Narrative review in the current role of angiotensin receptor-neprilysin inhibitors

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Abstract: Heart failure (HF) accounts for a tremendous burden on health care systems and the society. Since the landmark PARADIGM-HF trial, sacubitril/valsartan, the first in the class of angiotensin receptor neprilysin inhibitor (ARNI) showed superiority to enalapril in patients with HF with reduced ejection fraction (HFrEF). We performed a narrative literature review, hand-searched the reference lists of included articles and relevant reviews. Inhibition of neprilysin increases bradykinin, natriuretic peptides and adrenomedullin levels counteract the neurohormal activation that leads to sodium retention, vasoconstriction, and cardiac remodeling. In PARADIGM-HF the primary outcome of CV death or HF hospitalization was reduced 20% in the ARNI group (HR 0.80, P<0.001) similar to mortality due to cardiovascular cause (HR 0.80, P<0.001) in patients with HFrEF, rendering a number needed to treat of 21 patients. This effect was consistent across subgroups. The safety of starting ARNI inpatient once the acute decompensation of HF is stabilized was demonstrated in PIONEER-HF trial. With willingness-to-pay thresholds commonly acceptable in the United States, sacubitril/valsartan is likely to be cost effective, which might not be in other health systems. Although its safety has been reassured in some clinical trials, common side effects are hypotension, worsening kidney function, hyperkalemia and angioedema. In HFpEF (PARAGON-HF), sacubitril/valsartan showed decrease in the level of the cardiac biomarkers, with improve functional NYHA and decrease in hospitalizations, predominately in women and patients with borderline ejection fraction. Some ongoing studies aim to demonstrate the effects of ARNI in acute coronary syndrome, stable ischemic heart disease, advanced HF, mitral regurgitation, aortic impedance and pulmonary hypertension. In conclusion, sacubitril/valsartan has proven to be an effective addition to the HFrEF arsenal, with safety comparable to current standard of care. In HFpEF, it improves quality of life, particularly in women and in patients with borderline ejection fraction, with no effect on mortality.

Keywords: Sacubitril; sacubitril/valsartan; neprilysin; LCZ696; angiotensin receptor neprilysin inhibitor (ARNI)

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Introduction

Chronic heart failure (HF) accounts for 2% of health care costs in developed countries. Almost 34.8 billion dollars spent on this, make it the largest expenditure entity in the USA. It is estimated to rise by 127% by 2030 (1-3).

With the landmark PARADIGM-HF trial in 2014 (4), the management of HF advanced into a new era when LCZ696, now known as sacubitril/valsartan became the novel therapy and first in its class of angiotensin receptor neprilysin inhibitor (ARNI). It was compared with enalapril in addition to recommended treatment in chronic HF with

class II–IV HF with reduced ejection fraction (HFrEF) of 40% or less.

Due to extensive literature on the only approved ARNI, we performed a narrative literature review on the topic aiming to clarify its current role in the spectrum of cardiovascular disease. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, and PubMed databases through April 30th, 2020, with no restrictions on language. Key words of sacubitril, sacubitril/valsartan, neprilysin, LCZ696 and ARNi were utilized, crossed with HF. Randomized clinical trials, large prospective studies, systematic reviews and metanalysis were included. We hand-searched the reference lists of included articles and relevant reviews. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4038).

Pharmacology of ARNI

The natriuretic peptide system regulates volume, sodium levels, vasodilation, among other integral compensatory processes in HF. Neprilysin degrades beneficial natriuretic proteins namely ANP (atrial natriuretic peptide), BNP (B-type natriuretic peptide), and CNP (C-type natriuretic peptide). NT-proBNP is not a substrate for neprilysin, hence not being degraded (5). The protective and compensatory mechanisms of natriuretic peptides in HF seems to be deficient in early HF (6).

Cumulatively, the natriuretic peptide system has beneficial effects by inhibition of renin release, sympathetic nervous system, antidiuretic hormone release, lusitropic properties, enhancing vagal tone, and prevention of cardiac hypertrophy and fibrosis (7). Inhibition of neprilysin increases bradykinin, natriuretic peptides and adrenomedullin levels, counteracting the neurohormonal activation that leads to sodium retention, vasoconstriction, and cardiac remodeling (8,9). Because neprilysin inhibition simultaneously increases angiotensin II levels, concurrent renin-angiotensin-aldosterone system (RAAS) inhibition is necessary (10,11).

Another neprilysin inhibitor, omapatrilat, showed early promise for hypertension and HF. Phase II trials returned good results, attributed to its inhibition of neprilysin, ACE, and aminopeptidase (12). Unfortunately, the phase III OVERTURE trial (13), failed to achieve its primary endpoint of death or HF hospitalization. Significant results were found in post-hoc analysis with a more contemporary definition of HF hospitalization, but further investigation of omapatrilat was stopped due to an unacceptable level of angioedema (14).

ARNIs in HFrEF

Angiotensin converting enzyme (ACE) inhibitors had long been the cornerstone for HF therapy due to their numerous benefits including mortality reduction seen in the SOLVD-T, SOLVD-P, and CONSENSUS trials (15-17). PARADIGM-HF (4) involved 8,399 patients from 47 countries with left ventricular ejection fraction (LVEF) ≤40%, NYHA II–IV and on at least 1 month of a stable dose of beta blocker and ACEi [or angiotensin receptor blocker (ARB)]. Approximately one-half of participants were also taking a mineralocorticoid receptor antagonist (MRA). Patients with hypotension, glomerular filtration rate (GFR) <30 mL/min/m^2, hyperkalemia and a history of angioedema were excluded from the trial (18,19). There was a run-in period of 4–6 weeks before randomization, assuring that patients tolerated the target doses and both medications were held the day before randomization to minimized risk of angioedema.

The primary outcome of CV death or HF hospitalization was less in the in sacubitril/valsartan group, 21.8% compared to 26.5% in the enalapril group, HR 0.80 (95% CI: 0.73–0.87; P<0.001), as was the secondary outcome of mortality due to cardiovascular cause, from 16.5% to 13.3%, HR: 0.80 (95% CI: 0.71–0.89; P<0.001). This conferred a number needed to treat of 21 patients to prevent one primary event. The secondary endpoints of death from any cause, 19.8% in sacubitril/valsartan group and 17.0% in enalapril group; HR 0.84 (95% CI: 0.76–0.93; P<0.001) and improved symptoms with less decline in Kansas City CM Questionnaire (KCCQ) scores (P=0.001) in the sacubitril/valsartan group.

During the run-in portion, the enalapril group, had more participants withdraw due to adverse effects like cough, decline in renal function (worsening of >25% in GFR, later increased by protocol to >35%), and progression to ESRD. In the sacubitril/valsartan group, there was more angioedema (n=19 versus n=10, none causing airway compromise) and hypotension. The trial was ended early after the prespecified limit for "overwhelming benefit" was reached (4). On further analysis of PARADIGM-HF, it was found that less participants in the sacubitril/valsartan arm needed dose increases in HF therapy (HR 0.84, 95% CI:

0.74–0.94) or emergency room care for HF decompensation (HR 0.66, 95% CI: 0.52–0.85). The sacubitril/valsartan arm was less likely to require intensive care or IV inotropes, receive less HF device placement or cardiac transplant, and had lower NT pro-BNP and troponin levels compared to the enalapril group (20).

The benefits of sacubitril/valsartan over ACE inhibitor were significant regardless if HFrEF was optimized on guideline directed medical therapy or not. This included those with and without implanted defibrillator, on MRA, and on varying doses of beta-blocker (21).

Single center studies and reports have shown that ARNI improves LVEF, LV end systolic and end diastolic volumes, less mitral regurgitation and parameters of diastolic dysfunction (E/A ratio, diastolic filling time, restrictive mitral filling pattern) in a dose dependent fashion (22,23).

The PIONEER-HF trial (24), sought to evaluate ARNI in hospitalized HFrEF patients. Patients included had a NT-proBNP ≥1,600 pg/mL or BNP ≥400 pg/mL and LVEF <40%. To be randomized and allocated to either the ARNI or enalapril group, patients had to first be stabilized from acute decompensated HF, (systolic blood pressure greater than 100 mmHg and no intravenous vasodilator or intravenous diuretic). Starting ARNI during hospitalization resulted in larger decreases in NT-proBNP compared with the enalapril group. More importantly, occurrence of angioedema, hyperkalemia, symptomatic hypotension, and renal dysfunction were similar between with ARNI and enalapril arms. These findings support the use of sacubitril/valsartan in the setting of acute stabilized HF, and initiating therapy in the index hospitalization.

Meta-analysis of IMPRESS (12), OVERTURE (13) and PARADIGM-HF trials (4), further supports the use of ARNI over ACE inhibitor to decrease mortality, pooled HR 0.88 (95% CI: 0.80–0.98) and decreasing composite death or HF hospitalization, pooled HR 0.86 (95% CI: 0.76–0.97) (25).

ARNIs in HF with preserved ejection fraction

Neprilysin inhibition may be of particular benefit in positively altering the course of difficult to treat HF with preserved ejection fraction (HFpEF) (26). Increased natriuretic peptides from neprilysin inhibition can modulate cyclic GMP pathways, and possibly reduce the stiffness of myocardium by further phosphorylating rigid titin isoforms (27). Responsiveness to endothelium derived adrenomedullin was improved in animal studies, resulting in improved diuresis, natriuresis, and vasodilation (28). Therefore, several biological pathways exist in complement to the RAAS system, which are potential targets for neprilysin inhibitors.

RAAS inhibition has been of interest in HFpEF with ACEi and ARB showing improvement in functional capacity, symptoms, and hospital admissions (29,30), without evidence for reduction in mortality, and until now there remains a lack of proven regimens to guide management (31). Consequently, mortality and morbidity has been worse in this population compared to HFrEF (32,33).

In 2012, the multinational, phase 2 PARAMOUNT trial (34) compared sacubitril/valsartan with valsartan in patients with HFpEF (n=301). Patients were mostly NYHA class II but also included classes I and III. Decreased levels of NT-proBNP, surrogate marker of reduced left ventricular stress, has been correlated with improved outcomes in HF (35-37) and sacubitril/valsartan reduced NT-proBNP levels more than valsartan at a ratio of change 0.77 (95% CI: 0.064–0.92; P=0.005) at 12 weeks. There was no change in LV mass, function, size as well as tricuspid regurgitant velocity or diastolic function. There was a significant reduction in left atrium volumes at week 36, suggestive of improved left ventricular filling pressures. Quality of life, hypotension, renal function or hyperkalemia was not statistically different between the arms. There was a significant improvement in NYHA class at 36 weeks. Overall sacubitril/valsartan was well tolerated and had a similar side-effect profile to valsartan. The effects on biomarkers and functional class were independent of the reduction in systolic blood pressure (38).

In PARAGON-HF (39), participants included NYHA II–IV (n=4,822), LVEF ≥45% elevated natriuretic peptides. They were randomized to an ARNI or valsartan group with a target dose of sacubitril 97 mg twice daily or valsartan 160 mg twice daily. The primary composite outcome of total HF hospitalizations and cardiovascular death had a trend towards reduction in the ARNI group, HR 0.87 (95% CI: 0.75–1.01; P=0.06). Quality of life at 8 months were 1.0 point lower in the ARNI arm (95% CI: 0.0–2.1) by the KCCQ scores. Similarly, NYHA class improved with less deterioration in renal function, 1.4% and 2.7% respectively, HR 0.50 (95% CI: 0.33–0.77). Further analysis of PARAGON-HF suggested a potential benefit for ARNI in patients with borderline or "mid-range" LVEF (40–50%) (31,40) as well as in females (41).

Pooled analysis of PARAGON-HF and PARADIGM-

HF to evaluate outcomes across the LVEF spectrum demonstrated that the benefit of ARNI was related to LVEF (treatment-by-continuous LVEF interaction P=0.02). The effect had a U-shape relationship with benefit in those with reduced LVEF that diminished at a lower LVEF. This was mostly driven by HF hospitalizations. These benefits extended to higher LVEF range predominantly in women when compared to men (42).

A meta-analysis of 5 clinical trials evaluating RAAS inhibitors/ARNIs in HFpEF (43) showed that ARNI compared with controls reduced hospitalization for HF, OR 0.73 (95% CI: 0.61–0.87) and compared with ARB, OR 0.80 (95% CI: 0.71–0.91), not presenting heterogeneity between trials. Unfortunately, those trials failed to reveal statistical significance for cardiovascular or all-cause mortality between RAAS inhibition and placebo.

Coronary artery disease (CAD)

Natriuretic peptides increase after myocardial infarction (MI) have been linked to increased mortality (7). Animal models have shown that ARNI modulates natriuretic peptides thereby decreasing subsequent myocardial stiffness and remodeling, sparing of LVEF and mechanics, and decreasing LV dilation and fibrosis (44). In rat models with coronary artery ligation and secondary reduced LVEF, compared with enalapril therapy, sacubitril/valsartan modified CaMKII-p expression, upregulated expression of potassium channels, attenuated post-MI LV dysfunction and electrophysiologic remodeling reducing ventricular arrhythmia inducibility (45,46).

PARADISE-MI (Prospective ARNI *vs.* ACE Inhibitor Trial to Determine Superiority in Reducing HF Events after MI, NCT02924727) aims to be the first large trial for sacubitril/valsartan use in acute coronary syndrome. Patients are randomized post-MI if LVEF ≤40% to start an ARNI or ramipril within 12 hours to 7 days after index event (26).

Similarly, data is lacking for neprilysin inhibition for stable CAD but post-hoc analysis of PARADIGM-HF provides some insights. Of the 8399 in PARADIGM-HF, 4796 (57.1%) had prior MI, coronary revascularization, angiographic proof of CAD or stable/unstable angina. CAD related events were grouped into a "coronary" composite outcome of unstable angina, procedures for coronary revascularization, nonfatal MI or death from cardiovascular cause. In the ARNI arm, only death from cardiovascular cause was significantly reduced, but all other components of the composite were decreased in the ARNI compared to enalapril arm (47).

Hypertension

Multiple trials have shown the efficacy of ARNI in decreasing blood pressure. Sacubitril/valsartan provided larger blood pressure reduction in 1,328 participants as compared to a valsartan or placebo, without increase incidence of angioedema (48). The effectiveness and safety of sacubitril/valsartan has also been demonstrated when compared to placebo in a small population (49). There is yet to be a phase 3 trial for ARNI use in hypertension management for patients without cardiac involvement (7). The PARAMETER trial (50) randomized 454 geriatric participants with pulse pressures above 60 mmHg to receive sacubitril/valsartan or olmesartan and those in the ARNI group required less additional antihypertensives, showed improved 24-hour ambulatory hypertension control and reduced central aortic blood pressures at 12 weeks.

Cost-effectiveness

Every country has individual willingness-to pay thresholds, so the high cost of sacubitril/valsartan may be prohibitive to health systems and patients in low to middle income countries while cost-effective in more expensive health care systems. In a comparison with enalapril in two separate trials in the United States, sacubitril/valsartan was found to have a cost per QALY gained of US$45,017 and $50,959, making it a cost-effective option in that health setting (51,52). Sacubitril/valsartan can offset other high and prevalent costs in the health system such as HF hospitalizations. Furthermore, the current willingness-to-pay thresholds in the United States range from $50,000 to $100,000 per QALY gained but might be much lower in other countries. More affordable costs would likely expand the use of sacubitril/valsartan to other health systems.

Safety and complications

Sacubitril/valsartan has the benefits of dual RAAS and neprilysin inhibition without the life-threatening angioedema of omapatrilat because valsartan does not have the bradykinin and aminopeptidase inhibition that ACEi have. Consequently, by activating both systems, it has greater blood pressure reduction then ARB alone (48).

The robust reduction in blood pressure carries the

potential complication of hypotension in some patients. In PARADIGM-HF (4), significant hypotension was minimized by excluding those with systolic blood pressure <95 mmHg. Safety was further ensured by a 4–6 week run-in period with both sacubitril/valsartan and enalapril at trial target doses. Throughout the trial and run-in period, significant hypotension affected 13% of patients (53). Those in the ANRI arm had more frequent symptomatic hypotension, but rarely significant enough to discontinue the medication. While symptomatic hypotension increased the likelihood of the primary study outcome, HR 2.63 (95% CI: 2.21–3.13), the benefits of ARNI as compared to enalapril were similar in all groups including hypotensive patients. Consequently, only significant symptomatic hypotension leading to pre-syncope, syncope or other end organ damage should justify decreasing dosing of ARNI, ACEI, ARB, or MRA (26).

Although severe hyperkalemia was less frequent in the sacubitril/valsartan group in PARADIGM-HF trial, regular precautions for hyperkalemia and worsening renal function secondary to RAAS inhibition should be considered when prescribing sacubitril/valsartan. It is recommended to check creatinine and serum potassium 1–2 weeks after initiation and regularly thereafter (4).

The increase in bradykinin from neprilysin inhibition poses a theoretical risk for angioedema that was evident in omapatrilat trials, although studies with sacubitril/valsartan have not showed similar risk. Existing trials repeatedly show no significant difference in the rate of angioedema between ARNI and ACE inhibitors. Angioedema incidence is rare overall, and more trials are needed to strengthen these results (24,54). In PARAGON-HF (33) angioedema was more common in the sacubitril/valsartan arm. Similar to other trials, the ARNI arm had more hypotension but less hyperkalemia. In PARADIGM-HF, enalapril was more likely to result in cough than sacubitril-valsartan.

Dementia has been a key topic of investigation. Because neprilysin inhibition may decrease degradation of amyloid-beta proteins in the brain (55), there remains a theoretical increased risk of Alzheimer's dementia (56). PARADIGM-HF did not show any difference in dementia-related, memory, or cognitive adverse events (25), but the follow up time might have not been long enough. The ongoing PERSPECTIVE trial (NCT02884206) aims to address continued concern by using florbetapir-18F positron emission tomography imaging to the brain to track amyloid plaque deposition. It will also utilize a comprehensive set of cognitive testing while comparing sacubitril/valsartan against valsartan in HFpEF.

Cancer risk has also been postulated since by facilitating the metabolism of mitogenic peptides, neprilysin may function as a tumor cell proliferation checkpoint, particularly in prostate (57), breast (58) and other cancers (7,59). It is likely that longer follow up might be necessary to show the clinical implications of neprilysin inhibition outside the cardiovascular system (7).

Future directions and ongoing trials

Most trials have focused on NYHA class II and III. The 60 patients with NYHA class IV HF only represented <1% of PARADIGM enrollment (4). It also excluded those with low GFR, lower systolic blood pressure and higher NTproBNP, all of which are markers of poor prognosis and are highly prevalent in class IV patients. The HFN-LIFE trial (NCT02816736) is an ongoing randomized, double-blind trial that compares sacubitril/valsartan with valsartan in 400 HFrEF patients with advanced NYHA class IV HFrEF.

The benefits of ARNI in reverse cardiac remodeling are actively being investigated. PROVE-HF (NCT02887183) is an open label trial of NYHA class II–IV HFrEF patients, and will correlate NT pro-BNP with static and dynamic echocardiographic parameters. EVALUATE-HF (NCT02874794) will compare aortic impedance, among other echocardiographic parameters in patients with NYHA class I–III HFrEF randomized to sacubitril/valsartan or enalapril. The PRIME trial (NCT02687932) will evaluate reduction in functional mitral regurgitation in HF patients on sacubitril/valsartan versus valsartan alone.

Systemic effects and benefits are of equal concern. Renal function and albuminuria will be evaluated between ARNI and irbesartan in the UK HARP-III trial (ISRCTN 11958993). Mean pulmonary arterial pressures are being longitudinally measured by the CardioMEMS device in HFrEF patients on sacubitril/valsartan in the PARENT trial (NCT02788656), compared to standard of care.

Sacubitril/valsartan's benefits in class II–IV HF have led to multiple trials exploring the utility of ARNI at all stages of HF. The PARABLE trial evaluates the ability of sacubitril/valsartan to attenuate left atrial volume index in patients not yet diagnosed with HF or left ventricular dysfunction. Optimal timing to initiate sacubitril/valsartan will be evaluated in the TRANSITION trial (NCT02661217), randomizing subjects for inpatient or outpatient initiation (day 1–14 post-discharge).

As described above, PARADISE-MI will provide information in patients post MI with LVEF. The SILICOFCM trial (60) (NCT03832660), will provide insights into the effect of sacubitril/valsartan in patients with nonobstructive hypertrophic cardiomyopathy. Functional outcomes are equally important such as quality of life, symptom burden and exercise capacity, all of which will be measured in the PARALLAX study comparing sacubitril/valsartan with standard of care (61).

The effect of neprilysin inhibition on sleep-wakefulness is being addressed in 2 current trials. AWAKE-HF trial (NCT02970669) will compare sacubitril/valsartan with enalapril on objective daytime activity by wrist worn accelerometer. ENTRESTO-SAS (NCT02916160) seeks to determine if sacubitril/valsartan therapy for HF patients with sleep apnea syndrome may improve apnea-hypopnea indices (7).

Conclusions

Sacubitril/valsartan has proven to be an effective and potent addition to the HFrEF arsenal, with safety comparable to ACEI and ARB. In HFpEF, it improves quality of life, particularly in women and in patients with borderline ejection fraction, with no effect on mortality. Future studies will elucidate promising benefits in the fields of cardiovascular disease.

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