to therapy that may have been partially explained by differential regional enrollment in the prior hospitalization vs. BNP strata (39, 40). As a result, it is notable that participation in *PARAGON-HF* is contingent upon the presence of signs and symptoms of HF requiring treatment with a diuretic, evidence of structural heart disease (i.e. defined as left atrial enlargement and/or left ventricular hypertrophy), and an elevated NT-proBNP in order to improve diagnostic accuracy and enroll a sufficiently high-risk patient population. In contrast to prior pivotal trials in HFpEF, the control arm of *PARAGON-HF* is an active comparator (i.e. valsartan) as opposed to placebo as ARBs are commonly prescribed and have been shown to be safe in HFpEF and may lead to a modest reduction in hospitalizations for worsening HF (41). In addition, the use of an active comparator will allow the neurohormonal benefits of neprilysin inhibition to be studied in isolation from RAS blockade in HFpEF. The major limitation of the *PARAGON-HF* trial is that requiring objective evidence of structural heart disease and an elevated NT-proBNP may limit its generalizability. It is well-established that upwards of 30% of patients with symptomatic HFpEF may have a normal BNP in the setting of an elevated pulmonary capillary wedge pressure (42). In addition, prior research has shown that although elevated BNP/NT-proBNP levels may denote an overall higher risk HFpEF cohort, these patients may be less responsive to treatment (43, 44). Thus, there may be a dissociation between disease severity and response to therapy in HFpEF which requires further exploration. Regardless, the *PARAGON-HF* trial will determine whether the short-term effects of sacubitril/valsartan on cardiac injury (45), myocardial stress, and left

atrial remodeling translate into improved long-term prognosis in an adequately powered CV outcomes study.

POST-MYOCARDIAL INFARCTION

PARADISE-MI

The *PARADISE-MI* trial (**ClinicalTrials.gov Identifier**: NCT02924727) will test the hypothesis that ARNI therapy will reduce CV morbidity and mortality compared to conventional RAS inhibition in patients post-MI with additional risk factors. *PARADISE-*MI will enroll patients diagnosed with a spontaneous acute MI with an EF $\leq$40% and/or pulmonary congestion requiring IV therapy, one or more enrichment criteria, and documented hemodynamic stability. An estimated 4650 patients will be randomized 1:1 to double-blind treatment with sacubitril/valsartan vs. rampiril and followed for the composite of CV mortality, hospitalization for worsening HF, and HF treated in the outpatient setting.

The *PARADISE-MI* trial follows a strong precedent whereby traditional RAS inhibitors were first studied in the setting of chronic HF and later found to be equally beneficial in post-MI patients with evidence of systolic dysfunction and/or signs and symptoms of HF (46-50). However, due to the widespread availability of early revascularization and advances in medical therapy, the incidence of previously asymptomatic patients experiencing a MI complicated by a reduced EF and/or pulmonary edema has declined dramatically over time. For example, in a national quality improvement registry of patients admitted for acute coronary syndrome, less than 20% of patients had a moderately-severely reduced EF (i.e. <40) (51). Thus, although the

enrichment criteria will likely be necessary to identify patients at sufficiently high-risk to ensure an adequately powered study, this requirement may also make it more challenging to recruit patients and limit the generalizability of the findings.

HYPERTENSION

The combination of neprilysin inhibition and RAS blockade has also been explored as a treatment for hypertension. In a phase II study 1328 patients with mild-to-moderate essential hypertension were randomized to sacubitril/valsartan, valsartan, or placebo (52). After 8 weeks of treatment, sacubitril/valsartan, compared to the appropriate comparator dose of valsartan, led to a greater reduction in mean DBP (-2.17 mmHg, 95% CI -3.28 mmHg, -1.06 mmHg; p-value = 0.0023). The difference was significant for all pairwise comparisons except for the lowest dose of sacubitril/valsartan vs. valsartan.

Despite the strong evidence-basis for aggressive BP control in high-risk individuals, epidemiologic data suggest that the standard BP goal is achieved in only 50% of patients (53). Thus, treating hypertension to achieve goal BP remains an important public health objective and an unmet therapeutic need. Given the demonstrated superiority of ARNI therapy compared to conventional RAS inhibitors as an anti-hypertensive agent, pivotal trials should be designed and conducted to study the efficacy and safety of sacubitril/valsartan as a monotherapy and as part of combination therapy in patients with hypertension and risk factors for CVD as well as medically refractory hypertension (54).

CONCLUSION

Despite major therapeutic advances in the management of CVD, patients post-MI with evidence of systolic dysfunction or symptomatic HF irrespective of EF receiving optimal medical therapy including traditional RAS inhibitors remain at high-risk for CV morbidity and mortality. The *PARADIGM-HF* trial demonstrated that ARNI therapy, compared to an ACEI, led to a robust benefit on both fatal and non-fatal endpoints independent of baseline risk and current clinical status in patients with HFrEF and predominantly mild symptoms. Thus, the available data suggest there is little rationale to wait for clinical progression or deterioration and it is reasonable to switch stable HFrEF patients with minimal symptoms from an ACEI or an ARB to an ARNI. Ongoing phase IV clinical trials promise to clarify the efficacy, safety, and tolerability of sacubitril/valsartan in HFrEF patients with NYHA functional class IV symptoms and/or hospitalized for acute decompensated HF. In addition, the role of ARNI therapy in the post-MI setting and in the management of patients with HFpEF is being evaluated in well-powered CV outcome trials. Future research should clarify the potential scope of sacubitril/valsartan across the spectrum of CVD including subgroups of interest such as patients with HTN and additional risk factors, diabetes mellitus, and chronic kidney disease.

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Figure Legends

Figure 1. Forest plots for the primary, secondary, and exploratory outcomes of the *PARADIGM-HF* trial.

Figure 2. The incidence of adverse events occurring during the PARADIGM-HF trial.

Table 1. Summary of prescribing information for Entresto™ (Sacubitril/Valsartan).

Entresto™ (Sacubitril/Valsartan)[1]	
Indication	To reduce the risk of CV death and hospitalization for HF in patients with chronic HF (NYHA functional class II-IV) and reduced EF
Mechanism of Action	• Sacubitril: Prodrug that inhibits neprilysin and increases circulating levels of natriuretic peptides • Valsartan: Antagonist of the angiotensin II receptor
Dosage Forms and Strengths	24/26 mg (50 mg), 49/51 mg (100 mg), and 97/103 mg (200 mg)
Dosage and Administration	• The recommended starting dose is 49/51 mg twice-daily • Reduce the starting dose to 24/26 mg twice-daily for patients not currently taking or previously taking a low dose of an ACEI or ARB[2] • Double the dose every 2 to 4 weeks to the target maintenance dose of 97/103 mg twice-daily as tolerated • If switching from an ACEI allow a washout period of

	36 hours between administrations of the two drugs.
Contraindications	• Hypersensitivity to any component • History of angioedema related to prior ACEI or ARB therapy • Concomitant use with an ACEI
Adverse Reactions[3]	Hypotension, Hyperkalemia, Cough, Dizziness, and Renal Failure

[1]https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/entresto.pdf

[2]Defined as <10 mg/day of enalapril or an equivalent dose of another ACEI or ARB

[3]Incidence ≥5%

Abbreviations: CV = cardiovascular; HF = heart failure; NYHA = New York Heart Association; EF = ejection fraction; mg = milligram; ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker.

Table 2. Guideline recommendations for the use of ARNIs in patients with HFrEF. *Level of evidence for an ARNI.

2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure		
COR	**LOE**	**RECOMMENDATION**
I	**B-R***	The clinical strategy of inhibition of the renin-angiotensin system with ACEIs OR ARBs OR ARNI in conjunction with evidence-based β-blockers and aldosterone antagonists in select patients is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
I	**B-R**	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEI or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.
III	**B-R**	ARNI should not be administered concomitantly with an ACEI or within 36 hours of the last dose of an ACEI.
III	**C-EO**	ARNI should not be administered to patients with a history of angioedema.
2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure		
I	**A**	An ACEI is recommended in addition to a β-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.

I	**B**	Sacubitril/valsartan is recommended 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, β-blocker, and mineralocorticoid receptor antagonist.
I	**B**	An ARB is recommended to reduce the risk of HF hospitalization and CV death in symptomatic patients unable to tolerate ACEI (patients should also receive a β-blocker and an MRA).
IIb	**C**	An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a β-blocker who are unable to tolerate an MRA.

Abbreviations: ACC = American College of Cardiology; AHA = American Heart Association; HFSA = Heart Failure Society of America; COR = class (strength) of recommendation; LOE = level of evidence; R = randomized; EO = expert opinion; ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; HFrEF = Heart Failure with a Reduced Ejection Fraction; NYHA = New York Heart Association; CV = cardiovascular.

Table 3. Select completed and ongoing clinical trials of sacubitril/valsartan in CVD.

Trial	Sample Size	Study Population	Enrollment Criteria	Active Comparator[2]	Primary Endpoint
PARADIGM-HF[1]	8442	HFrEF	• Chronic HF with an EF ≤40% • NYHA II-IV • Elevated BNP or NT-proBNP • Stable dose of ACEI/ARB equivalent to ≥10 mg of enalapril daily	Enalapril 10 mg	CVM+First HF Hospitalization
LIFE	400	HFrEF, NYHA IV	• Chronic HF with an EF <35% • NYHA IV • Minimum of 3 months of GDMT • SBP ≥90 mmHg • Elevated BNP or NT-proBNP • ≥1 Enrichment Criteria[3]	Valsartan 160 mg	NT-proBNP over 24 weeks
PIONEER-HF	736	Hospitalized HFrEF	• Chronic HF with an EF ≤40% • Admitted ≥24 hrs • Elevated BNP or NT-proBNP • SBP ≥100 mmHg • Stable IV Diuretics for Prior 6 hrs	Enalapril 10 mg	NT-proBNP over 8 weeks

			• No Recent IV Vasodilators and/or Inotropes		
PARAMOUNT[1]	301	HFpEF	• Chronic HF with an EF ≥45% • Elevated NT-proBNP • Chronic Oral Diuretic Therapy • SBP <140 mmHg or <160 mmHg on ≥3 anti-HTN Agents	Valsartan 160 mg	NT-proBNP over 12 weeks
PARAGON	4500	HFpEF	• Chronic HF with an EF >45% • Elevated NT-proBNP • Chronic Oral Diuretic Therapy, • Structural Heart Disease (i.e. Left Atrial Enlargement or Left Ventricular Hypertrophy) Documented on Echocardiogram	Valsartan 160 mg	CVM+Total HF Hospitalizations
PARADISE-MI	4650	High-Risk Post-MI	• Spontaneous MI between 12 hrs and 7 days • EF ≤40% or Pulmonary Congestion Requiring IV Therapy • Hemodynamic Stability • ≥1 Risk Factor[4]	Ramipril 5 mg	Time to CVM+HF Hospitalization+Outpatient HF

[1]Completed

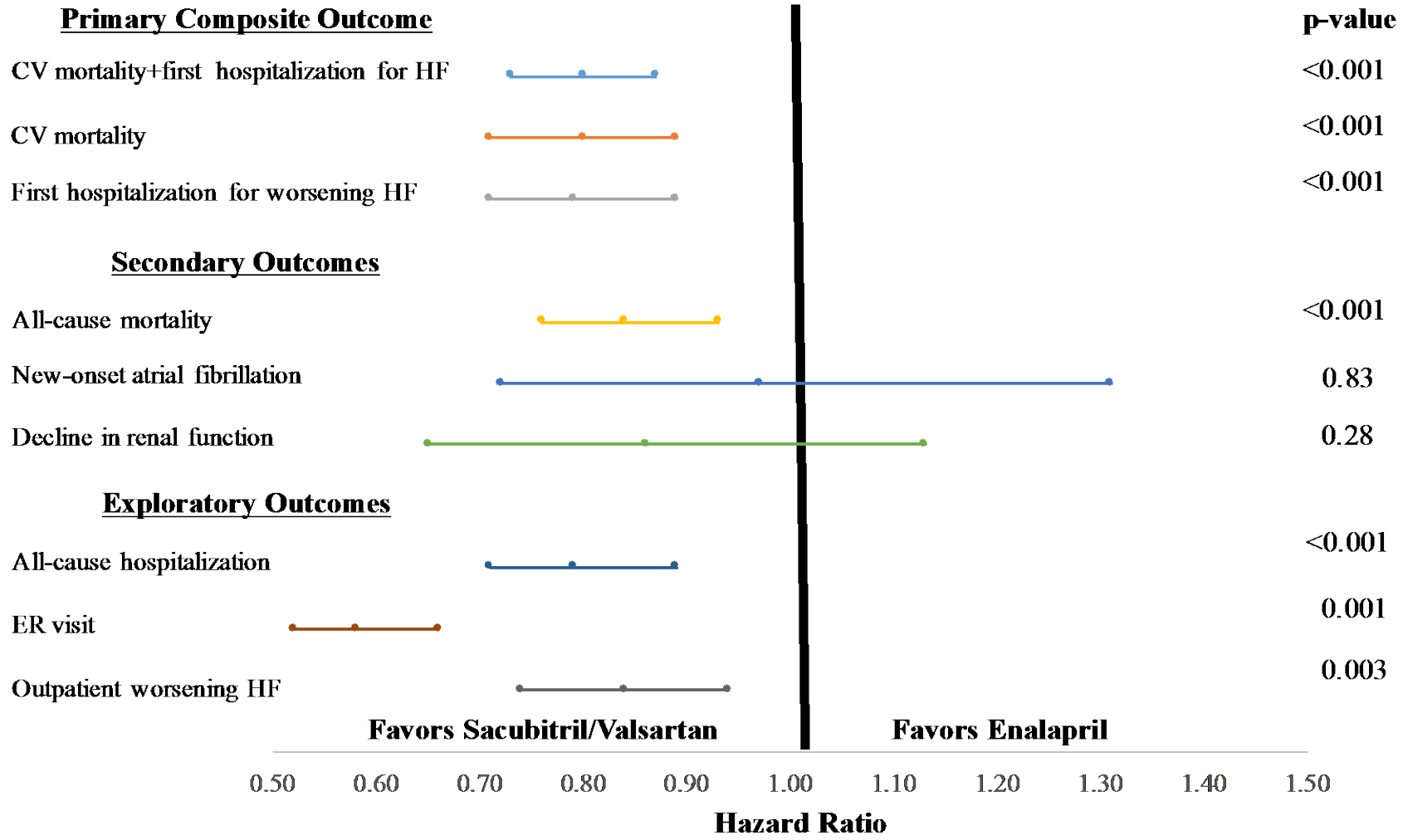
[2]Twice-daily dosing

[3]Current inotropic therapy or use of inotropes in the past 6 months, >1 hospitalizations for HF excluding index admission (6 months), EF $\leq$25% (12 months), Peak VO_2 <55% predicted or peak VO_2 $\leq$16 for men or $\leq$14 for women (RER >1.05) (6 months), 6-MWT Distance <300 m (3 months)

[4]Age >70 years, eGFR <60 mL/min/1.73 m^2, History of DM type I or type II, History of Prior MI, Documented Afib During Index Admission, EF <30%, Worst Killip Class III or IV Requiring IV Therapy, and/or STEMI Without Reperfusion

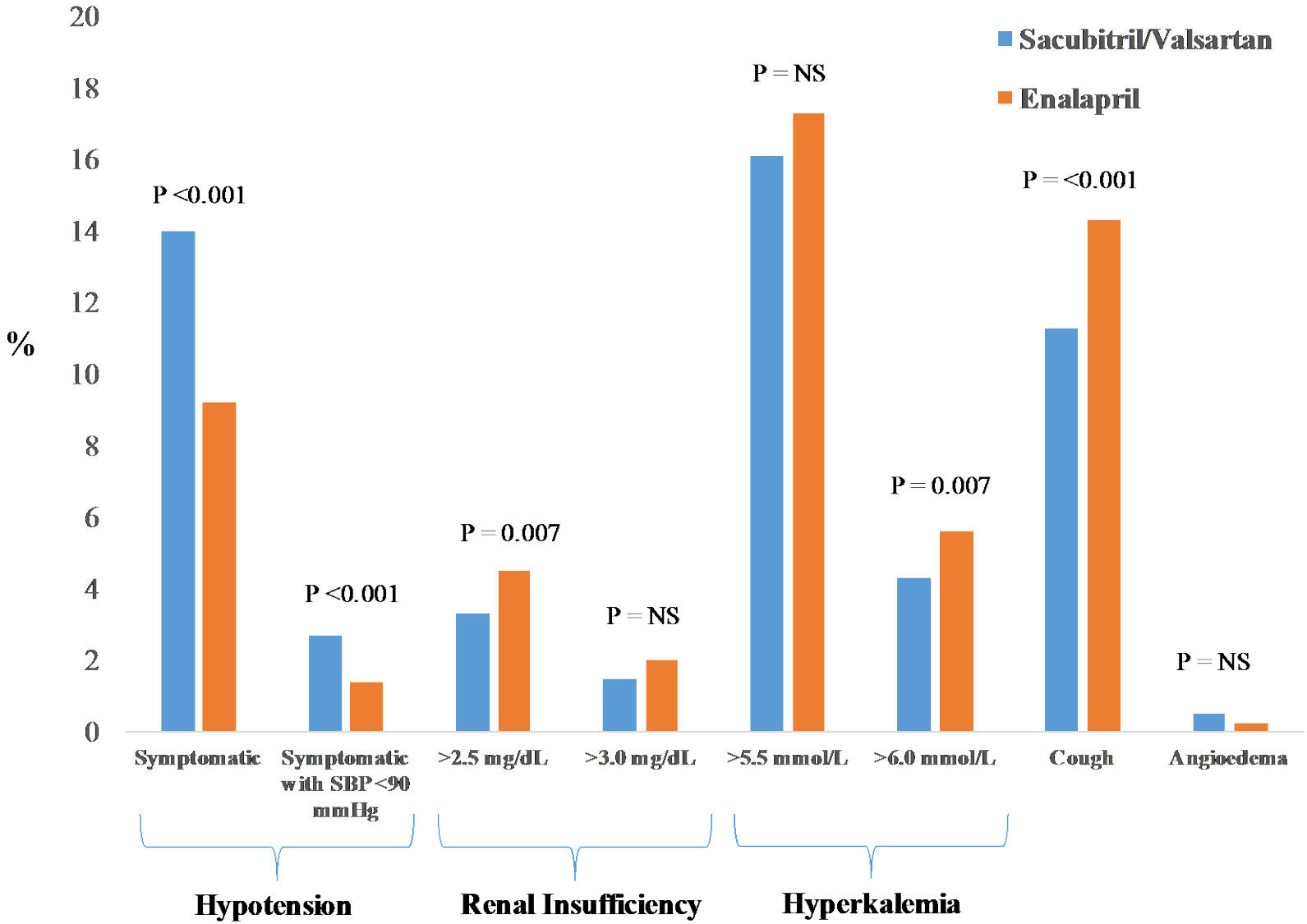
Abbreviations: CVD = cardiovascular disease; HF = heart failure; EF = ejection fraction; HFrEF = heart failure with a reduced ejection fraction; HFpEF = heart failure with a preserved ejection fraction; NYHA = New York Heart Association; BNP = b-type natriuretic peptide; NT-proBNP = amio terminal prob-type natriuretic peptide; ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; mg = milligrams; CVM = cardiovascular mortality; eGFR = estimated glomerular filtration rate; GDMIT = guideline-directed medical therapy; SBP = systolic blood pressure; hrs = hours; IV = intravenous; HTN = hypertension; MI = myocardial infarction; VO_2 = oxygen consumption; RER = respiratory exchange ratio; 6-MWT = 6-minute walk test; DM = diabetes mellitus; afib = atrial fibrillation; STEMI = ST-elevation myocardial infarction.

Figure 1



Abbreviations: CV = cardiovascular; HF = heart failure; ER = emergency room.

Figure 2


20
18
16
14
12
10
8
6
4
2
0
%
Sacubitril/Valsartan
Enalapril
P <0.001
P <0.001
P = 0.007
P = NS
P = NS
P = 0.007
P = <0.001
P = NS
Symptomatic
Symptomatic with SBP<90 mmHg
>2.5 mg/dL
>3.0 mg/dL
>5.5 mmol/L
>6.0 mmol/L
Cough
Angioedema
Hypotension
Renal Insufficiency
Hyperkalemia

Abbreviations: p = probability value; SBP = systolic blood pressure; NS = not significant