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Comparative Efficacy of Sacubitril/Valsartan versus Ramipril in HFrEF: A Review of a Prospective Randomized Trial

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ABSTRACT:

Heart failure affects approximately 6.2 million adults in the United States and remains a leading cause of morbidity, mortality, and healthcare costs despite the use of guideline-directed medical therapies. The search for more effective treatments gained momentum following the PARADIGM-HF trial, which showed that sacubitril/valsartan a combination of an angiotensin receptor blocker and neprilysin inhibitor (ARNI) significantly reduced cardiovascular events and mortality compared to enalapril, an angiotensin-converting enzyme inhibitor, in patients with heart failure and reduced ejection fraction (HFrEF). These ground breaking results prompted the 2016 American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) guidelines to recommend sacubitril/valsartan/ Ramipril as a replacement for ACE inhibitors or angiotensin receptor blockers. This review aims to explore the advantages and limitations of sacubitril/valsartan/ Ramipril in heart failure treatment by examining subgroup analyses from the PARADIGM-HF trial, along with subsequent retrospective studies and randomized controlled trials that followed this landmark research.

Keywords: Heart failure, American Heart Association, PARADIGM-HF trial, cardiovascular.

INTRODUCTION

Heart failure is a chronic condition characterized by the heart's inability to pump blood effectively to meet the body's needs, leading to symptoms such as fatigue, shortness of breath, and fluid retention. Management of heart failure, particularly heart failure with reduced ejection fraction (HFrEF), involves a combination of lifestyle modifications, medications, and sometimes device-based therapies or surgery. Among the cornerstone pharmacologic treatments are agents targeting the renin-angiotensin-aldosterone system (RAAS), including angiotensin-converting enzyme inhibitors (ACE inhibitors) like ramipril, angiotensin receptor blockers (ARBs) such as valsartan, and the newer angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan.

Ramipril, an ACE inhibitor, works by blocking the conversion of angiotensin I to angiotensin II, thereby reducing vasoconstriction and aldosterone-mediated fluid retention, which improves cardiac workload and outcomes. Valsartan, an ARB, similarly inhibits the effects of angiotensin II but through receptor blockade, offering an alternative for patients intolerant to ACE inhibitors. Sacubitril/valsartan combines valsartan with sacubitril, a neprilysin inhibitor that enhances levels of beneficial vasoactive peptides, leading to vasodilation, natriuresis, and reduced cardiac remodeling. This dual mechanism has been shown to provide superior benefits in reducing mortality and hospitalizations compared to ACE inhibitors alone.

Together, ramipril, valsartan, and sacubitril/valsartan represent key therapeutic options in heart failure management, with sacubitril/valsartan increasingly recognized as a preferred agent in patients with symptomatic HFrEF due to its enhanced efficacy in improving survival and quality of life.

Development of Combination Therapy: Sacubitril/Valsartan/ramipril

The combination therapy of sacubitril and valsartan represents a significant advancement in the treatment of heart failure with reduced ejection fraction (HFrEF). This fixed-dose combination, marketed as sacubitril/valsartan (brand name Entresto), was developed to simultaneously target two critical pathways involved in heart failure pathophysiology: the renin-angiotensin-aldosterone system (RAAS) and the neprilysin enzyme system.

Rationale for Combination

Valsartan is an angiotensin II receptor blocker (ARB) that inhibits the AT1 receptor, reducing vasoconstriction and aldosterone-mediated sodium retention, thereby decreasing cardiac workload.

Sacubitril is a prodrug converted to sacubitrilat, a neprilysin inhibitor that prevents the breakdown of beneficial vasoactive peptides such as natriuretic peptides, bradykinin, and adrenomedullin. These peptides promote vasodilation, natriuresis, and anti-fibrotic effects.

Neprilysin inhibition alone was found to be insufficient due to increased angiotensin II levels, which could worsen heart failure. Combining sacubitril with valsartan counteracts this by blocking angiotensin II receptors, thus enhancing the therapeutic effect while minimizing adverse outcomes like angioedema seen with earlier combinations of neprilysin inhibitors and ACE inhibitors.

Clinical Development and Approval

The pivotal Phase III PARADIGM-HF trial was instrumental in the development and approval of sacubitril/valsartan. This large, randomized, double-blind study enrolled 8,442 patients with HFrEF and New York Heart Association (NYHA) class II–IV symptoms. Patients were randomized to receive either sacubitril/valsartan or enalapril (an ACE inhibitor) alongside standard heart failure therapies.

Key findings from PARADIGM-HF included:

A 20% relative risk reduction in the composite endpoint of cardiovascular death or first hospitalization for worsening heart failure. Significant reductions in cardiovascular mortality (13.3% vs. 16.5%) and all-cause mortality (17.0% vs. 19.8%) compared to enalapril.

Improved safety and tolerability profile compared to ACE inhibitors alone. Based on these results, sacubitril/valsartan received FDA approval in 2015 for the treatment of chronic HFrEF (NYHA class II–IV), marking it as the first angiotensin receptor-neprilysin inhibitor (ARNI) approved for this indication.

Mechanism of action

Sacubitril/valsartan is a combination drug that exerts its therapeutic effects through two complementary mechanisms targeting key pathways involved in heart failure with reduced ejection fraction (HFrEF).

Sacubitril is a neprilysin inhibitor. Neprilysin is an enzyme responsible for degrading natriuretic peptides (NPs) such as atrial natriuretic peptide and brain natriuretic peptide, which promote vasodilation, natriuresis (sodium excretion), diuresis, and have antihypertrophic and antifibrotic effects on the heart. By inhibiting neprilysin, sacubitril increases the levels of these beneficial peptides, thereby counteracting the harmful effects of neurohormonal activation in heart failure, including reducing myocardial remodeling and lowering blood pressure.

Valsartan is an angiotensin II receptor blocker (ARB) that selectively blocks the AT1 receptor. This prevents angiotensin II from inducing vasoconstriction, aldosterone secretion, sodium retention, myocardial hypertrophy, and fibrosis. By blocking these effects, valsartan reduces cardiac workload and adverse remodeling.

Together, sacubitril/valsartan enhances vasodilation and natriuresis through increased natriuretic peptides while simultaneously inhibiting the renin-angiotensin-aldosterone system (RAAS), providing superior cardiovascular protection compared to ACE inhibitors or ARBs alone.At the molecular level, sacubitril/valsartan also modulates multiple signaling pathways involved in cardiac remodeling, including inhibition of TGF-β1/Smad3 and Wnt/β-catenin pathways that reduce fibrosis, and improvement of mitochondrial function and calcium homeostasis in cardiomyocytes, which contribute to improved myocardial contractility and reduced apoptosis.

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor that works by blocking the activity of ACE, the enzyme responsible for converting angiotensin I to angiotensin II, a potent vasoconstrictor. By inhibiting this conversion, ramipril reduces levels of angiotensin II, leading to vasodilation, decreased aldosterone secretion, reduced sodium and water retention, and ultimately lower blood pressure. This inhibition also decreases stimulation of the angiotensin II type 1 receptor (AT1R), which mediates vasoconstriction, inflammation, fibrosis, and oxidative stress.

This dual mechanism results in reduced mortality, decreased hospitalizations for heart failure, and improved symptoms and quality of life in patients with HFrEF, as demonstrated in major clinical trials such as PARADIGM-HF.

Effects on Cardiac Remodeling and Aortic Stiffness

The PROVE-HF trial (2018) provided important evidence on the effects of sacubitril/valsartan in patients with heart failure with reduced ejection fraction (HFrEF), specifically regarding cardiac remodeling and biomarker changes. Over 12 months of therapy, patients experienced a significant reduction in NT-proBNP levels—from a median of 816 pg/mL at baseline to 455 pg/mL—reflecting improved cardiac stress and function. Echocardiographic assessments revealed marked improvements in cardiac structure: left ventricular ejection fraction (LVEF) increased from 28.2% to 37.8%, and both left ventricular end-diastolic and end-systolic volume indices (LVEDVI and LVESVI) decreased significantly. These changes, many of which occurred early and even at lower doses of sacubitril/valsartan, highlight the potential benefits of initiating therapy early in the disease course.

The EVALUATE-HF trial (2019) investigated the impact of sacubitril/valsartan versus enalapril on aortic stiffness in HFrEF patients. While no significant reduction in central aortic stiffness was observed with sacubitril/valsartan compared to enalapril, the study did find that sacubitril/valsartan led to greater improvements in cardiac remodeling parameters, including reductions in left atrial volume, LVEDVI, and LVESVI. These findings reinforce the role of sacubitril/valsartan in promoting reverse cardiac remodeling, even if its effects on vascular stiffness are limited.

Overall, these trials demonstrate that sacubitril/valsartan therapy is associated with substantial improvements in cardiac structure and function, as evidenced by reductions in cardiac volumes and increases in ejection fraction, although its impact on aortic stiffness appears minimal. The early and significant changes in cardiac remodeling parameters suggest a strong rationale for early initiation of sacubitril/valsartan in appropriate HFrEF patients.

Sacubitril/Valsartan and CKD

The observation of a lower incidence of renal impairment and hyperkalemia in patients treated with sacubitril/valsartan compared to enalapril in the PARADIGM-HF trial has prompted investigation into the potential nephroprotective properties of sacubitril/valsartan. To further assess these effects, the UK HARP-III trial—a randomized, double-blind study—was conducted in 2017–2018 among individuals with chronic kidney disease (CKD). Over a 12-month period, the trial found no significant difference in measured glomerular filtration rate (GFR) between those receiving sacubitril/valsartan and those assigned to irbesartan; GFR values were nearly identical in both groups. However, sacubitril/valsartan was associated with greater reductions in blood pressure and cardiac biomarkers among CKD patients, supporting its cardiovascular benefits and providing evidence for its safe use in this population.

These findings align with systematic reviews and meta-analyses, which indicate that sacubitril/valsartan is associated with a lower risk of worsening renal function compared to renin-angiotensin system inhibitors alone, particularly in patients with heart failure. Long-term observational data also suggest that sacubitril/valsartan exerts favorable effects on renal function in both CKD and non-CKD patients, with only a minor decline in renal function over time—less than what is typically expected in heart failure cohorts.

In summary, while sacubitril/valsartan may not provide a direct improvement in GFR compared to other agents, it demonstrates a favorable renal safety profile, effective blood pressure reduction, and can be safely used in patients with CKD, especially those with concurrent heart failure.

Further Investigation

Several ongoing clinical trials are actively investigating the broader benefits and future role of sacubitril/valsartan in heart failure management. These studies aim to address key questions about the drug's efficacy and safety across diverse patient populations and clinical scenarios.

The PARALLEL-HF trial (Study of Efficacy and Safety of LCZ696 in Japanese Patients With Chronic Heart Failure and Reduced Ejection Fraction) is a Phase III study designed to determine whether the reductions in cardiovascular death and heart failure hospitalizations observed with sacubitril/valsartan in previous global trials can be replicated in Japanese patients. This trial will help assess the generalizability of sacubitril/valsartan's benefits in a real-world Japanese heart failure population.

Meanwhile, the PARADISE-MI trial (Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction) is evaluating the impact of initiating sacubitril/valsartan compared to ramipril in patients who have recently experienced an acute myocardial infarction and have evidence of left ventricular systolic dysfunction (ejection fraction <40%) and/or pulmonary congestion, but without a prior history of chronic heart failure. This study focuses on whether sacubitril/valsartan can reduce cardiovascular death and heart failure hospitalizations in this high-risk, post-infarction group.

The RECOVER-LV trial (Effects of Sacubitril/Valsartan Compared to Valsartan on Left Ventricular Remodelling in Asymptomatic Left Ventricular Systolic Dysfunction After Myocardial Infarction) takes a different approach by comparing sacubitril/valsartan with valsartan. It aims to provide mechanistic insights into the cardiovascular benefits of sacubitril/valsartan in patients with asymptomatic left ventricular systolic dysfunction after myocardial infarction, utilizing advanced cardiac imaging and biomarker analysis to evaluate effects on cardiac remodeling.

Collectively, these ongoing trials are expected to clarify the therapeutic scope of sacubitril/valsartan, inform its use in specific subgroups, and potentially expand its indications in heart failure management.

Limitations

In the PARADIGM-HF and PARAMOUNT trials, sacubitril/valsartan was associated with a higher incidence of symptomatic hypotension—reported in 18% and 19% of patients, respectively-as well as an increased rate of non-serious angioedema compared to enalapril. Despite these risks, sacubitril/valsartan demonstrated a lower incidence of other adverse effects commonly seen with ACE inhibitors, such as hyperkalemia, cough, and worsening renal function.

Concerns have also been raised regarding the potential cognitive effects of sacubitril/valsartan, given that neprilysin is involved in the degradation of amyloid-beta, a protein implicated in dementia. A 2018 analysis by Perlman et al. using the FDA adverse event reporting system found that cognition and dementia-related adverse events (CDRAE) were reported in 5.1% of cases with sacubitril/valsartan, which was actually lower than the 6.6% reported with other medications (reporting odds ratio 0.72, 95% CI 0.65–0.79). However, the authors emphasized the need for further studies to fully assess the long-term cognitive safety of sacubitril/valsartan/Ramipril.

Overall, while sacubitril/valsartan/ramipril is linked to a higher risk of symptomatic hypotension and non-serious angioedema compared to enalapril, it appears to have a safer profile regarding hyperkalemia, cough, and renal impairment. Ongoing surveillance and future studies are necessary to clarify its long-term effects, particularly on cognitive function.

Conclusion

Since its introduction, sacubitril/valsartan/Ramipril has transformed the management of heart failure with reduced ejection fraction (HFrEF), demonstrating clear superiority over ACE inhibitors in reducing cardiovascular mortality and heart failure hospitalizations for eligible patients. Large-scale trials, such as PARADIGM-HF, established sacubitril/valsartan/Ramipril as a cornerstone therapy, leading to its widespread adoption and guideline endorsement. Ongoing research and recent data continue to suggest additional therapeutic benefits, indicating that further expansion of sacubitril/valsartan's clinical indications is likely in the near future as evidence accumulates.

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