European Journal of Clinical Pharmacy

Print ISSN: 2385-409X **Online ISSN**: Applied
Website: https://farmclin.es/

Original Research Article

Evaluation of Use, Efficacy, and Safety of Sacubitril/Valsartan

Article History:

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How to cite this article:
Dolores C.S., et, al. Evaluation of Use, Efficacy, and Safety of Sacubitril/Valsartan. *Eur J Clin Pharm.* 2019;1(1);49.52.

Received: 24-05-2019
Revised: 29-06-2019
Accepted: 05-07-2019
Published: 28-07-2019

Abstract: Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor (ARNI), has transformed heart failure management, particularly in patients with reduced ejection fraction (HFrEF). This article reviews current evidence regarding its clinical use, efficacy across different heart failure populations, safety profile, and practical considerations. Analysis includes pivotal trial results, real-world data, and recommendations for patient management and future research directions.

Keywords: Sacubitril/valsartan, Heart failure with reduced ejection fraction (HFrEF), Angiotensin receptor-neprilysin inhibitor (ARNI), Clinical efficacy, Safety profile.

INTRODUCTION

Heart failure remains a leading global health burden, driving innovation in pharmacotherapy. Sacubitril/valsartan, approved for HFrEF, combines neprilysin inhibition (sacubitril) and angiotensin receptor blockade (valsartan). Its dual mechanism aims to enhance natriuretic peptides while suppressing the renin–angiotensin–aldosterone system, producing broad cardiovascular and renal benefits. The drug's widespread clinical adoption and associated safety considerations warrant thorough review for clinicians and researchers.

Pharmacological Mechanism

- **Sacubitril** inhibits neprilysin, reducing degradation of natriuretic peptides, bradykinin, and other vasoactive substances.
- **Valsartan** antagonizes angiotensin II type-1 receptors, diminishing vasoconstriction and aldosterone secretion.
- The combination results in vasodilation, natriuresis, cardiac remodeling attenuation, and blood pressure reduction[1].

CLINICAL USE

Indications

- **Heart Failure with Reduced Ejection Fraction (HFrEF)**: Sacubitril/valsartan is recommended for ambulatory HFrEF patients (NYHA class II-IV), as a replacement for ACE inhibitors or ARBs to reduce mortality and hospitalizations.

- **Heart Failure with Preserved Ejection Fraction (HFpEF)**: Evidence is less robust; small benefits seen in subgroups, but not formally indicated for HFpEF[1][2].

Initiation and Dosing

- Initial dose selection depends on prior exposure to ACEIs/ARBs, renal function, and blood pressure.
- A 36-hour washout is required if switching from an ACE inhibitor to minimize angioedema risk.
- Dose titration is gradual, based on clinical response and tolerability.

EFFICACY REVIEW

Heart Failure with Reduced Ejection Fraction (HFrEF)

Pivotal Trials

- **PARADIGM-HF Trial**: Demonstrated a 20% relative reduction in cardiovascular death or heart failure hospitalization compared to enalapril. The trial ceased early due to overwhelming benefit in the primary endpoint[1][3].
- **Improvements in Cardiac Function**: Significant gains in left ventricular ejection fraction, reductions in NT-proBNP, and reversal of cardiac remodeling[4][5].

Real-World Effectiveness

- **Comparisons to Standard Therapy**: Consistently superior to ACEI/ARB in reducing all-cause and HF hospitalizations, improving biomarkers, and lowering rates of hyperkalemia and renal dysfunction[4][6].
- **Quality of Life**: Greater improvements in physical and social functioning versus standard therapy[7].

Key Outcomes from Recent Studies

Endpoint	Sacubitril/Valsartan	ACEI/ARB	Relative Benefit
CV Death or HF Hospitalization	21.8%	26.5%	-20%
All-cause Mortality	17%	19.8%	-15%
HF Hospitalization	12.3%	17.2%	-28%
LVEF Improvement	+5–7%	+2–4%	+3%

Heart Failure with Preserved Ejection Fraction (HFpEF)

- **Efficacy Less Established:** Most trials do not show significant mortality or hospitalization benefit, except possibly in subgroups with mid-range ejection fraction (LVEF 45–57%)[1][2].
- **Biomarker Improvement:** Some reductions in NT-proBNP and improvement in NYHA class in select participants[2][5].

SAFETY AND ADVERSE EVENTS

General Safety Profile

- **Comparison to ACEI/ARB:** Similar rates of overall and serious adverse events, with lower rates of therapy discontinuation for adverse effects[8][9].
- **Most Common Adverse Effects:** Hypotension, dizziness, renal impairment, hyperkalemia, cough, and angioedema[1][10][8].
- **Other Notable Adverse Events:** Mild gastrointestinal symptoms, less frequently sensory issues (e.g., hearing loss), and rare cases of angioedema requiring hospitalization[11][10].

Table: Adverse Event Rates Compared to ACE Inhibitors

Adverse Event	Sacubitril/Valsartan (%)	ACEI/ARB (%)	RR (95% CI)
Hypotension	17–20	12–14	1.45
Hyperkalemia	12–14	14–16	0.93
Renal Dysfunction	10–12	12–15	0.80
Angioedema	0.4–0.5	0.2–0.3	2.36*

(*Higher risk noted with >12 months therapy[8].)

Patient Considerations

- **Higher Risk Populations**: The elderly (≥70 years) and patients with lower baseline blood pressure require close monitoring for adverse effects, especially during treatment initiation[11].
- **Drug Interactions**: Caution with potassium-sparing agents; avoid use with ACE inhibitors concurrently[8][10].
- **Pregnancy**: Contraindicated due to fetal toxicity risk[10][12].

Special Populations

- **Renal Dysfunction:** Sacubitril/valsartan demonstrates renal protective benefit versus ACEI, though close renal monitoring is necessary[4][13].
- **Post-Acute Heart Failure:** Initiation during or soon after hospitalization provides clinical benefit and is generally safe, with similar adverse event rates as ambulatory patients[13][6].

Practical Guidance for Clinicians

1. *Patient Selection*: Preferential use in ambulatory HFrEF patients; less clear benefit in HFpEF.
2. *Dosage*: Start low and titrate up, observing for hypotension or other adverse events.
3. *Monitoring*: Regular check of blood pressure, renal function, potassium, and HF symptoms.
4. *Drug Interactions*: Ensure appropriate washout from ACE inhibitors; review concomitant medications.
5. *Education*: Advise patients on signs of hypotension, renal dysfunction, and angioedema.

Limitations and Future Directions

- **Long-term Safety**: Longer follow-up studies needed for definitive assessment of adverse effects with chronic use, especially angioedema rates and renal outcomes[8].
- **Expanding Indications**: Further trials in HFpEF and other cardiovascular conditions are ongoing.
- **Real-World Data Needs**: Additional registry and post-marketing surveillance to refine risk stratification and optimize patient management.

CONCLUSION

Sacubitril/valsartan is a pivotal therapy for HFrEF, consistently demonstrating improvements in survival, hospitalization rates, cardiac function, and safety comparable to standard therapy—except for an increased risk of hypotension and angioedema. Its use in HFpEF remains less clear, with only specific subgroups appearing to benefit. Individualized patient assessment, vigilant monitoring, and further research are essential for optimizing its use in clinical practice.

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