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Review Article

Beyond ACE Inhibitors: Exploring the Benefits of Angiotensin Receptor-Neprilysin Inhibitors in Managing HFrEF

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Abstract

Around 115 million people in the US suffer from hypertension, 100 million are obese, 92 million have prediabetes, 26 million have diabetes, and 125 million have atherosclerotic CVD, all of which are high-risk factors that contribute to the development of HF [41]. As a result, a considerable number of the US population can be classified as either at risk of HF or in stage A HF. Common causes of HF include ischemic heart disease, myocardial infarction (MI), hypertension, and valvular heart disease (VHD) [41]. The traditional pharmacotherapy for HF has mainly targeted chronic HF with reduced ejection fraction (HFrEF) and includes angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers (BB), and mineralocorticoid receptor antagonists (MRAs). Despite the effectiveness of ACE inhibitors, a new therapy called angiotensin receptor-neprilysin inhibitors (ARNI) have surfaced and demonstrated encouraging outcomes comparable to ACE inhibitors. This poses questions about whether ACE inhibitors or ARNIs are superior in the management of HFrEF. This review focuses on the clinical effectiveness of ACE inhibitors and ARNI in the management of HFrEF.

Keywords: *Heart Failure with Reduced Ejection Fraction; Ace Inhibitor; Enalapril; Angiotensin Receptor-Neprilysin Inhibitor; Sacubitril/Valsartan; Cardiac Failure; Congestive Heart Failure*

Abbreviations

LVEF: Left-Ventricular Ejection Fraction; ESV: Left-Ventricular End-Systolic Volume; EDV: Left-Ventricular End-Diastolic Volume; ESD: Left-Ventricular End-Systolic Diameter; EDD: Left-Ventricular End-Diastolic Diameter

Background and Pathophysiology

Heart failure (HF) is a prevalent clinical syndrome caused by either structural or operative changes in the ventricles, resulting in atypical filling or ejection patterns [5]. It is estimated that around 5.1 million Americans currently suffer from heart failure, and this number is expected to rise by 25% by 2030 [1]. Consequently, heart failure accounts for almost one million hospital admissions yearly [2].

Impairments to the pericardium, myocardium, endocardium, heart valves, or vessels can precede the changes that lead to heart failure. However, left ventricular (LV) myocardial function is typically the primary culprit. Heart failure can be classified based on ejection fraction (EF), though it's important to note that systolic and diastolic dysfunction can coexist in both groups. Heart failure with reduced ejection fraction (HFrEF) is depicted by a dilated LV and EF < 40%, while HF with preserved ejection fraction (HFpEF) indicates EF > 50% and normal

LV size [5]. The latest update to the American College of Cardiology (ACC)/American Heart Association (AHA) HF guidelines subdivides HFpEF into borderline (EF 41% - 49%) and improved (EF > 40%) [5]. Nevertheless, few studies have evaluated pharmacotherapies in these populations. The purpose of this particular review will be to concentrate on patients with heart failure and reduced ejection fraction (HFrEF).

Heart failure can result from several influential mechanisms, such as neurohormonal stimulus, endothelial impairment, venous obstruction, and myocardial remodeling. In the initial stages, neurohormonal stimulation, particularly the renin-angiotensin-aldosterone system (RAAS), can increase cardiac contractility, the retainment of fluid, and marginal vasoconstriction to enhance organ perfusion [4,8]. However, over time, these mechanisms lead to cardiac dysfunction and transformation through fibroblast proliferation, oxidative stress, and extracellular matrix deposition, ultimately resulting in apoptosis and fibrosis[4]. Venous obstruction, whether from gradual volume overload or rapid fluid shifts that activate the sympathetic system, can also trigger neurohormonal stimulation and its downstream effects [9,10]. Additionally, vascular endothelium plays a crucial role by emitting and metabolizing nitric oxide, which, along with cytokines and prostaglandins, can alter myocardial function, hemodynamics, and circulation to the coronary and renal systems [6].

Some of the most powerful predictors of decompensated heart failure are orthopnea, paroxysmal nocturnal dyspnea (PND), the presence of an S3, signs of jugular venous distension (JVD) or hepatojugular reflux, chest X-ray indicating edema, and B-type natriuretic peptide (BNP) levels > 250 pg/mL [12]. The Framingham clinical criteria employ symptoms like orthopnea, paroxysmal nocturnal dyspnea, and elevated jugular venous pressure, requiring at least two major, or one major and two minor, criteria to diagnose heart failure [13]. Other than historical and clinical symptoms and signs, diagnostic imaging such as electrocardiography, chest X-ray, and transthoracic echocardiography can assist in diagnosing heart failure. Laboratory tests are a critical component of diagnosing heart failure. For instance, elevated levels of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) are often seen in heart failure [7]. When ventricular myocytes are strained, they produce prohormone pre-proBNP, which is converted into BNP and NT-proBNP [7]. Excretion of these peptides provokes vasodilation, diuresis, and inhibits the production of renin and aldosterone [7]. Decompensated heart failure is just one of the many cardiac and non-cardiac disorders in which elevated levels have been observed, such as cirrhosis, renal failure, pulmonary embolism, sepsis, or infiltrative diseases. Natriuretic peptides have a helpful prognosis. Amplified BNP levels have been associated with increased mortality and cardiovascular events in all patients with heart failure. In fact, in-hospital mortality is higher in patients with decompensated heart failure and a BNP > 1730 pg/mL compared to those with a BNP < 430 pg/mL [11].

The efficacy of BNP in administrative therapy for heart failure has been an area of contest. A systematic review compared BNP-guided therapy with clinical-guided therapy in heart failure patients. It demonstrated that in the BNP-guided therapy cohort, there was a substantial reduction in hospitalization due to HF, cardiovascular disease (CVD), and all-cause mortality in patients under 75 years old [29]. However, the PRIMA II trial is currently investigating the power of NT-proBNP-guided treatment during admittance for acute heart failure (AHF) on clinical conclusions such as HF readmission and death frequency.

Heart failure can be categorized based on symptoms or disease advancement. The NYHA functional classification categorizes patients into four classes based on the effort needed to provoke clinical symptoms. On the other hand, the ACC/AHA HF phases accentuate the progressive advancement of heart failure and acknowledge risk factors and predisposition to the disease. Distinct from current NYHA classification, which can show variability contingently on the patient's symptoms, the ACC/AHA categorization is fixed and cannot be annulled.

Methods

Literature search was done using PubMed, Google Scholar, A.T. Still University OneSearch, Elsevier, EBSCO, and ClinicalTrials.gov using keywords such as angiotensin-converting enzyme inhibitor, angiotensin receptor/neprilysin inhibitor, and heart failure. AI model,

chatGPT assisted in creating the title of this paper, giving recommended topics of discussion and links to articles that might be relevant to our research. Additionally, chatGPT aided in the rewording and rephrasing of the occasional sentence for better clarity. Our investigative group inspected article titles, abstracts, and reviewed full-text articles for inclusion. Extracted data using a standardized data collection form: lead author, publication year, sample size, inclusion criteria (ejection fraction, NYHA class), standard descriptions (age, sex NYHA class, ischemic cardiomyopathy, atrial fibrillation, ejection fraction, serum natriuretic peptide concentration), standard use of HFrEF medications, intervention, and comparator characteristics (agent, target dose and achieved dose). Varieties of studies were included such as randomized controlled trials, meta-analysis, systematic reviews, and literature reviews. Data extraction was fixated on the efficacy of angiotensin receptor-neprilysin inhibitors and angiotensin-converting enzyme inhibitors in patients with heart failure with reduced ejection fraction assessing NYHA functional class and 6-minute walking distance, cardiac remodeling criteria ((cardiac structure [LV volume and dimensions: LVEF*, ESV*, EDV*, ESD*, EDD*, hypertrophy); LV mass and atrial remodeling)), and cardiac biomarkers caused by wall stress and fibrosis (NT-proBNP). Exclusion criteria include studies without control groups, patients < 18 years old, and non-English. We aimed to discover studies discussing mechanism of action of ACE inhibitors and ARNIs, the comparison of ACE inhibitors and ARNIs, clinical trials for patients with HFrEF receiving ARNI and ACE inhibitor treatment, ARNIs in clinical practice, adverse effects and safety of the drugs included, and, finally, the future direction of ARNIs in the clinical setting.

Mechanism of action

Angiotensin-converting enzyme inhibitors

Numerous studies have determined that ACE (ACE) inhibitors can ameliorate ventricular remodeling and improve ventricular function in patients with heart failure (HF) [31]. This reversal of remodeling is due to several insinuated mechanisms. ACE inhibitors contain a considerable influence on the neurohormonal status of HF patients by interfering with the renin-angiotensin-aldosterone system (RAAS) through the inhibition of angiotensin I to angiotensin II conversion [41]. This results in diminished angiotensin II levels, thereby stimulating natriuresis and reducing sympathetic activity, aldosterone, and vasopressin release along with vasoconstriction resulting in a reduction of blood pressure. Moreover, ACE inhibitors prevents the degradation of bradykinin inducing vasodilation and further lowering blood pressure [35]. Reduced arterial and venous pressure, in turn, leads to decreased preload, and essentially, afterload, resulting in increased stroke volume and enhanced ejection fraction. ACE inhibitors can delay ventricular remodeling by functioning at a cellular level, specifically by limiting cardiac hypertrophy and myocardial fibrosis while also mitigating cardiomyocyte programmed cell death. Consequently, ACE inhibitors have been discovered to have advantageous effects in chronic HF [32-34].

Angiotensin receptor-neprilysin inhibitors

Sacubitril-valsartan is a combination therapy utilized to treat heart failure with reduced ejection fraction (HFrEF). This drug is comprised of two distinct components: valsartan-an angiotensin receptor blocker (ARB) that is recognized to block angiotensin type I, and sacubitril-a neprilysin inhibitor (NEPI) prodrug that is converted to an enzyme that inhibits NEP and breaks down atrial natriuretic peptide (ANP), BNP, and C-type natriuretic peptide [38]. Thus, inhibiting this enzyme leads to elevated concentrations of natriuretic peptides such as BNP, bradykinin, and adrenomedullin, a vasodilator and hormone regulator [43].

As a result, there is an enhanced production of myocardial cyclic guanosine monophosphate (cGMP), leading to augmented myocardial relaxation and reduced hypertrophy. These results mutually counteract the overstimulated neurohormonal state in patients with heart failure (HF) [36], resulting in reduced vasoconstriction, sodium retention, and adverse ventricular remodeling, which may produce favorable clinical outcomes in HF patients [37].

The potential of a drug to inhibit two systems that cause heart failure development was observed in earlier NEPI trials. However, some trials conveyed an increased risk of angioedema. In a study comparing NEPI and ACE inhibitors versus ACE inhibitors alone, the NEPI/ACE inhibitor group had a higher risk of angioedema [40]. Thus, the prospective comparison of ARNI with ACE inhibitors to

determine impact on global mortality and morbidity in heart failure study evaluated an ARB/NEPI compared to ACE inhibitors. This study included patients with NYHA class II-IV with EF ≤ 40%, plasma BNP ≥ 150 or BNP ≥ 100 if hospitalized for heart failure within the past 12 months. The primary endpoint was a composite of cardiovascular mortality or hospitalization for heart failure. The study was double-blind, randomized, and patients were randomly assigned to either sacubitril/valsartan or enalapril. The study was stopped early due to significant reductions in both the primary endpoint and cardiovascular death. Sacubitril/valsartan reduced cardiovascular death or heart failure-related hospitalization by 20% and all-cause mortality by 16% [28]. There was no difference in the risk of angioedema between the groups, but the valsartan/sacubitril group had a higher risk of symptomatic hypotension. Recently, the Food and Drug Administration (FDA) approved this new therapy for heart failure treatment in patients with NYHA class II-IV with the goal of reducing mortality.

Efficacy/comparison

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial was a revolutionary study that assessed the impact of enalapril on mortality paralleled to a placebo in patients presenting severe congestive heart failure with reduced ejection fraction (HFrEF) [20,25]. The study discovered that at six and twelve months, mortality rates were 40% ($P = 0.002$) and 31% ($P = 0.001$) lower in the enalapril group, respectively. At the study's conclusion, there was a 27% ($P = 0.003$) decrease in mortality in the enalapril group compared to the placebo group (68 vs. 50). More importantly, there was a 50% decrease in mortality attributable to the progression of heart failure in the enalapril-treated group ($P < 0.001$).

Nevertheless, patients taking vasodilators at baseline did not show a meaningful improvement in mortality rates ($P = 0.11$), proposing that the added advantage of enalapril over vasodilator therapy is inadequate. Moreover, 42% of enalapril-treated patients experienced an improvement in their New York Heart Association (NYHA) classification, compared to only 22% of placebo-treated patients ($P < 0.001$). It is worth noting that the validity of the NYHA classification in characterizing HF progression has been questioned due to variable results and high inter-operator variability [19]. Additional advantages of enalapril treatment included a reduction in heart size ($P = 0.02$), though the final heart sizes in the two groups were analogous. Furthermore, enalapril-treated patients were more likely to receive other cardiovascular medications than placebo-treated patients.

To reduce selection bias and confounding, 253 patients were randomized in a double-blind, placebo-controlled, parallel-group trial. Nonetheless, the lack of ethnicity data and the higher frequency of atrial fibrillation in the selected patients compared to most patients with NYHA IV HF might limit the generalizability of the results [21,22]. The trial only included patients with NYHA IV HF, and it is ambiguous whether less severely compromised patients with HF would also benefit from enalapril. Additionally, the trial's premature finish resulted in incomplete follow-up, making it difficult to determine the duration of the benefits. Although the reduction in mortality rates was primarily due to the decrease in HF progression, it is challenging to determine the mode of death in patients with HF, and the exact cause of death is debatable [24]. Therefore, the improvement in mortality rates may not have been related to the improvement in HF progression but rather a decrease in sudden death rates. Moreover, the study did not identify a specific mechanism for the beneficial effects of enalapril.

The Studies of Left Ventricular Dysfunction trial (SOLVD-T), a four-year, double-blind, placebo-controlled, parallel-group trial, surveyed the effect of enalapril on mortality and hospitalization for congestive HFrEF in 2569 patients [25]. To minimize bias, patients were selected randomly and assigned to treatment groups to ensure covariates affecting treatment outcomes were equally distributed. The results showed a 16% reduction in cumulative mortality rate in the enalapril group compared to the placebo group ($P = 0.0036$). Notably, the most significant difference in mortality was related to deaths due to progressive HF (risk reduction 22%; $P < 0.0045$). Additionally, 57% of the placebo group experienced either death or hospitalization due to worsening HF compared to 48% in the enalapril group (risk reduction 26%; $P < 0.0001$). Treatment of 1000 congestive HF patients like those in this study with enalapril for three years could prevent

50 premature deaths and 350 hospitalizations. Furthermore, the benefits of enalapril were likely underestimated as more placebo patients than enalapril patients received other vasodilators during the trial for worsening HF. It was proposed that the reduction in mortality and hospitalization rates may have been due to improvements in ejection fraction, exercise capacity, and decreased symptoms of congestion, all of which are attributed to decreased preload and afterload by enalapril.

This study was conducted using a well-randomized, double-blind, multi-center and placebo-controlled design, with a longer follow-up period and a wider range of patients with HF (NYHA I-IV) compared to other similar trials such as CONSENSUS. Yet, the study was limited by under-representation of most ethnicities and females (80% white and 80% male patients), which could introduce selection bias. Like CONSENSUS, the leading benefit of enalapril was a diminution in deaths from progressive HF, but in patients with class IV HF, there was no significant difference in mortality rate between the treatment and placebo groups in SOLVD, although this may have been accidental due to the small sample size in this subgroup. The study also demonstrated that the predictive benefit of enalapril was limited to patients with severe compromise, i.e. left ventricular ejection fraction (LVEF) < 30%, and the limited efficacy in patients with 30% < LVEF < 35% may have been due to the lack of power of the study, given the low mortality rate in this subgroup. Additionally, it was witnessed that even though the most common cause of death was worsening HF, it accounted for less than half of total deaths, proposing that more treatment tactics need to be investigated to accomplish a substantial overall mortality benefit in these patients.

The prospective comparison of ARNI with ACE inhibitors to determine impact on global mortality and morbidity in heart failure (PARADIGM-HF) trial aimed to evaluate the effectiveness of sacubitril/valsartan, an ARNI now approved for use, in comparison to enalapril for reducing cardiovascular mortality and hospitalizations due to HF [26]. The study included 8399 patients with HFrEF NYHA II-IV who were randomly assigned to receive either sacubitril/valsartan or enalapril and were followed-up for a median of 27 months. The results showed that the sacubitril/valsartan group had a lower incidence of deaths due to cardiovascular causes (13.3%) compared to the enalapril group (16.5%) with a hazard ratio (HR) of 0.80 ($P < 0.001$). Additionally, hospitalizations for HF were also lower in the sacubitril/valsartan group (12.8%) compared to the enalapril group (15.6%) with an HR of 0.79 ($P < 0.001$). The mortality benefit was consistent across different age groups, genders, ethnicities, ejection fractions, and NYHA classes, and was attributed to decreased cardiovascular risk rather than non-cardiovascular death. A further analysis revealed that the risk of sudden death and death due to worsening HF was significantly lower in the sacubitril/valsartan group (HR 0.80, $P = 0.008$ and HR 0.79, $P = 0.034$, respectively) [27]. This was reflected in the lower levels of NTproBNP, which indicated reduced cardiac wall stress in the sacubitril/valsartan group [28]. Finally, sacubitril/valsartan was found to reduce all-cause mortality significantly compared to enalapril (17.0% vs 19.8%, $P < 0.001$) and was shown to be superior to enalapril in reducing the risks of all-cause or cardiovascular mortality (including due to worsening HF) and hospitalization for HF. A network meta-analysis comparing the efficacy of drugs and their combinations regarding all-cause mortality in patients with HFrEF also showed that the combination of ARNI with BB and MRA resulted in greater overall mortality reduction than the combination of ACE inhibitors with BB and MRA [18]. Overall, the benefit observed in the PARADIGM-HF trial is likely related to the added neprilysin inhibition since ARBs and ACE inhibitors have previously shown comparable benefits in HF patients.

Although this trial had robust design features, including a large, randomized, double-blind, parallel group, and active-controlled methodology, there were several limitations. One major limitation was the under-representation of female, black, and short-expected survival patients, which could limit the generalizability of the findings [17]. Additionally, the average age of the population (63.8) was lower than typical clinical practice. Another limitation was the suboptimal background therapy, as only a small percentage of patients had received implantable cardioverter-defibrillator or cardiac resynchronization therapy before randomization [16]. Additionally, more than half of patients on enalapril were not on MRAs, which could lead to unopposed aldosterone escape and diminish anti-RAAS activity [15]. Although an ACE inhibitor-MRA combination may not necessarily reflect optimal therapy, effective application of background therapy is crucial to evaluate potential replacements for the cornerstone of HF therapy, i.e. ACE inhibitors. Furthermore, the dose of the two drugs

was not comparable, with the maximum tolerated dose of valsartan (320 mg) plus neprilysin compared to a moderate dose of enalapril (20 mg). The lower dose of enalapril may explain the decreased mean systolic blood pressure in the enalapril group compared to the sacubitril/valsartan group, although this could also be due to the added neprilysin inhibition. The authors stated that the enalapril dose was based on previous studies assessing its efficacy; however, in practice, doses up to 40 mg can be prescribed [14,19].

Finally, substituting enalapril for pre-randomization physician-selected ACE inhibitors may not have ensured dose equivalence and thus adequate RAAS inhibition. This was reflected in the significant decreases in cardiovascular mortality or hospitalizations for HF seen only in patients assigned to ACE inhibitors pre-randomization. Significant differences were not observed in those who were not on ACE inhibitors before the trial.

Conclusion

Heart failure (HF) is a major public health concern that poses a significant financial burden on healthcare systems. Due to its increasing prevalence and poor prognosis, effective management strategies are crucial. In this review, we discuss the mechanism of action and efficacy of enalapril compared to sacubitril/valsartan for treating HF with reduced ejection fraction (HFrEF). Enalapril has been a cornerstone of HF management for many years based on landmark studies such as CONSENSUS and SOLVD, which demonstrated its ability to significantly reduce all-cause and cardiovascular mortality as well as HF-related hospitalizations when compared to a placebo. However, sacubitril/valsartan, a new class of drugs known as ARNI, has recently been shown to be superior to enalapril in reducing cardiovascular mortality and HF-related hospitalizations in the PARADIGM-HF trial. As a result, it has been approved by both Europe and the US as an alternative to ACE inhibitors in HFrEF patients with NYHA II-IV. Nevertheless, more long-term trials are needed to compare the efficacy and safety of these two drugs, which is a crucial aspect to evaluate. It is important to note that the trials discussed here have limitations that may impact their generalizability and applicability in real-world clinical practice. Furthermore, comparing the efficacy of single pharmaceutical agents is challenging as most HF patients require a combination of several drugs, and few head-to-head trials exist. This issue should be addressed in future research.

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