

Real-World Comparison of Worsening Heart Failure and Acute Kidney Injury After Sacubitril/Valsartan Versus ARB Therapy in Older Patients: Incidence and Treatment Pathway Analysis

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Background

Sacubitril/valsartan demonstrated superiority over standard renin–angiotensin system inhibition in reducing cardiovascular mortality and heart failure hospitalization in the PARADIGM-HF randomized trial, establishing its role in selected patients with chronic heart failure under controlled clinical conditions¹. However, randomized trial populations are highly selected, and older adults, who account for a large proportion of patients with heart failure in routine practice, often present with greater comorbidity burden and treatment complexity. Recent real-world observational studies have extended evidence on sacubitril/valsartan to broader clinical populations and have reported differences in hospitalization patterns compared with angiotensin receptor blocker therapy². In older patients, worsening heart failure frequently manifests as acute care escalation, and renal vulnerability remains a clinically important safety concern. Evaluating real-world incidence of worsening heart failure and acute kidney injury, together with downstream care pathways, may therefore provide relevant insights into treatment patterns among older patients with heart failure within observational research frameworks.

Methods

We conducted a retrospective cohort study using an electronic health record database standardized to the OMOP Common Data Model based on Taipei Medical University Clinical Research Database from 2008 to 2023. The study population was restricted to patients aged 65 years or older with a diagnosis of heart failure who initiated sacubitril/valsartan or an angiotensin receptor blocker. Outcomes included incidence of worsening heart failure, defined by heart failure-related emergency department visits or hospitalizations, and acute kidney injury-related hospitalizations, as well as care pathway patterns following treatment initiation. Outcomes were summarized using incidence rates and pathway analyses.

Results

Outcome	Treatment	Persons	Events	Time at Risk (PY)	Incidence Rate (per 1,000 PY)
Worsening HF	ARNI	704	24	1,268	18.93
Worsening HF	ARB	8,288	1,246	34,381	36.24
AKI	ARNI	678	9	1,279	7.04

Outcome	Treatment	Persons	Events	Time at Risk (PY)	Incidence Rate (per 1,000 PY)
AKI	ARB	8,620	772	39,895	19.35

Table 1. Incidence Rates of Worsening Heart Failure and Acute Kidney Injury by Treatment Group

Among patients with heart failure, ARNI users demonstrated lower incidence rates of both worsening heart failure and acute kidney injury compared with ARB users. The incidence rate of worsening heart failure was 18.9 per 1,000 person-years in the ARNI group versus 36.2 per 1,000 person-years in the ARB group. Similarly, acute kidney injury occurred at a rate of 7.0 per 1,000 person-years among ARNI users compared with 19.4 per 1,000 person-years among ARB users.

Following the observed differences in incidence rates of worsening heart failure and acute kidney injury between treatment groups, treatment pathway analysis was conducted to further characterize real-world clinical trajectories after therapy initiation. While incidence rates quantify event frequency, pathway analysis provides insight into treatment persistence, switching patterns, and subsequent clinical outcomes that may underlie these differences.

A total of 1,966 patients newly initiated sacubitril/valsartan. During follow-up, treatment persistence was low, with 153 patients (7.8%) remaining on sacubitril/valsartan, while 1,813 patients (92.2%) exited the exposure pathway. Among patients exiting sacubitril/valsartan, 9 patients (0.5%) transitioned to angiotensin receptor blockers, whereas the majority discontinued or transitioned to alternative treatment pathways. In contrast, angiotensin receptor blocker users demonstrated substantially higher persistence, with 1,782 patients (90.6%) remaining on therapy.

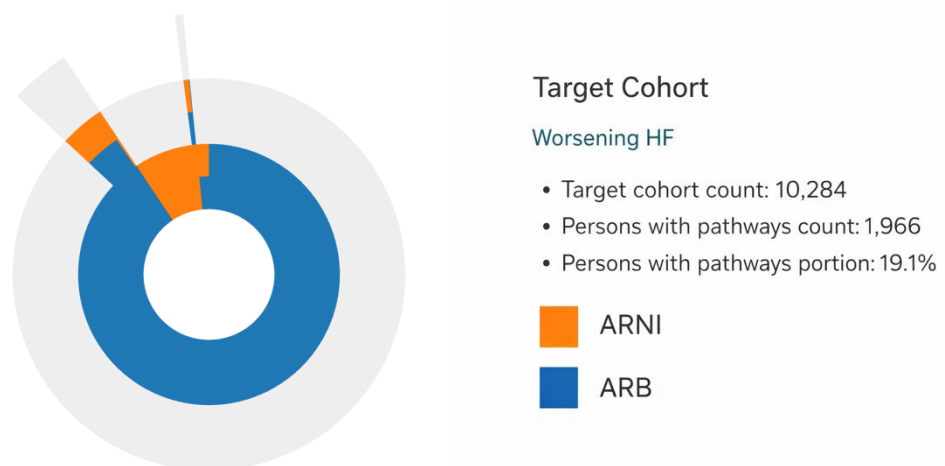


Figure 1. Treatment Pathways Following Worsening in Heart Failure Patients Treated With ARNI or ARB

Worsening heart failure events occurred predominantly in the context of early treatment discontinuation or switching, resulting in insufficient stable exposed person-time to support hazard ratio estimation. Consequently, outcomes were summarized using incidence rates and treatment pathway patterns rather than time-to-event effect. Worsening heart failure is frequently accompanied by hemodynamic instability, congestion, and impaired renal perfusion, all of which increase vulnerability to renal injury. Given this close pathophysiologic relationship, we subsequently evaluated the risk of acute kidney injury as a clinically relevant renal safety outcome.

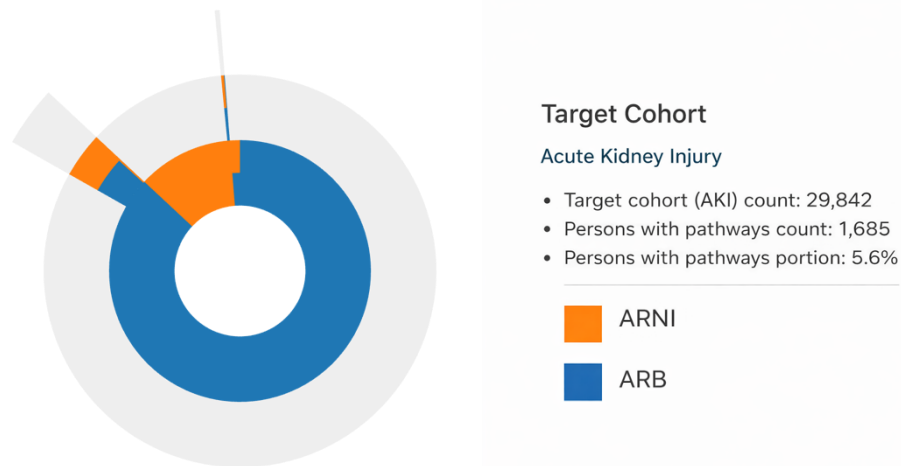


Figure 2. Treatment Pathways Following Acute Kidney Injury in Heart Failure Patients Treated With ARNI or ARB

Among 29,842 heart failure patients with acute kidney injury (AKI), 1,685 patients (5.6%) entered a post-AKI treatment pathway involving either sacubitril/valsartan (ARNI) or angiotensin receptor blockers (ARB). Of patients initiating ARNI after AKI, 199 (11.8%) remained on ARNI, while 1,486 (88.2%) discontinued or switched therapy; direct switching from ARNI to ARB was rare, occurring in only 4 patients (0.2%). In contrast, among patients initiating ARB after AKI, 1,465 (86.9%) remained on ARB, whereas 220 (13.1%) discontinued or switched treatment; 60 patients (3.6%) subsequently transitioned from ARB to ARNI. Overall, treatment persistence following AKI was substantially higher in ARB users compared with ARNI users, and bidirectional switching between ARNI and ARB was uncommon, indicating a conservative treatment pattern in real-world post-AKI management.

Conclusion

In this large real-world cohort of patients with heart failure, initiation of sacubitril/valsartan was associated with lower incidence rates of worsening heart failure and acute kidney injury compared with ARB therapy. Beyond event frequency, treatment pathway analyses revealed markedly different post-initiation trajectories between groups. Patients treated with sacubitril/valsartan demonstrated substantially higher treatment persistence and minimal switching, whereas ARB users exhibited more frequent treatment transitions, including escalation to sacubitril/valsartan. Notably, bidirectional switching between therapies was uncommon, suggesting conservative treatment decision-making following clinical destabilization.

These findings suggest that sacubitril/valsartan is not only associated with fewer adverse events but also supports more stable treatment trajectories following clinical deterioration. In contrast, frequent treatment changes among ARB users indicate persistent uncertainty or suboptimal disease control. Integrating incidence and pathway analyses therefore provides a more complete and clinically actionable picture of real-world heart failure management.

References

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