WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 8, 702-717. Review Article ISSN 2277–7105

OPTIMIZING HEART FAILURE MANAGEMENT WITH SACUBITRIL/VALSARTAN: A COMPREHENSIVE REVIEW

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Article Received on
28 February 2025,

Revised on 20 March 2025,
Accepted on 10 April 2025

DOI: 10.20959/wjpr20258-36331

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ABSTRACT

Heart failure treatment has improved dramatically over the past 30 years, saving lives and reducing hospital stays. Despite this progress, heart failure remains a major health concern, causing frequent hospitalizations, long-term care, and significant economic burden. A medication called sacubitril has become a crucial treatment for patients with heart failure. Recent breakthroughs in sacubitril therapy have transformed the management of heart failure, offering better outcomes, fewer side effects, and improved quality of life. However, the affordability of sacubitril remains a concern in developing countries. Heart failure is a major health concern worldwide, causing many deaths and illnesses. It also has a significant economic impact due to its high prevalence, frequent hospital visits, long-term care, missed workdays, and increased risk of death. For nearly 20 years, standard treatments for heart failure have included ACE inhibitors, ARBs, and beta-blockers. Although these treatments are effective and affordable, they haven't been able to reduce hospital readmissions or improve quality of life for heart failure patients.

KEYWORDS: Sacubitril, Heart failure, ACE inhibitor, Beta blockers.

INTRODUCTION

Heart failure (HF) is a rapidly growing heart condition that severely impacts healthcare systems worldwide. Over the past 15-20 years, there have been significant advancements in HF treatments. The main risk factors for HF are ischemic heart disease, high blood pressure, and diabetes. Other contributing factors include cardiomyopathies, infections, toxins, valvular disease, and irregular heart rhythms. HF can be classified into two types: systolic HF

(reduced ejection fraction) and diastolic HF (preserved ejection fraction). Systolic HF occurs when the heart's contractility is weakened, resulting in a left ventricular ejection fraction (LVEF) of 40% or less. Diastolic HF, on the other hand, occurs when the heart's relaxation and filling abilities are impaired, resulting in an LVEF of 50% or higher. There are two main types of heart failure: systolic heart failure (HFrEF) and diastolic heart failure (HFpEF). HFrEF occurs when the heart's pumping power is weakened, resulting in a left ventricular ejection fraction (LVEF) of 40% or less. HFpEF, on the other hand, occurs when the heart's relaxation and filling abilities are impaired, resulting in an LVEF of 50% or higher.

Heart failure can lead to prolonged hospital stays, with median lengths ranging from 4 to 20 days, and in-hospital mortality rates between 4% and 30%. Recurring hospital admissions, lost productivity, and death due to heart failure impose a significant socioeconomic burden, estimated at $108 billion worldwide in 2012.In regions like Africa, Asia, the Middle East, and South America, the socioeconomic burden of heart failure is even higher. This is partly due to the relatively young age of onset (average age 56.4 years) and the large proportion of patients lacking access to proper healthcare.

A new treatment for HF is Sacubitril, a combination of two medications. It works by increasing the levels of certain peptides that help relax blood vessels and reducing the activity of a system that constricts blood vessels. This treatment has been shown to improve symptoms and slow the progression of HF by reducing ventricular remodeling and improving heart function.

OBJECTIVES AND METHOD

Sacubitril is a new treatment for heart failure. This review looks at the guidelines for using Sacubitril in combination with other therapies, its benefits and drawbacks compared to traditional treatments, and how well it works and how safe it is for patients with a specific type of heart failure called HFrEF. We also examine whether Sacubitril is cost-effective, which is especially important for countries with limited resources. Our goal is to understand the potential benefits and challenges of using Sacubitril in real-world settings, particularly in developing countries.

We conducted a thorough search of the MEDLINE database (via PubMed) from 1990 to 2021 for clinical trials, observational studies, and reviews that reported on the effectiveness and safety of Sacubitril. We included articles in English, German, and French. Our search focused

on studies related to heart failure with reduced ejection fraction (HFrEF), as approved by the European Medicines Agency. We also considered studies on other types of heart failure, as well as data on the safety and tolerability of Sacubitril. To avoid duplicating information, we excluded individual case reports and studies already included in comprehensive reviews. When multiple reviews were available, we prioritized the most recent one to ensure the latest data and avoid outdated information. To get a complete picture, we combined data from existing research with new, unpublished information. This included proprietary data from Novartis Pharma AG, such as drug approvals and patient numbers in clinical trials and real-world practice. We also analyzed reports from regulatory agencies, like the European Medicines Agency and the US Food and Drug Administration, which provided insights into the safety and effectiveness of Sacubitril.

Additionally, we looked at data from the German Institute for Drug Use Evaluation to see how Sacubitril was being used in real-world clinical practice in Germany. This data came from over 80% of community pharmacies in Germany and covered the period from 2016 to 2021.We also used data from IQVIA, a healthcare data provider, to understand how Sacubitril was being prescribed by general practitioners and cardiologists in Germany. This data helped us identify trends and patterns in the use of Sacubitril. Finally, we analyzed data from the IQVIA longitudinal prescription database to understand how patients were being treated with Sacubitril over time. This data allowed us to track treatment patterns and identify patients who were also taking other medications, such as SGLT2 inhibitors. We searched PubMed for studies on the combination of Sacubitril and Valsartan (SAC/VAL) for treating heart failure, focusing on long-term outcomes. We used specific keywords like "Sacubitril", "Valsartan", "heart failure", and "LCZ 696" to find relevant studies. We also applied filters to only include studies published in English within the last 5 years. Our search resulted in 248 potential studies, which we reviewed to select the most relevant ones. We chose 26 clinical trials to include in our analysis. Additionally, we manually searched for and included 3 clinical practice guidelines to get a more comprehensive understanding of the topic

PATHOPHYSIOLOGY

Heart failure is a complex condition that occurs when the heart can't pump enough blood to meet the body's needs. Normally, the heart's pumping ability is balanced with the amount of blood circulating in the body. But in heart failure, the heart's pumping ability is weakened, leading to reduced blood flow and decreased blood pressure.

To compensate, the body uses several mechanisms to maintain blood flow and pressure. One of these mechanisms is the Frank-Starling mechanism, which helps the heart pump more blood by increasing the volume of blood in the heart. However, this mechanism can only work for so long, and eventually, the heart becomes exhausted.

Another mechanism is the activation of the sympathetic nervous system, which releases stress hormones like adrenaline to increase heart rate, pumping power, and blood pressure. However, long-term activation of this system can damage the heart and lead to further complications.

The renin-angiotensin-aldosterone system (RAAS) is also activated, causing blood vessels to constrict and the body to retain sodium and water. This system is normally balanced by the natriuretic peptide system (NPS), which helps to relax blood vessels and remove excess fluid. However, in heart failure, the NPS is overwhelmed, leading to a buildup of fluid and increased blood pressure.

As heart failure progresses, the heart undergoes changes in size, shape, and function, leading to ventricular remodeling. This creates a vicious cycle of worsening heart function, fluid buildup, and increased blood pressure, ultimately leading to further damage and death.

PHARMACOLOGY STUDY

Sacubitril/valsartan (LCZ696) is a groundbreaking medication that combines two powerful mechanisms to treat heart failure. By blocking the angiotensin receptor and inhibiting the enzyme neprilysin, it enhances the benefits of the body's natural natriuretic peptide system. This system helps to relax blood vessels, remove excess fluid, and reduce blood pressure.

Studies have shown that sacubitril/valsartan has superior benefits in reversing heart damage compared to other medications like ACE inhibitors and ARBs. It has been extensively tested in numerous clinical trials, involving over 30,000 participants, including more than 22,500 patients with heart failure.

The medication has been approved by the European Medicines Agency (EMA) for treating heart failure with reduced ejection fraction (HFrEF). We will focus on the benefits and outcomes of sacubitril/valsartan in patients with HFrEF.

PHARMACOVIGILANCE STUDY

Between July 2015 and July 2021, over 5.5 million patients received sacubitril/valsartan (S/V) outside of clinical trials. A thorough review of global safety data confirmed that S/V's benefits outweigh its risks for patients with heart failure.

The known risks, such as low blood pressure, kidney problems, high potassium levels, and swelling, have been well understood and reported. Notably, the number of reported cases has decreased over time.

There were initial concerns about a potential link between S/V and cognitive impairment. However, recent studies and data analyses have found no evidence to support this. An ongoing clinical trial, required by the FDA, is currently assessing S/V's long-term effects on cognitive function, with results expected in 2022.

Given the potentially low impact on individual patients' daily functioning and quality of life, the risk of cognitive impairment is considered low. Overall, the extensive real-world experience with S/V has shown no new or unexpected risks, confirming its long-term safety for patients with heart failure.

DEVELOPMENT

For a long time, treating heart failure (HF) focused on managing the underlying heart condition, related diseases, and fluid buildup. Doctors typically prescribed a combination of medications, including ACE inhibitors, ARBs, beta blockers, and MRAs. However, despite these treatments, the outlook for patients with HF remained unchanged over time. Studies have shown that patients with chronic HF have a survival rate of 80-90% after one year, 50-60% after five years, and 30% after ten years. This led researchers to explore new treatment approaches. They focused on the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) pathways.

A new class of medications, called angiotensin-receptor neprilysin inhibitors (ARNI), was developed. The first medication in this class, sacubitril/valsartan (SAC/VAL), combines an angiotensin II receptor blocker (valsartan) with a neprilysin inhibitor (sacubitril). This innovative treatment targets both the RAAS and the natriuretic peptide system (NPS) without increasing the risk of hemodynamic stress.

MECHANISM OF ACTION

Sacubitrilis a combination medication that pairs sacubitril, a precursor to the neprilysin inhibitor LBQ657, with valsartan, a blocker of angiotensin II receptors. When taken, SAC quickly breaks down into its two components. The sacubitril part boosts the body's natural natriuretic peptide system (NPS), while valsartan blocks the renin-angiotensin-aldosterone system (RAAS). This dual action helps alleviate heart failure symptoms and slows disease progression (Figure 1).

Research suggests SAC may also aid in recovery after a heart attack by reducing ventricular remodeling. A study using computer modeling and animal data found that SAC decreased heart cell death, enlargement, and impaired contraction. These findings support the use of SAC in treating heart failure patients.

There are two main reasons why people with heart failure may die suddenly. The first is a type of abnormal heart rhythm called ventricular tachycardia, which can often be treated with an implantable cardioverter-defibrillator (ICD). The second reason is when the heart's main pumping chamber, the left ventricle, suddenly fails.

In both cases, the underlying problem is often scarring and stretching of the heart muscle, which can disrupt the heart's normal rhythm and lead to sudden death. However, research has shown that a type of medication called an angiotensin-receptor neprilysin inhibitor (ARNI) can reduce the risk of death beyond what is possible with other treatments.

ARNIs work by reducing scarring and improving the heart's structure and function. They also have a calming effect on the heart's rhythm. In studies, the ARNI sacubitril/valsartan has been shown to reduce the risk of death and hospitalization due to heart failure, as well as improve patients' quality of life. Additionally, switching to an ARNI from other treatments has been shown to reduce abnormal heart rhythms and improve heart function.

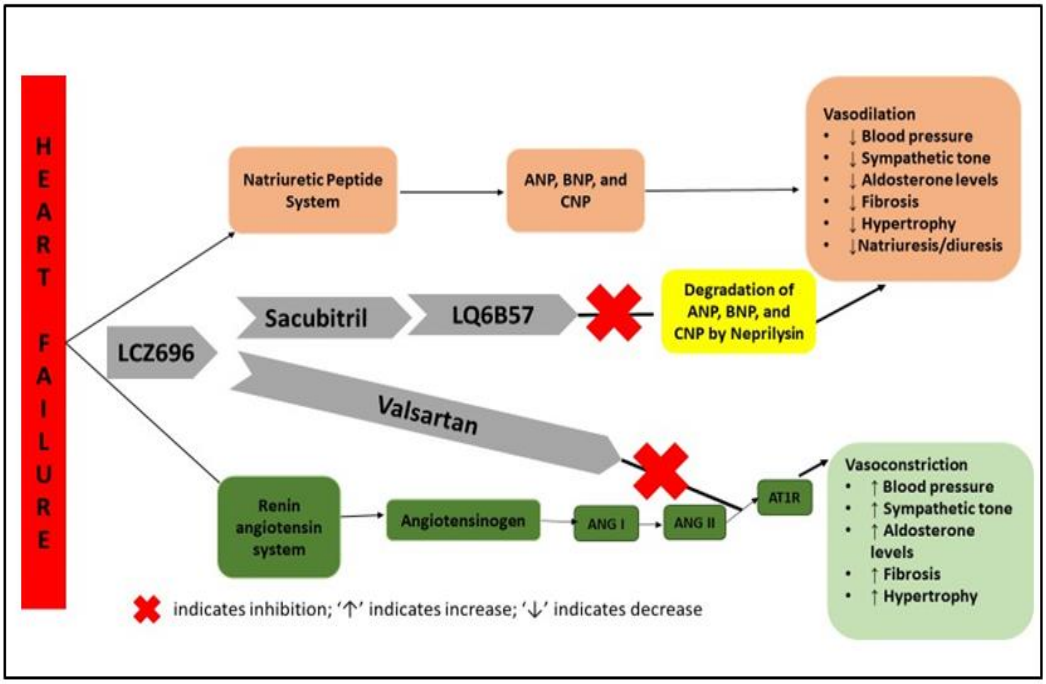

Figure 1: Mechanism of Action of Sacubitril/valsartan (ANP: Atrial natriuretic peptide, BNP: B-Type natriuretic peptide, CNP: C-Type natriuretic peptide, ANG I: Angiotensin I, ANG II: Angiotensin II, AT1R: Angiotensin 1 receptors).

EFFICACY

Researchers have been interested in studying the effectiveness of sacubitril/valsartan (SAC/VAL) in treating heart failure. Several trials have been conducted to evaluate its benefits.

One study found that even when patients took a lower dose of SAC/VAL, it was still more effective than enalapril in reducing the risk of heart failure and death.

Another study showed that SAC/VAL reduced hospital readmissions due to heart failure within 30 days of treatment, compared to enalapril.

Additionally, research found that SAC/VAL was effective in reducing blood pressure and improving outcomes in patients with heart failure, regardless of their blood pressure levels.

SAC/VAL has also been shown to be effective in patients taking other medications, such as diuretics, and in those with implanted cardiac defibrillators. Furthermore, studies have demonstrated that SAC/VAL is superior to other treatments, including valsartan, in reducing blood pressure and improving outcomes in patients with hypertension.

Overall, the findings suggest that SAC/VAL is a valuable treatment option for patients with heart failure and hypertension.

SAFETY

Patients with heart failure who received sacubitril/valsartan (SAC/VAL) therapy in the PARADIGM-HF trial reported improved quality of life. After 8 months, patients taking SAC/VAL showed significant improvements in their symptoms and physical limitations, as well as their social activities and relationships.

Compared to patients taking enalapril, those on SAC/VAL therapy reported better overall health and well-being. Fewer patients on SAC/VAL experienced a decline in their quality of life.

Another analysis of the same trial found that SAC/VAL improved patients' ability to perform daily activities, such as household chores, and also improved their sexual relationships. Overall, the findings suggest that SAC/VAL can significantly improve the quality of life for patients with heart failure.

COST- EFFECTIVENESS

For nearly 20 years, ACE inhibitors, ARBs, and beta blockers have been the standard treatment for heart failure with reduced ejection fraction (HFrEF). However, in 2015, a landmark trial showed that sacubitril/valsartan (SAC/VAL) was a safer and more effective treatment option.

Despite its benefits, SAC/VAL is more expensive than traditional treatments, which has raised questions about its cost-effectiveness. Studies have shown that while SAC/VAL reduces hospitalizations and improves quality of life, its high cost makes it unlikely to be cost-effective at current prices.

However, if a generic version of SAC/VAL becomes available, the cost is expected to drop significantly, making it more cost-effective. Additionally, studies have shown that SAC/VAL can lead to significant medical savings due to reduced hospitalizations.

The cost-effectiveness of SAC/VAL varies depending on the country and healthcare system. In some countries, such as the UK, Denmark, and Colombia, SAC/VAL has been shown to be cost-effective, while in others, such as the US, it is considered only marginally cost-effective.

Overall, while SAC/VAL is more expensive than traditional treatments, its benefits and potential cost savings make it a valuable treatment option for patients with HFrEF. However, its cost-effectiveness is highly dependent on the pricing strategy and healthcare system.

USES

USE IN HYPERTENSION

The PARADIGM-HF trial yielded compelling evidence for the efficacy of sacubitril/valsartan in reducing systolic blood pressure, surpassing that of enalapril. Nevertheless, an increased incidence of symptomatic hypotension was observed. Further investigation into its therapeutic potential in hypertension has been conducted, with results suggesting a potentially enhanced blood pressure-lowering effect compared to valsartan or olmesartan alone.

USE IN CHRONIC KIDNEY DISEASE

The inhibition of neprilysin has been shown to induce natriuresis and reduce intraglomerular pressure and proteinuria, thereby demonstrating potential therapeutic utility in the treatment of chronic kidney disease (CKD). The concomitant blockade of the renin-angiotensin system suggests that sacubitril/valsartan may offer a viable treatment option for CKD. Further investigation into the efficacy of sacubitril/valsartan in this context is currently underway, including the UK Heart And Renal Protection III (UK HARP-III) trial.

OTHER NEPRILYSIN INHIBITORS IN DEVELOPMENT

The development of neprilysin inhibitors has been an ongoing endeavor for over three decades, yet sacubitril (in combination with valsartan) is the only agent to have successfully completed clinical development and obtained regulatory approval. The early 2000s saw a decline in interest in this class of agents, resulting in a relative dearth of publicly available information regarding forthcoming neprilysin inhibitors. Nonetheless, Therevance Biopharma is presently advancing TD-0714 and TD-1439 through phase 1 clinical trials for the treatment of heart failure and chronic kidney disease, thereby indicating a continued interest in this therapeutic area.

PLACE IN THERAPY

It is clear from the above that there is a lot of evidence for sacubitril/valsartan, all from one phase 3 trial. It is argued that the trial was so large and the results so consistent that the quality of evidence it provides is equivalent to four or five separate trials. This was an innovative treatment, and one that made a big difference to patients who were symptomatic

despite standard therapy. Consequently, sacubitril/valsartan has already been incorporated into management guidelines – but at different steps. The guidance could hardly be more favourable. NICE recom mends sacubitril/valsartan as an option for people with chronic heart failure and reduced ejection fraction (≤35 per cent) who have NYHA class II–IV symptoms, despite stable treatment with an ACE inhibitor or an angiotensin II-receptor antagonist. It does not state that patients must be taking an aldosterone antagonist – formerly the next step – or that they should be intolerant of an ACE inhibitor. US guidance specifies a lower symptom severity but is more explicit, stating: "In patients with chronic symptomatic HFrEF [heart failure with reduced ejection fraction] NYHA class II or III who tolerate an ACE inhibitor or ARB [angiotensin II-receptor antagonist], replacement by an ARNI [angiotensin receptor neprilysin inhibitor] is recommended to further reduce morbidity and mortality". By contrast, the Scottish Intercollegiate Guidelines Network (SIGN) positions sacubitril/valsartan after the addition of an aldosterone antagonist and for patients with ejection fraction ≤40 per cent. An aldosterone antagonist is considered as effective as sacubitril/valsartan, though it is an addition to an ACE inhibitor rather than a substitute. A meta-analysis of eight trials involving almost 4000 patients showed that adding an aldosterone antagonist in this way reduces all-cause mortality (relative risk [RR] 0.79) and admission due to cardiac causes (RR 0.62). In PARADIGM-HF, about half of participants were taking an aldosterone antagonist but it made no difference to the efficacy of sacubitril/valsartan.

CONCLUSION

The introduction of sacubitril/valsartan (SAC/VAL) has transformed the treatment of heart failure (HF). Initial trials showed that SAC/VAL was more effective than enalapril in patients with HF with reduced ejection fraction (HFrEF). Although SAC/VAL has proven to be safe and effective, its use in patients with HF with preserved ejection fraction (HFpEF) and other special populations is still being explored. While SAC/VAL is more expensive than traditional HF treatments, it offers better safety and efficacy. In the long term, SAC/VAL has been shown to be more tolerable, effective at lower doses, and associated with fewer side effects. Overall, SAC/VAL can reduce healthcare costs by minimizing hospital readmissions and improving quality of life. However, its cost-effectiveness in developing countries remains uncertain due to limited data.

Currently, SAC/VAL is priced higher than standard HF treatments, making it inaccessible to many patients in developing countries. To address this, there is a need for pharmacoeconomic studies to assess the cost-effectiveness of SAC/VAL in these regions. Moreover, healthcare providers face challenges in recommending SAC/VAL to patients with limited financial resources. Therefore, long-term, real-world studies are necessary to fully understand the cost-effectiveness of SAC/VAL. To make SAC/VAL more accessible, measures such as lower pricing and improved healthcare policies are needed, particularly in developing countries.

DISCUSSION

Studies have shown that sacubitril/valsartan is a cost-effective and superior treatment option for patients with heart failure with reduced ejection fraction (HFrEF). It has been proven to reduce the risk of death and hospitalization due to heart failure, as well as sudden cardiac death. Starting treatment with sacubitril/valsartan has been shown to have significant benefits, even in the early stages, compared to treatment with enalapril. This medication has also been found to be safe and well-tolerated in a wide range of patients with HFrEF, leading to improved quality of life. The benefits of sacubitril/valsartan can be attributed to its effects on both the heart and other parts of the body. At the heart level, it helps reduce stress, inflammation, and cell death, leading to improved heart function and structure. Additionally, sacubitril/valsartan has positive effects on blood vessels, metabolism, and kidney function, providing greater protection against vascular disease, diabetes, and kidney impairment.

In conclusion, sacubitril/valsartan is a superior treatment option for patients with HFrEF, offering more benefits than traditional treatments that only target the renin-angiotensin-aldosterone system (RAAS).

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